
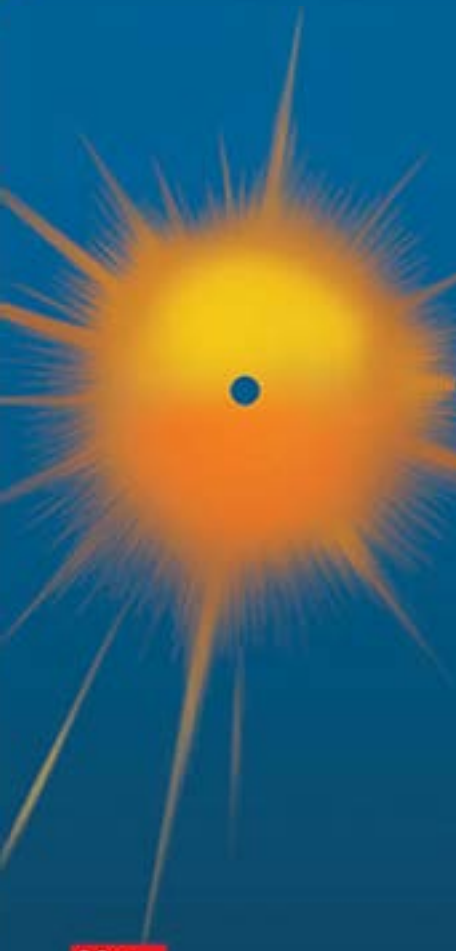


20th Edition



HARRISON'S[®] MANUAL OF MEDICINE

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Harrison's Principles of Internal Medicine (HPIM), the premier medical textbook for students and clinicians, provides a comprehensive resource for understanding of the biological and clinical aspects of quality patient care. *Harrison's Manual of Medicine* aims to fulfill a different need: As a concise, fact-rich resource for point-of-care, the *Manual* presents clinical information drawn from the 20th edition of *HPIM*, covering the key features of the diagnosis, clinical manifestations, and treatment of the major diseases that are likely to be encountered on a medical inpatient service and in the clinic.

First published 30 years ago, the *Manual* is well established as a trusted resource for rapid access to clinically practical information. With each edition, it is updated by experts and has become ever more useful with the rapid expansion of medical knowledge and the increasing time constraints associated with heavy patient-care responsibilities in modern health care settings. The *Manual's* popularity and value reflect its abbreviated format, which has proven extremely useful for initial diagnosis and management in time-restricted clinical settings. In particular, the book's full-color format allows readers to locate and use information quickly. In addition, numerous tables and graphics facilitate decisions at the point of care.

Although not a substitute for in-depth analysis of clinical problems, the *Manual* serves as a ready source of informative summaries that will be useful "on the spot" and that will prepare the reader for more in-depth analysis through more extensive reading at a later time. Of note, McGraw-Hill's *Access Medicine* website (www.accessmedicine.com) provides online access to both the *Manual* and *Harrison's Principles of Internal Medicine*, making it very easy to seek additional information when needed. The *Manual* is also available in a variety of eBook and app formats.

Like previous editions, this latest edition of the *Manual* is intended to keep up with the continual evolution of internal medicine practices. To this end, every chapter from the prior edition has been closely reviewed and updated, with substantial revisions and new chapters provided where appropriate. The Editors learned much in the process of updating the *Manual* and we hope that you will find this edition uniquely valuable as a clinical and educational resource.

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GLOSSARY

A₂	aortic second sound	EBV	Epstein-Barr virus
ABGs	arterial blood gases	ECG	electrocardiogram
ACE	angiotensin-converting enzyme	EEG	electroencephalogram
AF	atrial fibrillation	ELISA	enzyme-linked immunosorbent assay
AIDS	acquired immunodeficiency syndrome	EMG	electromyogram
ALS	amyotrophic lateral sclerosis	ENT	ear, nose, and throat
ANA	antinuclear antibody	EOM	extraocular movement
ARDS	acute respiratory distress syndrome	ESR	erythrocyte sedimentation rate
bid	two times daily	FDA	U.S. Food and Drug Administration
biw	twice a week	FEV₁	forced expiratory volume in first second
bp	blood pressure	GFR	glomerular filtration rate
BUN	blood urea nitrogen	GI	gastrointestinal
CAPD	continuous ambulatory peritoneal dialysis	G6PD	glucose-6-phosphate dehydrogenase
CBC	complete blood count	Hb	hemoglobin
CF	complement fixation	Hct	hematocrit
CHF	congestive heart failure	HDL	high-density lipoprotein
CLL	chronic lymphocytic leukemia	HIV	human immunodeficiency virus
CML	chronic myeloid leukemia	hs	at bedtime
CMV	cytomegalovirus	HSV	herpes simplex virus
CNS	central nervous system	ICU	intensive care unit
CPK	creatine phosphokinase	IFN	interferon
CSF	cerebrospinal fluid	Ig	immunoglobulin
CT	computed tomography	IL	interleukin
CVP	central venous pressure	IM	intramuscular
CXR	chest x-ray	IP	intraperitoneal
DIC	disseminated intravascular coagulation	IV	intravenous
DVT	deep-venous thrombosis	IVC	inferior vena cava
		IVP	intravenous pyelogram

GLOSSARY

JVP	jugular venous pulse	PVCs	premature ventricular contractions
LA	left atrium	QAM	every morning
LAD	left-axis deviation	qd	every day
LBBB	left bundle branch block	qh	every hour
LDH	lactate dehydrogenase	qhs	every bedtime
LDL	low-density lipoprotein	qid	four times daily
LFT	liver function test	qod	every other day
LLQ	left lower quadrant	RA	rheumatoid arthritis
LP	lumbar puncture	RBBB	right bundle branch block
LUQ	left upper quadrant	RBC	red blood (cell) count
LV	left ventricle	RLQ	right lower quadrant
MI	myocardial infarction	RR	respiratory rate
MIC	minimal inhibitory concentration	RUQ	right upper quadrant
MRI	magnetic resonance imaging	RV	right ventricle
NPO	nothing by mouth	S1 . . . S4	heart sounds, 1st to 4th
NSAIDs	nonsteroidal anti-inflammatory drugs	SARS	severe acute respiratory syndrome
P₂	pulmonic second sound	SC	subcutaneous
PaO₂	partial pressure of O ₂ in arterial blood	SL	sublingual
PAO₂	partial pressure of O ₂ in alveolar blood	SLE	systemic lupus erythematosus
PCR	polymerase chain reaction	SVC	superior vena cava
PFTs	pulmonary function tests	TIA	transient ischemic attack
PMNs	polymorphonuclear cells or leukocytes	tid	three times daily
PO	by mouth	tiw	thrice a week
PPD	purified protein derivative, skin test for tuberculosis	TLC	total lung capacity
prn	as needed	TNF	tumor necrosis factor
pt/pts	patient/patients	UA	urinalysis
PT	prothrombin time	URI	upper respiratory infection
PTT	partial thromboplastin time	UTI	urinary tract infection
		UV	ultraviolet
		VDRL	test for syphilis
		VZV	varicella-zoster virus
		WBC	white blood (cell) count

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1

Electrolytes

**SODIUM**

Disturbances of sodium concentration $[Na^+]$ result in most cases from abnormalities of H_2O homeostasis, which change the relative ratio of Na^+ to H_2O . Disorders of Na^+ balance per se are, in contrast, associated with changes in extracellular fluid volume, either hypo- or hypervolemia. Maintenance of “arterial circulatory integrity” is achieved in large part by changes in urinary sodium excretion and vascular tone, whereas H_2O balance is achieved by changes in both H_2O intake and urinary H_2O excretion (Table 1-1). Confusion can result from the coexistence of defects in both H_2O and Na^+ balance. For example, a hypovolemic pt may have an appropriately low urinary Na^+ due to increased renal tubular reabsorption of filtered $NaCl$; a concomitant increase in circulating arginine vasopressin (AVP)—part of the defense of effective circulating volume (Table 1-1)—will cause the renal retention of ingested H_2O and the development of hyponatremia.

■ HYPONATREMIA

This is defined as a serum $[Na^+] < 135$ mmol/L and is among the most common electrolyte abnormalities encountered in hospitalized pts. Symptoms include nausea, vomiting, confusion, lethargy, and disorientation; if severe (< 120 mmol/L) and/or abrupt, seizures, central herniation, coma, or death may result (see Acute Symptomatic Hyponatremia, below). Hyponatremia is almost always the result of an increase in circulating AVP and/or increased renal sensitivity to AVP; a notable exception is in the setting of low solute intake (“beer potomania”), wherein a markedly reduced urinary solute excretion is inadequate to support the excretion of sufficient free H_2O . The serum $[Na^+]$ by itself does not yield diagnostic information regarding total-body Na^+ content; hyponatremia is primarily

TABLE 1-1 Osmoregulation versus Volume Regulation

	OSMOREGULATION	VOLUME REGULATION
What is sensed	Plasma osmolality	Arterial filling
Sensors	Hypothalamic osmoreceptors	Carotid sinus Afferent arteriole Atria
Effectors	AVP Thirst	Sympathetic nervous system Renin-angiotensin-aldosterone system ANP/BNP AVP
What is affected	Urine osmolality H_2O intake	Urinary sodium excretion Vascular tone

Note: See text for details.

Abbreviations: ANP, atrial natriuretic peptide; AVP, arginine vasopressin; BNP, brain natriuretic peptide.

Source: Adapted from Rose BD, Black RM (eds): *Manual of Clinical Problems in Nephrology*. Boston, Little Brown, 1988.

a disorder of H₂O homeostasis. Pts with hyponatremia are thus categorized diagnostically into three groups, depending on their clinical volume status: hypovolemic, euvoletic, and hypervolemic hyponatremia (Fig. 1-1). All three forms of hyponatremia share an exaggerated, “nonosmotic” increase in circulating AVP, in the setting of reduced serum osmolality. Notably, hyponatremia is often multifactorial; clinically important nonosmotic stimuli that can cause a release of AVP and increase the risk of hyponatremia include drugs, pain, nausea, and strenuous exercise.

Laboratory investigation of a pt with hyponatremia should include a measurement of serum osmolality to exclude “pseudohyponatremia” due to hyperlipidemia or hyperproteinemia. Serum glucose also should be measured; serum [Na⁺] falls by approximately 1.4 mM for every 100-mg/dL increase in glucose, due to glucose-induced H₂O efflux from cells. Hyperkalemia may suggest adrenal insufficiency or hypoaldosteronism; increased blood urea nitrogen (BUN) and creatinine may suggest a renal cause. Urine electrolytes and osmolality are also critical tests in the initial evaluation of hyponatremia. In particular, a urine Na⁺ <20 meq/L is consistent with hypovolemic hyponatremia in the clinical absence of a “hypervolemic,” Na⁺-avid syndrome such as congestive heart failure (CHF) (Fig. 1-1). Urine osmolality <100 mosmol/kg is suggestive of polydipsia or, in rare cases, of decreased solute intake; urine osmolality >400 mosmol/kg suggests that AVP excess is playing a more dominant role, whereas intermediate values are more consistent with multifactorial pathophysiology (e.g., AVP excess with a component of polydipsia). Finally, in the right clinical setting, thyroid, adrenal, and pituitary function should also be tested.

Hypovolemic Hyponatremia

Hypovolemia from both renal and extrarenal causes is associated with hyponatremia. Renal causes of hypovolemia include primary adrenal insufficiency and hypoaldosteronism, salt-losing nephropathies (e.g., reflux nephropathy, nonoliguric acute tubular necrosis), diuretics, and osmotic diuresis. Random “spot” urine Na⁺ is typically >20 meq/L in these cases but may be <20 meq/L in diuretic-associated hyponatremia if tested long after administration of the drug. Nonrenal causes of hypovolemic hyponatremia include GI loss (e.g., vomiting, diarrhea, tube drainage) and integumentary loss (sweating, burns); urine Na⁺ is typically <20 meq/L in these cases.

Hypovolemia causes profound neurohumoral activation, inducing systems that preserve arterial circulatory integrity, such as the renin-angiotensin-aldosterone (RAA) axis, the sympathetic nervous system, and AVP (Table 1-1). The increase in circulating AVP serves to increase the retention of ingested-free H₂O, leading to hyponatremia. The optimal treatment of hypovolemic hyponatremia is volume administration, generally as isotonic crystalloid, i.e., 0.9% NaCl (“normal saline”). If the history suggests that hyponatremia has been “chronic,” i.e., present for 48 h, care should be taken to avoid overcorrection (see below), which can easily occur as AVP levels plummet in response to volume-resuscitation; if necessary, the administration of desmopressin (DDAVP) and free water can reinstate or arrest the correction of hyponatremia (see below). An alternative strategy is to “clamp” AVP bioactivity by administering DDAVP while correcting the serum [Na⁺] with hypertonic saline in a more controlled, linear fashion.

Hypervolemic Hyponatremia

The edematous disorders (CHF, hepatic cirrhosis, and nephrotic syndrome) are often associated with mild to moderate degrees of hyponatremia ([Na⁺] = 125–135 mmol/L); occasionally, pts with severe CHF or cirrhosis may present with serum [Na⁺] <120 mmol/L. The pathophysiology is similar to that in hypovolemic hyponatremia, except that arterial filling and circulatory integrity are

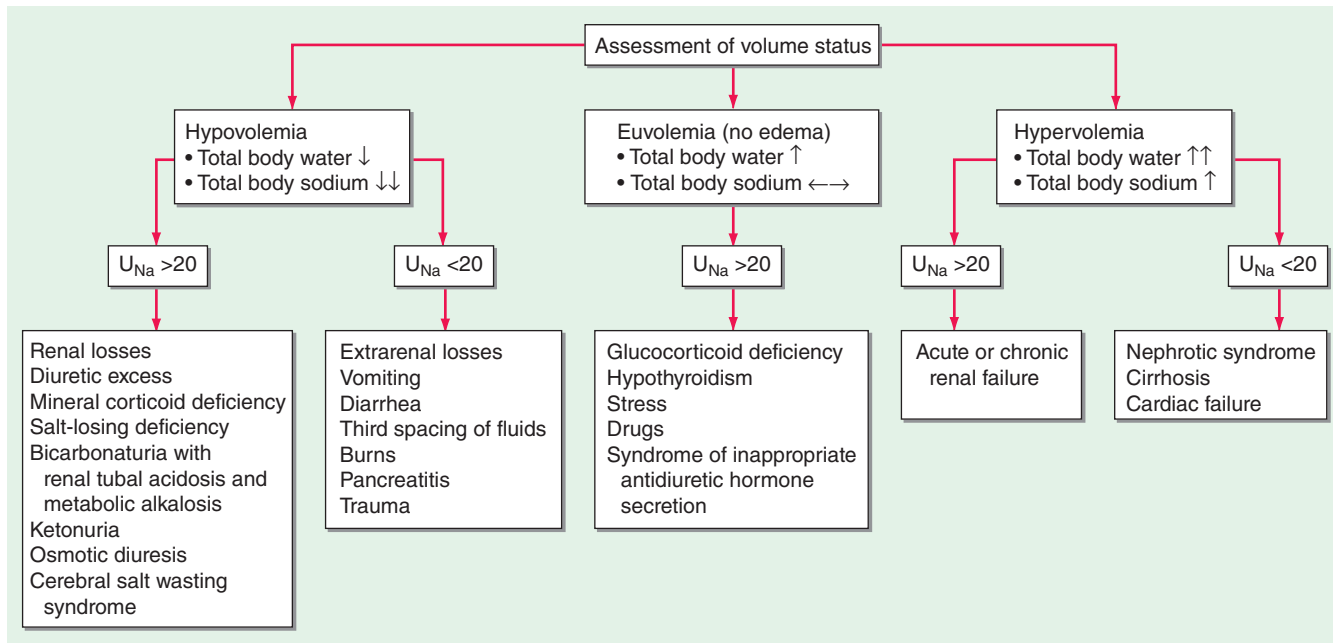


FIGURE 1-1 The diagnostic approach to hyponatremia. See text for details. (Reprinted from Kumar S, Berl T: Diseases of water metabolism. In: Atlas of Diseases of the Kidney, Vol 1, Schrier RW [ed]. Philadelphia, Current Medicine, Inc, 1999; with permission.)

decreased due to the specific etiologic factors, i.e., cardiac dysfunction, peripheral vasodilation in cirrhosis, and hypoalbuminemia in nephrotic syndrome. The degree of hyponatremia is an indirect index of the associated neurohumoral activation (Table 1-1) and an important prognostic indicator in hypervolemic hyponatremia.

Management consists of treatment of the underlying disorder (e.g., afterload reduction in heart failure, intravenous administration of albumin in cirrhosis, immunomodulatory therapy in some forms of nephrotic syndrome), Na^+ restriction, diuretic therapy, and, in some pts, H_2O restriction. Vasopressin antagonists (e.g., tolvaptan and conivaptan) are also effective in normalizing hypervolemic hyponatremia associated with CHF; hepatic toxicity of tolvaptan limits its clinical utility in cirrhosis.

Euvolemic Hyponatremia

The syndrome of inappropriate ADH secretion (SIADH) characterizes most cases of euvolemic hyponatremia. Other causes of euvolemic hyponatremia include hypothryroidism and secondary adrenal insufficiency due to pituitary disease; notably, repletion of glucocorticoid levels in the latter may cause a rapid drop in circulating AVP levels and overcorrection of serum $[\text{Na}^+]$ (see below).

Common causes of SIADH include pulmonary disease (e.g., pneumonia, tuberculosis, pleural effusion) and central nervous system (CNS) diseases (e.g., tumor, subarachnoid hemorrhage, meningitis); SIADH also occurs with malignancies (primarily small cell carcinoma of the lung) and drugs (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants, nicotine, vincristine, carbamazepine, narcotic analgesics, antipsychotic drugs, cyclophosphamide, ifosfamide). Optimal treatment of euvolemic hyponatremia includes treatment of the underlying disorder. H_2O restriction to <1 L/d is a cornerstone of therapy, but may be ineffective or poorly tolerated. However, vasopressin antagonists are predictably effective in normalizing serum $[\text{Na}^+]$ in SIADH. Alternatives include the administration of loop diuretics to inhibit the countercurrent mechanism and reduce urinary concentration, combined with oral salt tablets to abrogate diuretic-induced salt loss and attendant hypovolemia. More recently, a palatable form of oral urea has become available; oral urea is equivalent to tolvaptan in the management of SIADH, increasing urinary solute (urea) and, thus, urinary H_2O excretion.

Acute Symptomatic Hyponatremia

Acute symptomatic hyponatremia is a medical emergency; a sudden drop in serum $[\text{Na}^+]$ can overwhelm the capacity of the brain to regulate cell volume, leading to cerebral edema, seizures, and death. Women, particularly premenopausal women, are particularly prone to such sequelae; neurologic consequences are comparatively rare in male pts. Many of these pts develop hyponatremia from iatrogenic causes, including hypotonic fluids in the postoperative period, prescription of a thiazide diuretic, colonoscopy preparation, or intraoperative use of glycine irrigants. Polydipsia with an associated cause of increased AVP may also cause acute hyponatremia, as can increased H_2O intake in the setting of strenuous exercise, e.g., a marathon. The recreational drug Ecstasy (methylenedioxymethamphetamine [MDMA]) can cause acute hyponatremia, rapidly inducing both AVP release and increased thirst.

Severe symptoms may occur at relatively modest levels of serum $[\text{Na}^+]$, e.g., in the mid-120s. Nausea and vomiting are common premonitory symptoms of more severe sequelae. An important concomitant is respiratory failure, which may be hypercapnic due to CNS depression or normocapnic due to neurogenic, noncardiogenic pulmonary edema; the attendant hypoxemia amplifies the impact of hyponatremic encephalopathy.

TREATMENT**Hyponatremia**

Three considerations are critical in the therapy of hyponatremia. First, the presence, absence, and/or severity of symptoms determine the urgency of therapy (see above for acute symptomatic hyponatremia). Second, pts with hyponatremia that has been present for >48 h (“chronic hyponatremia”) are at risk for osmotic demyelination syndrome, typically central pontine myelinolysis, if serum Na^+ is corrected by >10–12 mM within the first 24 h and/or by >18 mM within the first 48 h. Third, the response to interventions, such as hypertonic saline or vasopressin antagonists, can be highly unpredictable, such that frequent monitoring of serum Na^+ (initially every 2–4 h) is imperative.

Treatment of acute symptomatic hyponatremia should include hypertonic saline to acutely increase serum Na^+ by 1–2 mM/h to a total increase of 4–6 mM; this increase is typically sufficient to alleviate acute symptoms from cerebral edema, after which corrective guidelines for “chronic” hyponatremia are appropriate (see below). A number of equations and algorithms have been developed to estimate the required rate of hypertonic solution; one popular approach is to calculate a “ Na^+ deficit,” where the Na^+ deficit = $0.6 \times \text{body weight} \times (\text{target } [\text{Na}^+] - \text{starting } [\text{Na}^+])$. Regardless of the method used to determine the rate of administered hypertonic saline, the increase in serum $[\text{Na}^+]$ can be highly unpredictable, due to rapid changes in the underlying physiology; serum $[\text{Na}^+]$ should be monitored every 2–4 h during and after treatment with hypertonic saline. The administration of supplemental O_2 and ventilatory support can also be critical in acute hyponatremia, if pts develop acute pulmonary edema or hypercapnic respiratory failure. IV loop diuretics will help treat associated acute pulmonary edema and will also increase free H_2O excretion by interfering with the renal countercurrent multiplier system. It is noteworthy that vasopressin antagonists do not have a role in the management of acute hyponatremia.

The rate of correction should be comparatively slow in *chronic* hyponatremia (<10–12 mM in the first 24 h and <18 mM in the first 48 h), so as to avoid osmotic demyelination syndrome. Vasopressin antagonists are highly effective in SIADH and in hypervolemic hyponatremia due to heart failure. Abnormalities in liver function tests have been reported during the use of tolvaptan, prohibiting use in cirrhosis; in pts without preexisting liver disease, therapy with this agent should be restricted to 1–2 months with close monitoring of liver function. Should pts overcorrect serum $[\text{Na}^+]$ in response to vasopressin antagonists, hypertonic saline, or isotonic saline (in chronic hypovolemic hyponatremia), hyponatremia can be safely reinduced or stabilized by the administration of the vasopressin agonist DDAVP and the administration of free H_2O , typically IV D_5W ; again, close monitoring of the response of serum $[\text{Na}^+]$ is essential to adjust therapy. Alternatively, the treatment of pts with marked hyponatremia can be initiated with the twice-daily administration of DDAVP to maintain constant AVP bioactivity, combined with the administration of hypertonic saline to slowly correct the serum $[\text{Na}^+]$ in a more controlled fashion, thus reducing upfront the risk of overcorrection.

■ HYPERNATREMIA

This is rarely associated with hypervolemia, where the association is typically iatrogenic, e.g., administration of hypertonic sodium bicarbonate. More commonly, hypernatremia is the result of a combined H_2O and volume deficit, with losses of H_2O in excess of Na^+ . Elderly individuals with reduced thirst and/or diminished access to fluids are at the highest risk of hypernatremia due to decreased free

TABLE 1-2 Correction of Hypernatremia**H₂O Deficit**

1. Estimate TBW: 50–60% body weight (kg) depending on body composition
2. Calculate free-water deficit: $[(\text{Na}^+ - 140)/140] \times \text{TBW}$
3. Administer deficit over 48–72 h

Ongoing H₂O Losses

4. Calculate free-water clearance, $C_e \text{H}_2\text{O}$:

$$C_e \text{H}_2\text{O} = V \left(1 - \frac{U_{\text{Na}} + U_{\text{K}}}{S_{\text{Na}}} \right)$$

where V is urinary volume, U_{Na} is urinary $[\text{Na}^+]$, U_{K} is urinary $[\text{K}^+]$, and S_{Na} is serum $[\text{Na}^+]$.

Insensible Losses

5. ~10 mL/kg per day: less if ventilated, more if febrile

Total

6. Add components to determine H₂O deficit and ongoing H₂O loss; correct the H₂O deficit over 48–72 h and replace daily H₂O loss.

Abbreviation: TBW, total-body water.

H₂O intake. Common causes of renal H₂O loss are osmotic diuresis secondary to hyperglycemia, postobstructive diuresis, or drugs (radiocontrast, mannitol, etc.); H₂O diuresis occurs in central or nephrogenic diabetes insipidus (DI) (**Chap. 172**). In pts with hypernatremia due to renal loss of H₂O, it is critical to quantify *ongoing* daily losses in addition to calculation of the baseline H₂O deficit (**Table 1-2**).

TREATMENT**Hypernatremia**

The approach to correction of hypernatremia is outlined in Table 1-2. As with hyponatremia, it is advisable to correct the H₂O deficit slowly to avoid neurologic compromise, decreasing the serum $[\text{Na}^+]$ over 48–72 h. Depending on the blood pressure or clinical volume status, it may be appropriate to initially treat with hypotonic saline solutions (1/4 or 1/2 normal saline); blood glucose should be monitored in pts treated with large volumes of D₅W, should hyperglycemia ensue. Calculation of urinary electrolyte-free H₂O clearance is helpful to estimate daily, ongoing loss of free H₂O in pts with nephrogenic or central DI (Table 1-2). Other forms of therapy may be helpful in selected cases of hypernatremia, once water deficits have been repleted. Pts with central DI may respond to the administration of intranasal DDAVP. Stable pts with nephrogenic DI may reduce their polyuria with hydrochlorothiazide (12.5–50 mg/d). This diuretic is thought to increase proximal H₂O reabsorption and decrease distal solute delivery, thus reducing polyuria. Pts with lithium-associated nephrogenic DI may respond to amiloride (2.5–10 mg/d), which decreases the entry of lithium into principal cells in the distal nephron by inhibiting the amiloride-sensitive epithelial sodium channel (ENaC). Notably, however, most pts with lithium-induced nephrogenic DI can adequately accommodate by increasing their H₂O intake. Occasionally, nonsteroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors have also been used to treat polyuria associated with nephrogenic DI, reducing the negative effect of local prostaglandins on urinary concentration; however, the nephrotoxic potential of these drugs typically makes them a less attractive therapeutic option.

POTASSIUM

Because potassium (K^+) is the major intracellular cation, discussion of disorders of K^+ balance must take into consideration changes in the exchange of intra- and extracellular K^+ stores. (Extracellular K^+ constitutes <2% of total-body K^+ content.) Insulin, β_2 -adrenergic agonists, and alkalosis tend to promote K^+ uptake by cells; acidosis, insulinopenia, or acute hyperosmolality (e.g., after treatment with mannitol or $D_{50}W$) promotes the efflux or reduced uptake of K^+ . A corollary is that tissue necrosis and the attendant release of K^+ can cause severe hyperkalemia, particularly in the setting of acute kidney injury. Hyperkalemia due to rhabdomyolysis is thus particularly common, due to the enormous store of K^+ in muscle; hyperkalemia may also be prominent in tumor lysis syndrome.

The kidney plays a dominant role in K^+ excretion. Although K^+ is transported along the entire nephron, it is the principal cells of the connecting segment and cortical collecting duct that play a dominant role in K^+ excretion. Apical Na^+ entry into principal cells via the amiloride-sensitive ENaC generates a lumen-negative potential difference, which drives passive K^+ exit through apical K^+ channels. *This relationship is key to the bedside understanding of potassium disorders.* For example, decreased distal delivery of Na^+ tends to blunt the ability to excrete K^+ , leading to hyperkalemia. Abnormalities in the renin-angiotensin-aldosterone system (RAAS) can cause both hypo- and hyperkalemia; aldosterone has a major influence on potassium excretion, increasing the activity of ENaC channels and the basolateral Na^+/K^+ -ATPase, thus amplifying the driving force for K^+ secretion across the luminal membrane of principal cells.

■ HYPOKALEMIA

Major causes of hypokalemia are outlined in [Table 1-3](#). Atrial and ventricular arrhythmias are the most serious health consequences of hypokalemia. Pts with concurrent Mg deficit and/or digoxin therapy are at a particularly increased risk of arrhythmias. Hypokalemia can directly prolong the QT interval and is a significant cofactor in arrhythmias due to other causes of a prolonged QT interval. Other clinical manifestations include muscle weakness, which may be profound at serum $[K^+] < 2.5$ mmol/L, and, if hypokalemia is sustained, hypertension, ileus, polyuria, renal cysts, and even renal failure.

The cause of hypokalemia is usually obvious from history, physical examination, and/or basic laboratory tests. However, persistent hypokalemia may require a more thorough, systematic evaluation ([Fig. 1-2](#)). Initial laboratory evaluation should include electrolytes, BUN, creatinine, serum osmolality, Mg^{2+} , and Ca^{2+} , a complete blood count, and urinary pH, osmolality, creatinine, and electrolytes. Serum and urine osmolality are required for calculation of the transtubular K^+ gradient (TTKG), which should be < 3 in the presence of hypokalemia (see also Hyperkalemia). Alternatively, a urinary K^+ -to-creatinine ratio of > 13 -mmol/g creatinine (> 1.5 -mmol/mmol creatinine) is compatible with excessive K^+ excretion. Further tests such as urinary Mg^{2+} and Ca^{2+} and/or plasma renin and aldosterone levels may be necessary in specific cases.

TREATMENT

Hypokalemia

The goals of therapy in hypokalemia are to prevent life-threatening and/or serious chronic consequences, to replace the associated K^+ deficit, and to correct the underlying cause and/or mitigate future hypokalemia. The urgency of therapy depends on the severity of hypokalemia, associated clinical factors (cardiac disease, digoxin therapy, etc.), and the rate of decline in serum K^+ . Pts with a prolonged QT interval and/or other risk factors for arrhythmia should

TABLE 1-3 Causes of Hypokalemia

- | |
|---|
| <p>I. Decreased intake</p> <p>A. Starvation</p> <p>B. Clay ingestion</p> |
| <p>II. Redistribution into cells</p> <p>A. Acid-base</p> <p> 1. Metabolic alkalosis</p> <p>B. Hormonal</p> <p> 1. Insulin</p> <p> 2. Increased β_2-adrenergic sympathetic activity: post-myocardial infarction, head injury, theophylline</p> <p> 3. β_2-Adrenergic agonists: bronchodilators, tocolytics</p> <p> 4. α-Adrenergic antagonists</p> <p> 5. Thyrotoxic periodic paralysis</p> <p> 6. Downstream stimulation of Na^+/K^+-ATPase: theophylline, caffeine</p> <p>C. Anabolic state</p> <p> 1. Vitamin B_{12} or folic acid administration (red blood cell production)</p> <p> 2. Granulocyte-macrophage colony-stimulating factor (white blood cell production)</p> <p> 3. Total parenteral nutrition</p> <p>D. Other</p> <p> 1. Pseudohypokalemia</p> <p> 2. Hypothermia</p> <p> 3. Familial hypokalemic periodic paralysis</p> <p> 4. Barium toxicity: systemic inhibition of “leak” K^+ channels</p> |
| <p>III. Increased loss</p> <p>A. Nonrenal</p> <p> 1. Gastrointestinal loss (diarrhea)</p> <p> 2. Integumentary loss (sweat)</p> <p>B. Renal</p> <p> 1. Increased distal flow and distal Na^+ delivery: diuretics, osmotic diuresis, salt-wasting nephropathies</p> <p> 2. Increased secretion of potassium</p> <p> a. Mineralocorticoid excess: primary hyperaldosteronism (APAs), PAH or UAH, IHA due to bilateral adrenal hyperplasia and adrenal carcinoma, familial hyperaldosteronism (FH-I, FH-II, congenital adrenal hyperplasias), secondary hyperaldosteronism (malignant hypertension, renin-secreting tumors, renal artery stenosis, hypovolemia), Cushing’s syndrome, Bartter’s syndrome, Gitelman’s syndrome</p> <p> b. Apparent mineralocorticoid excess: genetic deficiency of 11β-dehydrogenase-2 (syndrome of apparent mineralocorticoid excess), inhibition of 11β-dehydrogenase-2 (glycyrrhetic acid/glycyrrhizic acid and/or carbenoxolone; licorice, food products, drugs), Liddle’s syndrome (genetic activation of ENaC)</p> |

(Continued)

TABLE 1-3 Causes of Hypokalemia (Continued)

- c. Distal delivery of nonreabsorbed anions: vomiting, nasogastric suction, proximal renal tubular acidosis, diabetic ketoacidosis, glue sniffing (toluene abuse), penicillin derivatives (penicillin, nafcillin, dicloxacillin, ticarcillin, oxacillin, and carbenicillin)
3. Magnesium deficiency, amphotericin B, Liddle's syndrome

Abbreviations: APA, aldosterone-producing adenoma; ENaC, epithelial Na⁺ channels; IHA, idiopathic hyperaldosteronism; PAH, primary adrenal hyperplasia; UAH, unilateral adrenal hyperplasia.

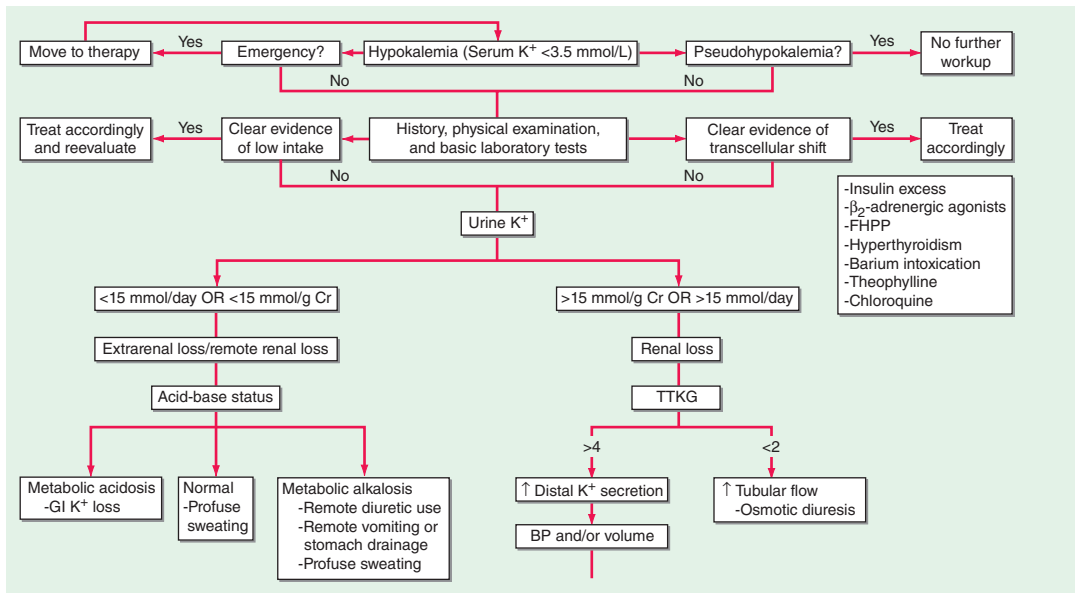
be monitored by continuous cardiac telemetry during repletion. Urgent but cautious K⁺ replacement should be considered in pts with severe redistributive hypokalemia (plasma K⁺ concentration <2.5 mM) and/or when serious complications ensue; however, this approach has a risk of rebound hyperkalemia following acute resolution of the underlying cause. When excessive activity of the sympathetic nervous system is thought to play a dominant role in redistributive hypokalemia, as in thyrotoxic periodic paralysis, theophylline overdose, and acute head injury, high-dose propranolol (3 mg/kg) should be considered; this nonspecific β -adrenergic blocker will correct hypokalemia without the risk of rebound hyperkalemia. It should be noted that hypokalemia is refractory to correction in the presence of Mg⁺⁺ deficiency, which also should be corrected when present; renal wasting of both cations may be particularly prominent after renal tubular injury, e.g., from cisplatin nephrotoxicity.

Oral replacement with K⁺-Cl⁻ is the mainstay of therapy in hypokalemia. Potassium phosphate, oral or IV, may be appropriate in pts with combined hypokalemia and hypophosphatemia. Potassium bicarbonate or potassium citrate should be considered in pts with concomitant metabolic acidosis. The deficit of K⁺ and the rate of correction should be estimated as accurately as possible; renal function, medications, and comorbid conditions such as diabetes should also be considered so as to gauge the risk of overcorrection. In the absence of abnormal K⁺ redistribution, the total deficit correlates with serum K⁺ such that serum K⁺ drops by approximately 0.27 mM for every 100-mmol reduction in total-body stores. Notably, given the delay in redistributing potassium into intracellular compartments, this deficit must be replaced gradually over 24–48 h, with frequent monitoring of plasma K⁺ concentration to avoid transient over-repletion and transient hyperkalemia if otherwise appropriate. If hypokalemia is severe (<2.5 mmol/L) and/or if oral supplementation is not feasible or tolerated, IV KCl can be administered through a central vein with cardiac monitoring in an intensive care setting, at rates that should not exceed 20 mmol/h. KCl should always be administered in saline solutions, rather than dextrose; the dextrose-induced increase in insulin can acutely exacerbate hypokalemia.

Strategies to minimize K⁺ losses should also be considered. These measures may include minimizing the dose of non-K⁺-sparing diuretics, restricting Na⁺ intake, and using clinically appropriate combinations of non-K⁺-sparing and K⁺-sparing medications (e.g., loop diuretics with angiotensin-converting enzyme inhibitors).

■ HYPERKALEMIA

Causes are outlined in [Table 1-4](#); in most cases, hyperkalemia is due to decreased renal K⁺ excretion. However, increases in dietary K⁺ intake can have a major effect in susceptible pts, e.g., diabetics with hyporeninemic hypoaldosteronism and chronic kidney disease (CKD). Drugs that impact on the RAA axis are also a major cause of hyperkalemia.



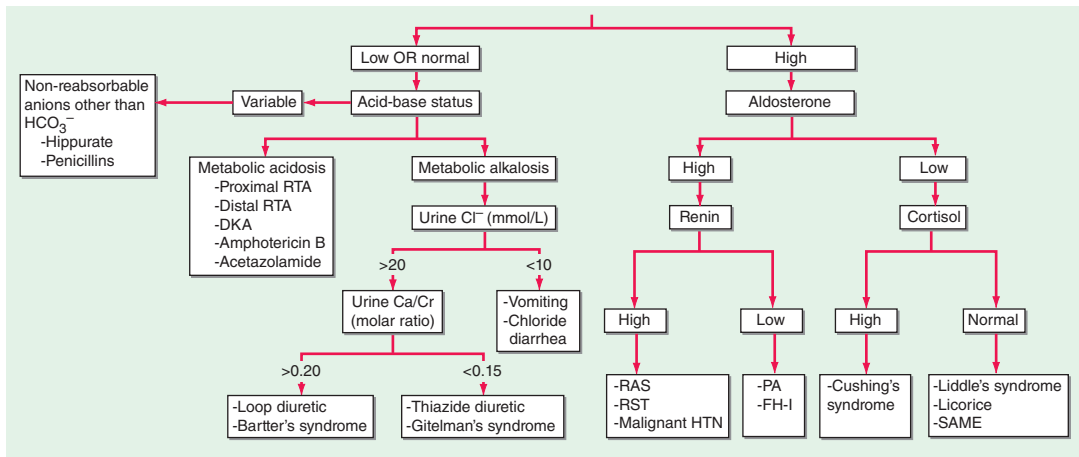


FIGURE 1-2 The diagnostic approach to hypokalemia. See text for details. bp, blood pressure; DKA, diabetic ketoacidosis; FH-I, familial hyperaldosteronism type I; FHPP, familial hypokalemic periodic paralysis; HTN, hypertension; PA, primary aldosteronism; RAS, renal artery stenosis; RST, renin-secreting tumor; RTA, renal tubular acidosis; SAME, syndrome of apparent mineralocorticoid excess; TTKG, transtubular potassium gradient. (Reprinted with permission from Mount DB, Zandi-Nejad K: *Disorders of potassium balance*. In: *Brenner and Rector's The Kidney*, 8th ed, Brenner BM [ed]. Philadelphia, Saunders, 2008.)

TABLE 1-4 Causes of Hyperkalemia

- I. “Pseudo” hyperkalemia
 - A. Cellular efflux: thrombocytosis, erythrocytosis, leukocytosis, in vitro hemolysis
 - B. Hereditary defects in red cell membrane transport
- II. Intra- to extracellular shift
 - A. Acidosis
 - B. Hyperosmolality; radiocontrast, hypertonic dextrose, mannitol
 - C. β -Adrenergic antagonists (noncardioselective agents)
 - D. Digoxin and related glycosides (yellow oleander, foxglove, bufadienolide)
 - E. Hyperkalemic periodic paralysis
 - F. Lysine, arginine, and ϵ -aminocaproic acid (structurally similar, positively charged)
 - G. Succinylcholine; thermal trauma, neuromuscular injury, disuse atrophy, mucositis, or prolonged immobilization
 - H. Rapid tumor lysis
- III. Inadequate excretion
 - A. Inhibition of the renin-angiotensin-aldosterone axis; \uparrow risk of hyperkalemia when used in combination or at higher than recommended dosages
 1. ACE inhibitors
 2. Renin inhibitors: aliskiren (in combination with ACE inhibitors or ARBs)
 3. ARBs
 4. Blockade of the mineralocorticoid receptor: spironolactone, eplerenone, drospirenone
 5. Blockade of ENaC: amiloride, triamterene, trimethoprim, pentamidine, nafamostat
 - B. Decreased distal delivery
 1. Congestive heart failure
 2. Volume depletion
 - C. Hyporeninemic hypoaldosteronism
 1. Tubulointerstitial diseases: SLE, sickle cell anemia, obstructive uropathy
 2. Diabetes, diabetic nephropathy
 3. Drugs: nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, β blockers, cyclosporine, tacrolimus
 4. Chronic kidney disease, advanced age
 5. Pseudohypoaldosteronism type II: defects in WNK1 or WNK4 kinases, Kelch-like 3 (KLHL3), or Cullin 3 (CUL3)
 - D. Renal resistance to mineralocorticoid
 1. Tubulointerstitial diseases: SLE, amyloidosis, sickle cell anemia, obstructive uropathy, post-acute tubular necrosis
 2. Hereditary: pseudohypoaldosteronism type I: defects in the mineralocorticoid receptor or ENaC. Advanced renal insufficiency with low GFR
 - E. Advanced renal insufficiency with low GFR
 1. Chronic kidney disease
 2. End-stage renal disease
 3. Acute oliguric kidney injury
 - F. Primary adrenal insufficiency
 1. Autoimmune: Addison’s disease, polyglandular endocrinopathy
 2. Infectious: HIV, cytomegalovirus, tuberculosis, disseminated fungal infection
 3. Infiltrative: amyloidosis, malignancy, metastatic cancer
 4. Drug-associated: heparin, low-molecular-weight heparin
 5. Hereditary: adrenal hypoplasia congenita, congenital lipoid adrenal hyperplasia, aldosterone synthase deficiency
 6. Adrenal hemorrhage or infarction, including in antiphospholipid syndrome

Abbreviations: ARB, angiotensin receptor blocker; COX-2, cyclooxygenase 2; ENaC, epithelial Na^+ channels.

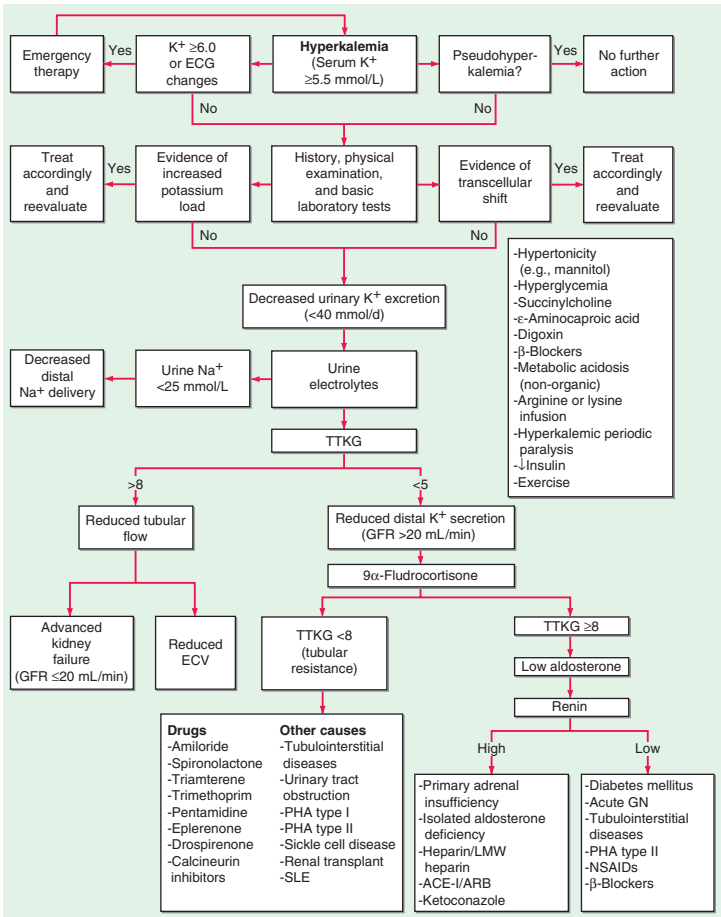


FIGURE 1-3 The diagnostic approach to hyperkalemia. See text for details. ACEI, angiotensin-converting enzyme inhibitor; acute GN, acute glomerulonephritis; ARB, angiotensin II receptor blocker; ECV, effective circulatory volume; LMW heparin, low-molecular-weight heparin; PHA, pseudohypoaldosteronism; TTKG, transtubular potassium gradient. (Reprinted with permission from Mount DB, Zandi-Nejad K: Disorders of potassium balance. In: Brenner and Rector's *The Kidney*, 8th ed, Brenner BM [ed]. Philadelphia, Saunders, 2008.)

The first priority in the management of hyperkalemia is to assess the need for emergency treatment (ECG changes and/or K⁺ ≥6.0 mM). This should be followed by a comprehensive workup to determine the cause (Fig. 1-3). History and physical examination should focus on medications (e.g., ACE inhibitors, NSAIDs, trimethoprim/sulfamethoxazole), diet and dietary supplements (e.g., salt substitute), risk factors for acute kidney failure, reduction in urine output, blood pressure, and volume status. Initial laboratory tests should include electrolytes, BUN, creatinine, serum osmolality, Mg²⁺, and Ca²⁺, a complete blood count, and urinary pH, osmolality, creatinine, and electrolytes. A urine [Na⁺] <20 meq/L suggests that distal Na⁺ delivery is a limiting factor in K⁺ excretion;

volume repletion with 0.9% saline or treatment with furosemide may then be effective in reducing serum $[K^+]$ by increasing distal Na^+ delivery. Serum and urine osmolality are required for calculation of the TTKG. The expected values of the TTKG are largely based on historic data: <3 in the presence of hypokalemia and $>7-8$ in the presence of hyperkalemia.

$$TTKG = \frac{[K^+]_{urine} \times OSM_{serum}}{[K^+]_{serum} \times OSM_{urine}}$$

TREATMENT

Hyperkalemia

The most important consequence of hyperkalemia is altered cardiac conduction, with the risk of bradycardic cardiac arrest. [Figure 1-4](#) shows serial ECG patterns of hyperkalemia; ECG manifestations of hyperkalemia should be considered a true medical emergency and treated urgently. However, ECG changes of hyperkalemia are notoriously insensitive, particularly in pts with CKD; given these limitations, pts with significant hyperkalemia ($K^+ \geq 6.5$ mmol/L) in the absence of ECG changes should also be aggressively managed.

Urgent management of hyperkalemia constitutes a 12-lead ECG, admission to the hospital, continuous cardiac monitoring, and immediate treatment. Treatment of hyperkalemia is divided into three categories: (1) antagonism of the cardiac effects of hyperkalemia, (2) rapid reduction in $[K^+]$ by redistribution into cells, and (3) removal of K^+ from the body. Treatment of hyperkalemia is summarized in [Table 1-5](#). Kayexalate, a mainstay of hyperkalemia treatment, has

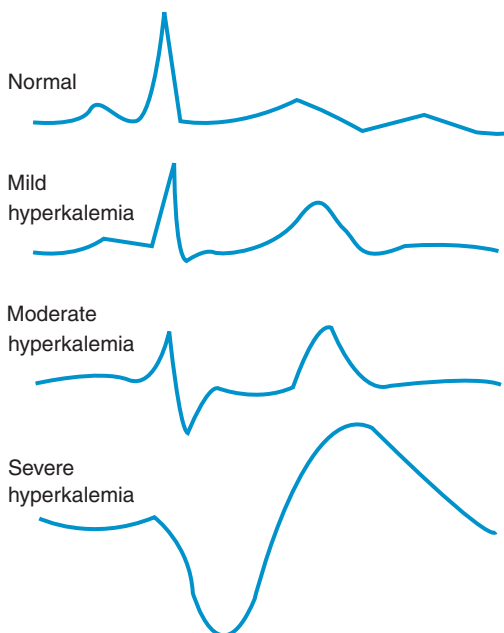


FIGURE 1-4 Diagrammatic ECGs at normal and high serum K. Peaked T waves (precordial leads) are followed by diminished R wave, wide QRS, prolonged P-R, loss of P wave, and ultimately a sine wave.

TABLE 1-5 Treatment of Hyperkalemia

MECHANISM	THERAPY	DOSE	ONSET	DURATION	COMMENTS
Stabilize membrane potential	Calcium	10% Ca gluconate, 10 mL over 10 min	1–3 min	30–60 min	Repeat in 5 min if persistent electrocardiographic changes; avoid in digoxin toxicity.
Cellular K ⁺ uptake	Insulin	10 U R with 50 mL of D ₅₀ , if blood sugar <250	30 min	4–6 h	Can repeat in 15 min; initiate D ₁₀ W IV at 50–75 mL/h to avoid rebound hypoglycemia.
	β ₂ -Agonist	Nebulized albuterol, 10–20 mg in 4-mL saline	30 min	2–4 h	Can be synergistic/additive to insulin; should not be used as sole therapy; use with caution in cardiac disease; may cause tachycardia/hyperglycemia.
K ⁺ removal	Kayexalate	30–60 g PO in 20% sorbitol	6 h	?	May cause fatal colonic necrosis; if available, sodium zirconium cyclosilicate (ZS-9) or patiromer is preferred to kayexalate.
	Furosemide Hemodialysis	20–250 mg IV	15 min Immediate	4–6 h	Depends on adequate renal response/function. Efficacy depends on pretreatment of hyperkalemia (with attendant decrease in serum K ⁺), the dialyzer used, blood flow and dialysate flow rates, duration, and serum to dialysate K ⁺ gradient.

been linked to fatal colonic necrosis; if available, sodium zirconium cyclosilicate (ZS-9) or patiromer, newer potassium binders that do not cause colonic necrosis, should be used in preference to kayexalate.

2

Acid-Base Disorders



Regulation of normal pH (7.35–7.45) depends on both the lungs and kidneys. By the Henderson-Hasselbalch equation, pH is a function of the ratio of HCO_3^- (regulated by the kidney) to PCO_2 (regulated by the lungs). The $\text{HCO}_3^-/\text{PCO}_2$ relationship is useful in classifying disorders of acid-base balance. Acidosis is due to gain of acid or loss of alkali; causes may be metabolic (fall in serum HCO_3^-) or respiratory (rise in PCO_2). Alkalosis is due to loss of acid or addition of base and is either metabolic (\uparrow serum $[\text{HCO}_3^-]$) or respiratory (\downarrow PCO_2) (Fig. 2-1).

To limit the change in pH, metabolic disorders evoke an immediate compensatory response in ventilation; full renal compensation for respiratory disorders is a slower process, such that “acute” compensations are of lesser magnitude than “chronic” compensations. Simple acid-base disorders consist of one primary disturbance and its compensatory response. In mixed disorders, a combination of primary disturbances is present.

The cause of simple acid-base disorders is usually obvious from history, physical examination, and/or basic laboratory tests. Initial laboratory evaluation depends on the dominant acid-base disorder, but for metabolic acidosis and alkalosis this should include electrolytes, BUN, creatinine, albumin, urinary pH, and urinary electrolytes. An arterial blood gas (ABG) is not always required for pts with a simple acid-base disorder, e.g., mild metabolic acidosis in the context of chronic renal failure. However, concomitant ABG and serum electrolytes are necessary to fully evaluate more complex acid-base disorders. The compensatory response should be estimated from the ABG; Winter’s formula [$\text{PaCO}_2 = (1.5 \times [\text{HCO}_3^-]) + 8 \pm 2$] is particularly useful for assessing the respiratory response to metabolic acidosis. The anion gap should also be calculated; the anion gap = $[\text{Na}^+] - ([\text{HCO}_3^-] + [\text{Cl}^-]) = \text{unmeasured anions} - \text{unmeasured cations}$. The anion gap should be adjusted for changes in the concentration of albumin, a dominant unmeasured anion; the “adjusted anion gap” = anion gap + $-2.5 \times (4 - \text{albumin mg/dL})$. Other supportive tests will elucidate the specific form of anion-gap acidosis (see below).

■ METABOLIC ACIDOSIS

The low HCO_3^- in metabolic acidosis results from the addition of acids (organic or inorganic) or from a loss of HCO_3^- ; causes of metabolic acidosis are classically categorized by presence or absence of an increase in the anion gap (Table 2-1). Increased anion-gap acidosis (>12 mmol/L) is due to addition of acid (other than HCl) and unmeasured anions to the body. Common causes include ketoacidosis (diabetes mellitus [DKA], starvation, alcohol), lactic acidosis, poisoning (salicylates, ethylene glycol, and methanol), and renal failure.

Rare and newly appreciated causes of anion-gap acidosis include D-lactic acidosis, propylene glycol toxicity, and 5-oxoprolinuria (also known as pyroglutamic aciduria). D-Lactic acidosis (an increase in the D-enantiomer of lactate) can occur in pts with removal, disease, or bypass of the short bowel, leading

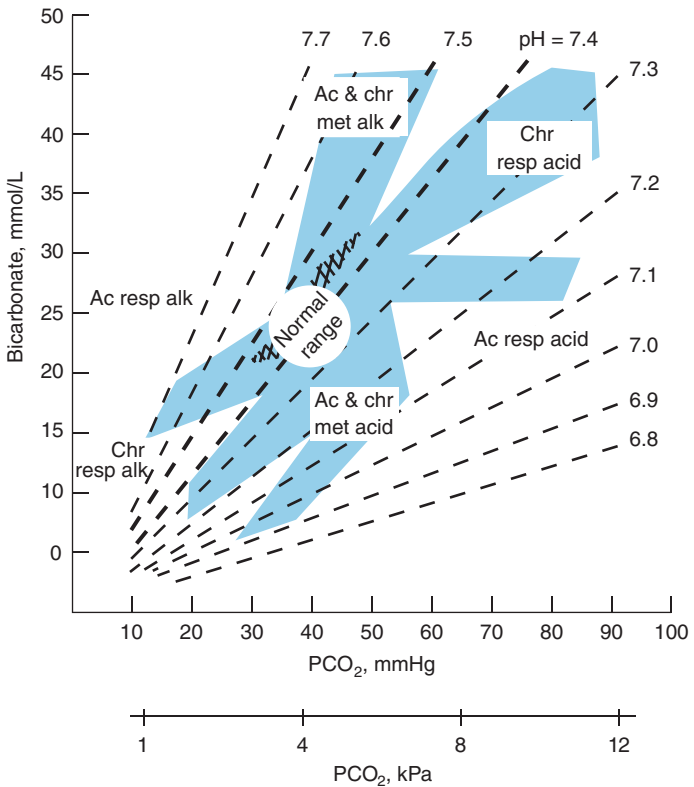


FIGURE 2-1 Nomogram showing bands for uncomplicated respiratory or metabolic acid-base disturbances in intact subjects. Each confidence band represents the mean ± 2 SD for the compensatory response of normal subjects or pts to a given primary disorder. Ac, acute; acid, acidosis; alk, alkalosis; chr, chronic; met, metabolic; resp, respiratory. (Reprinted with permission from Arbus GS. *An in vivo acid-base nomogram for clinical use.* *Can Med Assoc J* 109:291, 1973.)

to increased delivery of carbohydrates to colon. Intestinal overgrowth of organisms that metabolize carbohydrate to D-lactate results in D-lactic acidosis; a wide variety of neurologic symptoms can ensue, with resolution following treatment with appropriate antibiotics to change the intestinal flora. Propylene glycol is a common solvent for IV preparations of a number of drugs, most prominently lorazepam. Pts receiving high rates of these drugs may develop a hyperosmolar anion-gap metabolic acidosis, due mostly to increased lactate, often accompanied by acute kidney failure. Pyroglutamic aciduria (5-oxoprolinuria) is a high anion-gap acidosis caused by dysfunction of the γ -glutamyl cycle that replenishes intracellular glutathione; 5-oxoprolinone is an intermediate product of the cycle. Hereditary defects in the γ -glutamyl cycle are associated with 5-oxoprolinuria; acquired defects occur in the context of acetaminophen therapy, due to derepression of the cycle by reduced glutathione and overproduction of 5-oxoprolinone. Resolution occurs after withdrawal of acetaminophen; treatment with N-acetyl cysteine to replenish glutathione stores may hasten recovery.

TABLE 2-1 Metabolic Acidosis

NON-ANION-GAP ACIDOSIS		ANION-GAP ACIDOSIS	
CAUSE	CLUE	CAUSE	CLUE
Diarrhea enterostomy	Hx; ↑ K ⁺ drainage	DKA	Hyperglycemia, ketones
RF	Early chronic kidney disease	RF	Late chronic kidney disease
RTA		Lactic acidosis	Clinical setting + ↑ serum lactate
Proximal	↓ K ⁺ , presence of other proximal tubular defects (Fanconi syndrome)	(L-lactate)	
Distal—hypokalemic	↓ K ⁺ ; hypercalciuria; UpH >5.5	Alcoholic ketoacidosis	Hx; weak + ketones; + osm gap
Distal—hyperkalemic	↑ K ⁺ ; nl PRA/aldo; UpH >5.5	Starvation	Hx; mild acidosis; + ketones
Distal—hyporeninemic hypoaldosteronism	↑ K ⁺ ; ↓ PRA/aldo; UpH <5.5	Salicylates	Hx; tinnitus; high serum level; + ketones; + lactate
Dilutional	Massive volume expansion with saline	Methanol	Large AG; concomitant respiratory alkalosis; retinitis; + toxic screen; + osm gap
Ureterosigmoidostomy	Obstructed ileal loop	Ethylene glycol	RF; CNS symptoms; + toxic screen; crystalluria; + osm gap
Hyperalimentation	Amino acid infusion	D-lactic acidosis	Small-bowel disease; prominent neuro symptoms
Acetazolamide, NH ₄ Cl, lysine HCl, arginine HCl, sevelamer-HCl	Hx of administration of these agents	Propylene glycol	IV infusions, e.g., lorazepam; + osm gap; RF
		Pyroglutamic aciduria, 5-oxoprolinuria	Large AG; chronic acetaminophen

Abbreviations: AG, anion gap; DKA, diabetic ketoacidosis; osm gap, osmolar gap; PRA, plasma renin activity; RF, renal failure; RTA, renal tubular acidosis; UpH, urinary pH.

The differentiation of the various anion-gap acidoses depends on the clinical scenario and routine laboratory tests (Table 2-1) in conjunction with measurement of serum lactate, ketones, toxicology screens (if ethylene glycol or methanol ingestion are suspected), and serum osmolality. D-Lactic acidosis can be diagnosed by a specific assay for the D-enantiomer; 5-oxoprolinuria can be diagnosed by the clinical scenario and confirmed by gas chromatographic/mass spectroscopic (GC/MS) analysis of urine, a widely available pediatric screening test for inborn errors of metabolism (typically “urine for organic acids”).

Pts with ethylene glycol, methanol, or propylene glycol toxicity may have an “osmolar gap,” defined as a >10 -mosmol/kg difference between calculated and measured serum osmolality. Calculated osmolality = $2 \times \text{Na}^+ + \text{glucose}/18 + \text{BUN}/2.8$. Of note, pts with alcoholic ketoacidosis and lactic acidosis may also exhibit a modest elevation in the osmolar gap; pts may alternatively metabolize ethylene glycol or methanol to completion by presentation, with an increased anion gap and no increase in the osmolar gap. However, the rapid availability of a measured serum osmolality may aid in the urgent assessment and management of pts with these medical emergencies.

Normal anion-gap acidosis can result from HCO_3^- loss from the GI tract. Diarrhea is by far the most common cause, but other GI conditions associated with external losses of bicarbonate-rich fluids may lead to large alkali losses—e.g., in ileus secondary to intestinal obstruction, in which liters of alkaline fluid may accumulate within the intestinal lumen. Various forms of kidney disease are associated with non-anion-gap acidosis due to reduced tubular reabsorption of filtered bicarbonate and/or reduced excretion of ammonium (NH_4^+). The early stages of progressive renal disease are frequently associated with a non-anion-gap acidosis, with development of an anion-gap component in more advanced renal failure. Non-anion-gap acidosis is also seen in renal tubular acidosis or in the context of tubulointerstitial injury, e.g., after acute tubular necrosis, allergic interstitial nephritis, or urinary tract obstruction. Finally, non-anion-gap acidosis due to exogenous acid loads may occur after rapid volume expansion with saline-containing solutions, the administration of NH_4Cl (a component of cough syrup), lysine HCl, or treatment with the phosphate binder sevelamer hydrochloride.

Calculation of the urinary anion gap may be helpful in the evaluation of hyperchloremic metabolic acidosis, along with a measurement of urine pH. The urinary anion gap is defined as urinary $([\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] = [\text{unmeasured anions}] - [\text{unmeasured cations}])$; the NH_4^+ ion is the major unmeasured urinary cation in metabolic acidosis, wherein the urinary anion gap should be strongly negative. A negative anion gap thus suggests GI losses of bicarbonate, with appropriate renal response and increased NH_4^+ excretion; a positive anion gap suggests altered urinary acidification, as seen in renal failure or distal renal tubular acidoses. An important caveat is that the rapid renal excretion of unmeasured anions in anion-gap acidosis, classically seen in DKA, may reduce the serum anion gap and generate a positive value for the urinary anion gap, despite the adequate excretion of urinary NH_4^+ ; this may lead to misdiagnosis as a renal tubular acidosis.

TREATMENT

Metabolic Acidosis

Treatment of metabolic acidosis depends on the cause and severity. DKA responds to insulin therapy and aggressive hydration; close attention to serum $[\text{K}^+]$ and administration of KCl is essential, given that the correction of insulinopenia can cause profound hypokalemia. The administration of alkali in anion-gap acidoses

is controversial and is rarely appropriate in DKA. It is reasonable to treat severe lactic acidosis with IV HCO_3^- at a rate sufficient to maintain a pH >7.20 ; treatment of moderate lactic acidosis with HCO_3^- is controversial. IV HCO_3^- is however appropriate to reduce acidosis in D-lactic acidosis, ethylene glycol and methanol toxicity, and 5-oxoprolinuria.

Chronic metabolic acidosis should be treated when HCO_3^- is $<18\text{--}20$ mmol/L. In pts with CKD, there is some evidence that acidosis promotes protein catabolism and may worsen bone disease. There is also evidence that correction of metabolic acidosis in CKD leads to a reduced rate of progression to end-stage renal disease (ESRD). Sodium citrate may be more palatable than oral NaHCO_3 . Oral therapy with NaHCO_3 usually begins with 650 mg tid and is titrated upward to maintain serum $[\text{HCO}_3^-]$.

■ METABOLIC ALKALOSIS

Metabolic alkalosis is due to a primary increase in serum $[\text{HCO}_3^-]$, distinguished from chronic respiratory acidosis—with a compensatory increase in renal HCO_3^- reabsorption—by the associated increase in arterial pH (normal or decreased in chronic respiratory acidosis). Administered, exogenous alkali (HCO_3^- , acetate, citrate, or lactate) may cause alkalosis if the normal capacity to excrete HCO_3^- is reduced or if renal HCO_3^- reabsorption is enhanced. A recently resurgent problem is “milk alkali syndrome,” a triad of hypercalcemia, metabolic alkalosis, and acute renal failure due to ingested calcium carbonate, typically taken for the treatment or prevention of osteoporosis or for symptomatic relief of peptic ulcer disease.

Metabolic alkalosis is primarily caused by renal retention of HCO_3^- and is due to a variety of underlying mechanisms. Pts are typically separated into two major subtypes: Cl^- -responsive and Cl^- -resistant. Measurement of urine Cl^- affords this separation in the clinical setting (Fig. 2-2). The quintessential causes of Cl^- -responsive alkalosis are GI induced from vomiting or gastric aspiration through a nasogastric tube, and renal induced from diuretic therapy. Hypovolemia, chloride deficiency, activation of the RAA axis, and hypokalemia play interrelated roles in the maintenance of this hypochloremic or “contraction” alkalosis. The various syndromes of true or apparent mineralocorticoid excess cause Cl^- -resistant metabolic alkalosis (Fig. 2-2); most of these pts are hypokalemic, volume expanded, and/or hypertensive.

Common forms of metabolic alkalosis are generally diagnosed from the history, physical examination, and/or basic laboratory tests. ABGs will help determine whether an elevated $[\text{HCO}_3^-]$ is reflective of metabolic alkalosis or chronic respiratory acidosis; ABGs are required for the diagnosis of mixed acid-base disorders. Measurement of urinary electrolytes will aid in separating Cl^- -responsive and Cl^- -resistant forms. Urinary $[\text{Na}^+]$ may thus be >20 meq/L in Cl^- -responsive alkalosis despite the presence of hypovolemia; however, urinary $[\text{Cl}^-]$ will typically be very low, except in pts with severe hypokalemia. Notably, urinary $[\text{Cl}^-]$ may be variable in pts with diuretic-associated alkalosis, depending on the temporal relationship to diuretic administration. Other diagnostic tests—e.g., plasma renin, aldosterone, cortisol—may be appropriate in Cl^- -resistant forms with high urinary $[\text{Cl}^-]$ (Fig. 2-2).

TREATMENT

Metabolic Alkalosis

The acid-base disorder in Cl^- -responsive alkalosis will typically respond to saline infusion; however, the associated hypokalemia should also be corrected. Pts with true or apparent mineralocorticoid excess require specific treatment of

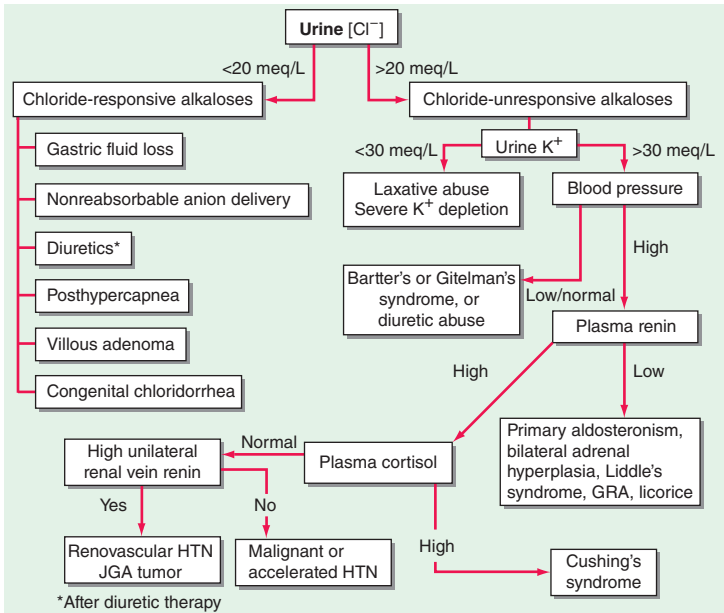


FIGURE 2-2 The diagnostic approach to metabolic alkalosis. See text for details. GRA, glucocorticoid-remediable aldosteronism; HTN, hypertension; JGA, juxtaglomerular apparatus. (Modified from Dubose TD. Disorders of acid-base balance. In: Brenner and Rector's *The Kidney*, 8th ed, Brenner BM [ed]. Philadelphia, Saunders, 2008 with permission.)

the underlying disorder. For example, hyperactive amiloride-sensitive ENaC channels cause Liddle's syndrome, which can respond to therapy with amiloride and related drugs; pts with hyperaldosteronism may in turn respond to blockade of the mineralocorticoid receptor with spironolactone or eplerenone. Finally, severe alkalosis in the critical care setting may require treatment with acidifying agents such as acetazolamide.

■ RESPIRATORY ACIDOSIS

Respiratory acidosis is characterized by CO₂ retention due to ventilatory failure. Causes include sedatives, stroke, chronic pulmonary disease, airway obstruction, severe pulmonary edema, neuromuscular disorders, and cardiopulmonary arrest. Symptoms include confusion, asterixis, and obtundation.

TREATMENT

Respiratory Acidosis

The goal is to improve ventilation through pulmonary toilet and reversal of bronchospasm. Intubation or noninvasive positive pressure ventilation (NPPV) may be required in severe acute cases. Acidosis due to hypercapnia is usually mild; however, combined respiratory and metabolic acidosis may cause a profound reduction in pH. Respiratory acidosis may accompany low tidal volume ventilation in ICU pts and may require metabolic "overcorrection" to maintain a neutral pH.

■ RESPIRATORY ALKALOSIS

Excessive ventilation causes a primary reduction in CO_2 and \uparrow pH in pneumonia, pulmonary edema, interstitial lung disease, and asthma. Pain and psychogenic causes are common; other etiologies include fever, hypoxemia, sepsis, delirium tremens, salicylates, hepatic failure, mechanical overventilation, and CNS lesions. Pregnancy is associated with a mild respiratory alkalosis. Severe respiratory alkalosis may acutely cause seizures, tetany, cardiac arrhythmias, or loss of consciousness.

TREATMENT

Respiratory Alkalosis

Treatment should be directed at the underlying disorders. In psychogenic cases, sedation or a rebreathing bag may be required.

■ "MIXED" DISORDERS

In many circumstances, more than a single acid-base disturbance exists. Examples include combined metabolic and respiratory acidosis with cardiogenic shock; metabolic alkalosis and anion-gap acidosis in pts with vomiting and diabetic ketoacidosis; and anion-gap metabolic acidosis with respiratory alkalosis in pts with salicylate toxicity. The diagnosis may be clinically evident and/or suggested by relationships between the PCO_2 and $[\text{HCO}_3^-]$ that diverge from those found in simple disorders. For example, the PCO_2 in a pt with metabolic acidosis and respiratory alkalosis will be considerably less than that predicted from the $[\text{HCO}_3^-]$ and Winter's formula $[\text{PaCO}_2 = (1.5 \times [\text{HCO}_3^-] + 8 + 2)]$.

In "simple" anion-gap acidosis, the anion gap increases in proportion to the fall in $[\text{HCO}_3^-]$. A lesser drop in serum $[\text{HCO}_3^-]$ than in the anion gap suggests a coexisting metabolic alkalosis. Conversely, a proportionately *larger* drop in $[\text{HCO}_3^-]$ than in the anion gap suggests the presence of a mixed anion-gap and non-anion-gap metabolic acidosis. Notably, however, these interpretations assume 1:1 relationships between unmeasured anions and the fall in $[\text{HCO}_3^-]$, which are not uniformly present in individual pts or as acidoses evolve. For example, volume resuscitation of pts with DKA will typically increase glomerular filtration and the urinary excretion of ketones, resulting in a decrease in the anion gap in the absence of a supervening non-anion-gap acidosis.

3

Diagnostic Imaging in Internal Medicine



Clinicians have a wide array of imaging modalities at their disposal to aid them in noninvasive diagnosis. Despite the introduction of highly specialized imaging modalities, radiologic procedures such as chest radiographs and ultrasound continue to serve a vital role in the diagnostic approach to pt care. Increasingly, ultrasound is used as a point-of-care procedure to assist with intravenous line placement, and to extend the physical examination of the thyroid thorax, heart, and abdomen. At most institutions, CT is available on an emergent basis and is invaluable for initial evaluation of pts with trauma, suspected CNS hemorrhage, or ischemic stroke. MRI and related techniques (MR angiography, functional

MRI, MR spectroscopy) provide high resolution of many tissues including the brain, vascular system, joints, and most large organs. Radionuclide scans including positron emission tomography (PET) can provide functional assessment of organs or specific regions within organs. Combination of PET with MRI or CT scanning provides highly informative images of the location and configuration of metabolically active lesions, such as cancers.

This chapter will review the indications and utility of the most commonly utilized radiologic studies used by internists.

CHEST RADIOGRAPHY (FIG. 3-1)

- Accessible and should be part of the standard evaluation for pts with cardiopulmonary complaints.
- Able to identify life-threatening conditions such as pneumothorax, intraperitoneal air, pulmonary edema, pneumonia, and aortic dissection.
- Often normal in a pt with an acute pulmonary embolus.
- Repeat in 4–6 weeks in a pt with an acute pneumonic process to document resolution of the radiographic infiltrate.
- Used in conjunction with the physical examination to support the diagnosis of congestive heart failure. The diagnosis of heart failure is supported by findings of cardiomegaly, cephalization, Kerley B lines, and pleural effusions.
- Repeat frequently in intubated pts to examine endotracheal tube position and the possibility of barotrauma.
- Features of alveolar or airspace disease include inhomogeneous, patchy opacities and air-bronchograms.
- Helps to document the free-flowing nature of pleural effusions. Decubitus views should be obtained to exclude loculated pleural fluid prior to attempts to extract such fluid.

ABDOMINAL RADIOGRAPHY

- Initial imaging modality in a pt with suspected bowel obstruction. Signs of small-bowel obstruction on plain radiographs include multiple air-fluid levels, absence of colonic distention, and a “stepladder” appearance of small-bowel loops.
- Should not be performed with barium enhancement when perforated bowel, portal venous gas, or toxic megacolon is suspected.
- Used to evaluate the size of bowel:
 1. Normal small bowel is <3 cm in diameter.
 2. Normal caliber of the cecum is up to 9 cm, with the rest of the large bowel up to 6 cm in diameter.

ULTRASOUND

- More sensitive and specific than CT scanning in evaluating for the presence of gallstone disease.
- Used to assist with central line placement and with peripheral access when challenging.
- Used to assess the size of the kidneys in a pt with renal insufficiency and to exclude the presence of hydronephrosis.
- Evaluates for the presence of peritoneal fluid in a pt with blunt abdominal trauma.
- Evaluates cardiac valves and wall motion.
- Used to localize loculated pleural and peritoneal fluid prior to draining such fluid.

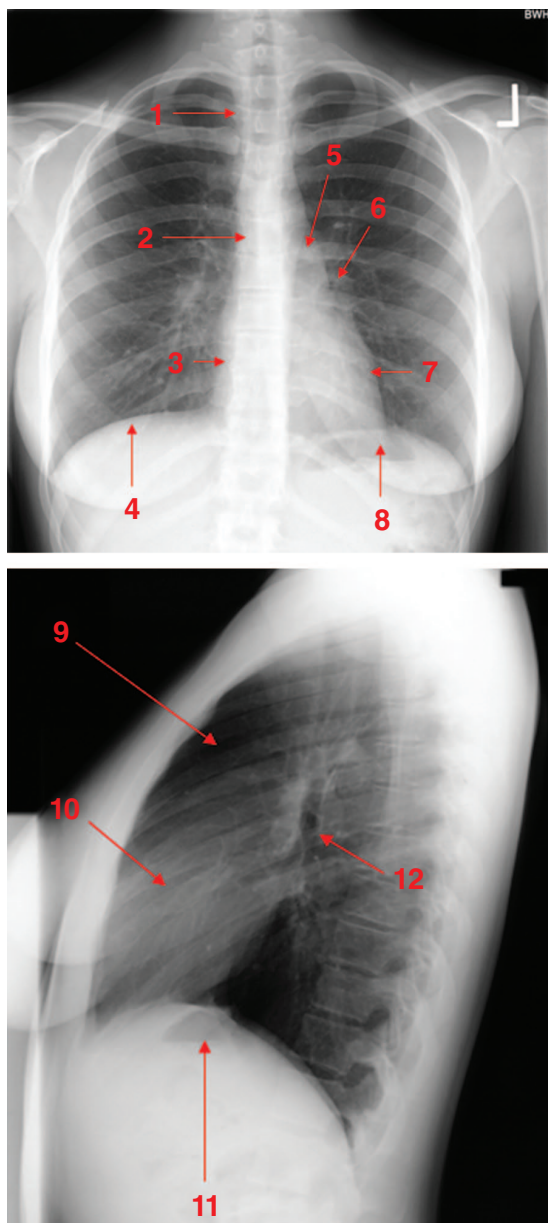


FIGURE 3-1 Normal chest radiograph—review of anatomy. **1.** Trachea. **2.** Carina. **3.** Right atrium. **4.** Right hemidiaphragm. **5.** Aortic knob. **6.** Left hilum. **7.** Left ventricle. **8.** Left hemidiaphragm (with stomach bubble). **9.** Retrosternal clear space. **10.** Right ventricle. **11.** Left hemidiaphragm (with stomach bubble). **12.** Left upper lobe bronchus.

- Determines the size of thyroid nodules and guide fine-needle aspiration biopsy.
- Determines the size and location of enlarged lymph nodes, especially in superficial locations such as in the neck.
- Modality of choice for assessing known or suspected scrotal pathology.
- Effective first imaging modality for evaluating the ovaries.

COMPUTED TOMOGRAPHY

- CT delivers a substantially higher radiation dose than conventional radiography; it should therefore be used judiciously.
- CT of the brain should be the initial radiographic modality in evaluating a pt with a potential stroke.
- Is highly sensitive for diagnosing an acute subarachnoid hemorrhage and, in the acute setting, is more sensitive than MRI.
- CT of the brain is an essential test in evaluating a pt with mental status changes to exclude entities such as intracranial bleeding, mass effect, subdural or epidural hematomas, and hydrocephalus.
- Is better than MRI for evaluating osseous lesions of the skull and spine.
- CT of the chest should be considered in the evaluation of a pt with chest pain to rule out entities such as pulmonary embolus or aortic dissection.
- CT of the chest is effective for evaluating lung nodules to assess for the presence of thoracic lymphadenopathy.
- CT, with high-resolution cuts through the lungs, is the imaging modality of choice for evaluating the lung interstitium in a pt with interstitial lung disease.
- Evaluates for the presence of pleural and pericardial fluid and to localize loculated effusions.
- Useful in a pt with unexplained abdominal pain to evaluate for conditions such as appendicitis, mesenteric ischemia or infarction, diverticulitis, or pancreatitis.
- CT of the abdomen is also the test of choice for evaluating for nephrolithiasis in a pt with renal colic.
- Evaluates the presence of an abscess in the chest or abdomen.
- Helps identify the cause of bowel obstruction.
- Identifies abdominal conditions such as intussusception and volvulus in a pt with abdominal pain.
- Effective for evaluating the retroperitoneum.
- Should be obtained expeditiously in a pt with abdominal trauma to evaluate for the presence of intraabdominal hemorrhage and to assess injury to abdominal organs.

MAGNETIC RESONANCE IMAGING

- Is more useful than CT in the evaluation of ischemic infarction, dementia, mass lesions, demyelinating diseases, and most nonosseous spinal disorders.
- Provides excellent imaging of large joints including the knee, hip, and shoulder.
- Can be used, often with CT or angiography, to assess possible dissecting aortic aneurysms and congenital anomalies of the cardiovascular system.
- Cardiac MRI is proving useful to evaluate cardiac wall motion and to assess cardiac muscle viability in ischemic heart disease.
- Is preferable to CT for evaluating adrenal masses such as pheochromocytoma and for helping to distinguish benign and malignant adrenal masses.
- Is preferable to CT for evaluating pituitary lesions and parasellar pathology.

RADIONUCLIDE IMAGING

- Radionuclides can be used in the form of radioactive ions (iodide, gallium, thallium) or radiolabeled substances with affinity for specific tissues (radiopharmaceuticals, e.g., bisphosphonates, sestamibi, octreotide, metaiodobenzylguanidine [MIBG], iodocholesterol, etc.), or in the form of fluorodeoxyglucose for PET scanning.
- Radionuclide scintigraphy can be combined/merged with CT or MRI for precise anatomic localization of the radionuclide-imaged tissue.
- Tomographic radionuclide scintigraphy (single-photon emission computed tomography [SPECT]) is similar to CT, using radionuclide emissions instead of x-rays. It permits visualization of sequential slices that can be computer-manipulated to yield a three-dimensional reconstruction.
- PET is very useful for detection of metabolically active tissues, such as cancers and their metastases, and has largely supplanted older modalities of radionuclide scanning (e.g., gallium scintigraphy).
- Radionuclide scans frequently ordered by the general internist are: (1) bone scans to identify metastatic disease in bone or osteomyelitis, (2) sestamibi scans for preoperative localization of parathyroid adenomas, (3) thyroid scans (technetium or iodine) to identify hot or cold thyroid nodules.
- Specialized radionuclide scans include thallium or sestamibi myocardial perfusion scans, pulmonary ventilation/perfusion scans, octreotide scans for neuroendocrine tumors, MIBG scans for pheochromocytoma, iodocholesterol scans for adrenocortical adenomas, and whole-body radioiodine scans for disseminated thyroid cancer.
- Radioiodine scanning of the thyroid can be used to obtain quantitative information on iodine uptake by the thyroid, which is useful to differentiate subacute thyroiditis from Graves' disease.

4

Procedures Commonly Performed by Internists



Internists perform a wide range of medical procedures, although practices vary widely among institutions and by specialty. Internists, nurses, or other ancillary health care professionals perform venipuncture for blood testing, arterial puncture for blood gases, endotracheal intubation, and insert IV lines, nasogastric (NG) tubes, and urinary catheters. These procedures are not covered here, but require skill and practice to minimize pt discomfort and potential complications. Here, we review more invasive diagnostic and therapeutic procedures performed by internists—thoracentesis, lumbar puncture (LP), and paracentesis. Many additional procedures are performed by specialists, and require additional training and credentialing, including the following:

- *Allergy*: skin testing, rhinoscopy
- *Cardiology*: stress testing, echocardiograms, coronary catheterization, angioplasty, stent insertion, pacemakers, electrophysiology testing and ablation, implantable defibrillators, cardioversion, transcatheter aortic valve implantation (TAVI)
- *Endocrinology*: thyroid biopsy, dynamic hormone testing, bone densitometry
- *Gastroenterology*: upper and lower endoscopy, esophageal manometry, endoscopic retrograde cholangiopancreatography, stent insertion, endoscopic ultrasound, liver biopsy

- *Hematology/oncology*: bone marrow biopsy, stem cell transplant, lymph node biopsy, plasmapheresis
- *Pulmonary*: intubation and ventilator management, bronchoscopy
- *Renal*: kidney biopsy, dialysis
- *Rheumatology*: joint aspiration

Increasingly, ultrasound, CT, and MRI are being used to guide invasive procedures, and flexible fiberoptic instruments are extending the reach into the body. For most invasive medical procedures, including those reviewed below, informed consent should be obtained in writing before beginning the procedure.

THORACENTESIS

Drainage of the pleural space can be performed at the bedside. Indications for this procedure include diagnostic evaluation of pleural fluid, removal of pleural fluid for symptomatic relief, and instillation of sclerosing agents in pts with recurrent, usually malignant pleural effusions.

■ PREPARATORY WORK

Familiarity with the components of a thoracentesis tray is a prerequisite to performing a thoracentesis successfully. Recent posterior-anterior (PA) and lateral chest radiographs with bilateral decubitus views should be obtained to document the free-flowing nature of the pleural effusion. Loculated pleural effusions should be localized by ultrasound or CT prior to drainage. Management should be individualized in pts with a coagulopathy of thrombocytopenia. Thoracentesis is more challenging in pts with mechanical ventilation and should be performed with ultrasound guidance if possible.

■ TECHNIQUE

A posterior approach is the preferred means of accessing pleural fluid. Comfortable positioning is a key to success for both pt and physician. The pt should sit on the edge of the bed, leaning forward with the arms abducted onto a pillow on a bedside stand. Pts undergoing thoracentesis frequently have severe dyspnea, and it is important to assess if they can maintain this positioning for at least 10 min. The entry site for the thoracentesis is based on the physical examination and radiographic findings. Percussion of dullness is utilized to ascertain the extent of the pleural effusion with the site of entry being the first or second highest interspace in this area. The entry site for the thoracentesis is at the superior aspect of the rib, thus avoiding the intercostal nerve, artery, and vein, which run along the inferior aspect of the rib (Fig. 4-1).

The site of entry should be marked with a pen to guide the thoracentesis. The skin is then prepped and draped in a sterile fashion with the operator observing sterile technique at all times. A small-gauge needle is used to anesthetize the skin, and a larger-gauge needle is used to anesthetize down to the superior aspect of the rib. The needle should then be directed over the upper margin of the rib to anesthetize down to the parietal pleura. The pleural space should be entered with the anesthetizing needle, all the while using liberal amounts of local anesthetic.

A dedicated thoracentesis needle with an attached syringe should next be utilized to penetrate the skin. This needle should be advanced to the superior aspect of the rib. While maintaining gentle negative pressure, the needle should be slowly advanced into the pleural space. If a diagnostic tap is being performed, aspiration of only 30–50 mL of fluid is necessary before termination

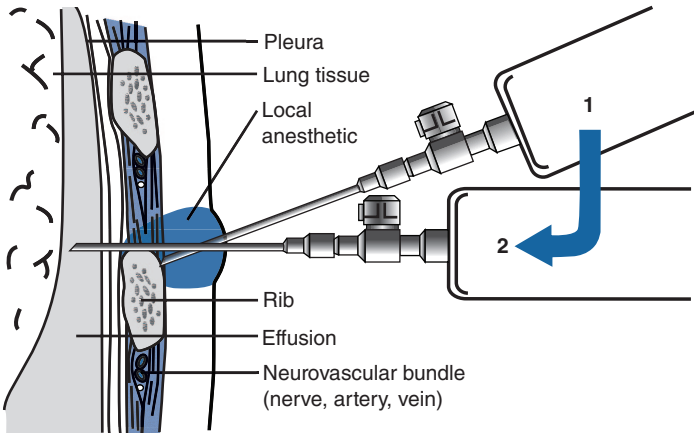


FIGURE 4-1 In thoracentesis, the needle is passed over the top of the rib to avoid the neurovascular bundle. (Used with permission from LG Gomella, SA Haist, [eds]: *Clinician's Pocket Reference*, 11th ed. New York, McGraw-Hill, 2007.)

of the procedure. If a therapeutic thoracentesis is being performed, a three-way stopcock is utilized to direct the aspirated pleural fluid into collection bottles or bags. No more than 1 L of pleural fluid should be withdrawn at any given time, because quantities >1–1.5 L can result in re-expansion pulmonary edema.

After all specimens have been collected, the thoracentesis needle should be withdrawn and the needle site occluded for at least 1 min.

■ SPECIMEN COLLECTION

The diagnostic evaluation of pleural fluid depends on the clinical situation. All pleural fluid samples should be sent for cell count and differential, Gram stain, and bacterial cultures. LDH and protein determinations should also be made to differentiate between exudative and transudative pleural effusions. The pH should be determined if empyema is a diagnostic consideration. Other studies on pleural fluid include mycobacterial and fungal cultures, glucose, triglyceride level, amylase, and cytologic determination.

■ POSTPROCEDURE

A postprocedural chest radiograph should be obtained to evaluate for a pneumothorax, and the pt should be instructed to notify caregivers if new shortness of breath develops.

LUMBAR PUNCTURE

Evaluation of cerebrospinal fluid (CSF) is essential for the diagnosis of suspected meningeal infection, subarachnoid hemorrhage, leptomenigeal neoplastic disease, and noninfectious meningitis. Relative contraindications to LP include local skin infection in the lumbar area and suspected intracranial or spinal cord mass lesion. Any bleeding diathesis should also be corrected prior to performing LP to prevent the possible occurrence of an epidural hematoma. Guidelines for performing LP in pts receiving anticoagulant or antiplatelet medications can be found in [Chap. S9](#) of *Harrison's Principles of Internal Medicine*, 20th edition.

A functional platelet count $>50,000/\mu\text{L}$ and an international normalized ratio (INR) <1.5 are advisable to perform LP safely.

In pts with an altered level of consciousness, focal neurologic deficits, or evidence of papilledema, an imaging study should generally be obtained prior to performing LP.

TECHNIQUE

Proper positioning of the pt is essential; either the lateral decubitus or the sitting position can be used. Most routine LPs should be performed using the lateral decubitus position (Fig. 4-2). (See Chap. CP6: Clinical Procedures Tutorial: Lumbar Puncture in *Harrison's Principles of Internal Medicine*, 20th edition via accessmedicine.com.) The sitting position may be preferable in obese pts. With either position, the pt should be instructed to flex the spine as much as possible. In the lateral decubitus position, the pt assumes a fetal position with the knees flexed toward the abdomen; the shoulders and pelvis should be vertically aligned without forward or backward tilt. In the sitting position, the pt should bend over a bedside table with the head resting on folded arms.

The entry site for an LP is below the level of the conus medullaris, which extends to L1–L2 in most adults. Thus, either the L3–L4 or L4–L5 interspace can be utilized as the entry site. The posterior superior iliac crest should be identified and the spine palpated at this level. This represents the L3–L4 interspace, with the other interspaces referenced from this landmark. The midpoint of the interspace between the spinous processes represents the entry point for the spinal needle. For elective LPs, topical anaesthesia can be achieved by application of a topical local anesthetic prior to the procedure. The skin is then prepped and draped in a sterile fashion with the operator observing sterile technique at all times. A small-gauge needle is then used to anesthetize the skin and subcutaneous tissue; this is usually performed with multiple small (0.5–1 mL), serial injections of local anesthetic as the needle is progressively advanced. The spinal needle should be introduced perpendicular to the skin in the midline and advanced slowly. The needle stylet can be withdrawn periodically as the spinal needle is advanced to assess when the subarachnoid space has been reached. As the needle enters the subarachnoid space, a “popping” sensation can sometimes be felt. If bone is encountered, the needle should be withdrawn to just below

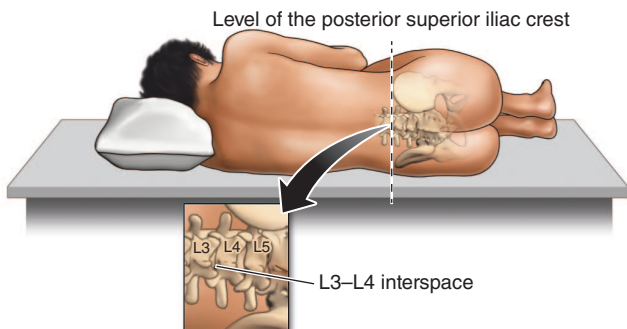


FIGURE 4-2 Proper positioning of a pt in the lateral decubitus position. Note that the shoulders and hips are in a vertical plane; the torso is perpendicular to the bed. (Adapted from RP Simon et al [eds]: *Clinical Neurology*, 7th ed. New York, McGraw-Hill, 2009.)

the skin and then redirected more caudally. Once CSF begins to flow, the opening pressure should be measured in the lateral decubitus position with the pt shifted to this position if the procedure was begun in the sitting position. The CSF can then be collected in a series of specimen tubes. A minimum of 10–15 mL of CSF is usually obtained. The stylet is then replaced and the spinal needle removed.

■ SPECIMEN COLLECTION

Diagnostic evaluation of CSF is based on the clinical scenario. In general, spinal fluid should always be sent for cell count with differential, protein, and glucose. Other studies that can be obtained on CSF include bacterial mycobacterial fungal, viral cultures, polymerase chain reaction (PCR) tests for microorganisms, smears (Gram and acid-fast stains), Venereal Disease Research Laboratory (VDRL), cryptococcal antigen, gamma globulins, oligoclonal bands, and cytology.

■ POSTPROCEDURE

Post dural-puncture headache, caused by a reduction in CSF pressure, represents the principal complication of LP, occurring in 10–30% of pts. Strategies to decrease the incidence of post-LP headache are listed in [Table 4-1](#). *The customary practice of remaining in a recumbent position post-LP is unnecessary.* The post-LP headache is dramatically positional; it begins when the pt sits or stands upright and is relieved upon reclining. Nausea and stiff neck often accompany headache, and occasionally, pts report blurred vision, photophobia, tinnitus, and vertigo. In more than three-quarters of pts, symptoms completely resolve within a week, but in a minority they can persist for weeks or even months. Bedrest, hydration, and oral analgesics are often helpful; caffeine tablets or beverages with caffeine sometimes provide relief. For post-LP headaches lasting more than a few days, consultation with an anesthesiologist should be considered for placement of an epidural blood patch; this usually provides rapid relief.

PARACENTESIS

Removal and analysis of peritoneal fluid is valuable for evaluating pts with new-onset ascites or ascites of unknown etiology. It is also indicated in pts with known ascites who have a decompensation in their clinical status. Relative contraindications include bleeding diathesis, prior abdominal surgery, distended bowel, or known loculated ascites.

TABLE 4-1 Reducing the Incidence of Post-LP Headache

Effective Strategies

- Use of atraumatic needle (Sprotte, Whitacre, and others)
- Replacement of stylet prior to removal of needle
- Performing LP in the lateral decubitus position
- Insertion of needle with bevel oriented in a cephalad to caudad direction (when using standard needle)

Ineffective Strategies

- Bed rest (up to 4 h) following LP
- Supplemental fluids
- Minimizing the volume of spinal fluid removed
- Immediate mobilization following LP

Abbreviation: LP, lumbar puncture.

■ PREPARATORY WORK

Prior to performing a paracentesis, any severe bleeding diathesis should be corrected. Bowel distention should also be relieved by placement of an NG tube, and the bladder should also be emptied before beginning the procedure. If a large-volume paracentesis is being performed, large vacuum bottles with the appropriate connecting tubing should be obtained.

■ TECHNIQUE

Proper pt positioning greatly improves the ease with which a paracentesis can be performed. The pt should be instructed to lie supine with the head of the bed elevated to 45°. This position should be maintained for ~15 min to allow ascitic fluid to accumulate in the dependent portion of the abdomen. Ultrasound can be helpful for documenting ascites and identifying the locations of peritoneal fluid.

The preferred entry site for paracentesis is a midline puncture halfway between the pubic symphysis and the umbilicus; this correlates with the location of the relatively avascular linea alba. The midline puncture should be avoided if there is a previous midline surgical scar, because neovascularization may have occurred. Alternative sites of entry include the lower quadrants, lateral to the rectus abdominis, but caution should be used to avoid collateral blood vessels that may have formed in pts with portal hypertension.

The skin is prepped and draped in a sterile fashion. The skin, the subcutaneous tissue, and the abdominal wall down to the peritoneum should be infiltrated with an anesthetic agent. The paracentesis needle with an attached syringe is then introduced in the midline perpendicular to the skin. To prevent leaking of ascitic fluid, “Z-tracking” can be helpful: After penetrating the skin, the needle is inserted 1–2 cm before advancing further. The needle is then advanced slowly while performing continuous aspiration. As the peritoneum is pierced, the needle will “give” noticeably. Fluid should flow freely into the syringe soon thereafter. For a diagnostic paracentesis, removal of 50 mL of ascitic fluid is adequate. For a large-volume paracentesis, direct drainage into large vacuum containers using connecting tubing is a commonly utilized option.

After all samples have been collected, the paracentesis needle should be removed and firm pressure applied to the puncture site.

■ SPECIMEN COLLECTION

Peritoneal fluid should be sent for cell count with differential, Gram stain, and bacterial cultures. Albumin measurement of ascitic fluid is also necessary for calculating the serum–ascitic albumin gradient. Depending on the clinical scenario, other studies that can be obtained include mycobacterial cultures, amylase, adenosine deaminase, triglycerides, and cytology.

■ POSTPROCEDURE

The pt should be monitored carefully after paracentesis and should be instructed to lie supine in bed for several hours. If persistent fluid leakage occurs, continued bedrest with pressure dressings at the puncture site can be helpful. For pts with hepatic dysfunction undergoing large-volume paracentesis, the sudden reduction in intravascular volume can precipitate hepatorenal syndrome. Administration of 25-g IV albumin following large-volume paracentesis has been shown to decrease the incidence of postprocedure renal failure. Finally, if the ascites fluid analysis shows evidence of spontaneous bacterial peritonitis, then antibiotics (directed toward gram-negative gut bacteria) and IV albumin should be administered as soon as possible.

5

Principles of Critical Care Medicine



■ INITIAL EVALUATION OF THE CRITICALLY ILL PT

Initial care of critically ill pts must often be performed rapidly and before a thorough medical history has been obtained. Physiologic stabilization begins with the principles of advanced cardiovascular life support and frequently involves invasive techniques such as mechanical ventilation and renal replacement therapy to support organ systems that are failing. A variety of severity-of-illness scoring systems, such as SOFA (Sequential Organ Failure Assessment), have been developed. Although these tools are useful for ensuring similarity among groups of pts involved in clinical trials, guiding resource allocation, or monitoring quality assurance, their relevance to individual pts is less clear. These scoring systems are not typically used to guide clinical management.

■ SHOCK

Shock, which is characterized by multisystem end-organ hypoperfusion and tissue hypoxia, is a frequent problem requiring ICU admission. A variety of clinical indicators of shock exist, including reduced mean arterial pressure, tachycardia, tachypnea, cool extremities, altered mental status, oliguria, and lactic acidosis. Although hypotension is usually observed in shock, there is not a specific blood pressure threshold that is used to define it. Shock can result from decreased cardiac output, decreased systemic vascular resistance, or both. The three main categories of shock are hypovolemic, cardiogenic, and high cardiac output/low systemic vascular resistance. Clinical evaluation can be useful to assess the adequacy of cardiac output, with narrow pulse pressure, cool extremities, and delayed capillary refill suggestive of reduced cardiac output. Indicators of high cardiac output (e.g., widened pulse pressure, warm extremities, and rapid capillary refill) associated with shock suggest reduced systemic vascular resistance. Reduced cardiac output can be due to intravascular volume depletion (e.g., hemorrhage) or cardiac dysfunction. Intravascular volume depletion can be assessed through changes in right atrial pressure with spontaneous respirations or changes in pulse pressure during positive pressure mechanical ventilation. Reduced systemic vascular resistance is often caused by sepsis, but high cardiac output hypotension is also seen in pancreatitis, liver failure, burns, anaphylaxis, peripheral arteriovenous shunts, and thyrotoxicosis. Early resuscitation of septic and cardiogenic shock may improve survival; objective assessments such as echocardiography and/or invasive vascular monitoring should be used to complement clinical evaluation and minimize end-organ damage. The approach to the pt in shock is outlined in [Fig. 5-1](#).

■ MECHANICAL VENTILATORY SUPPORT

Critically ill pts often require mechanical ventilation. During initial resuscitation, standard principles of advanced cardiovascular life support should be followed. Mechanical ventilation should be considered for acute hypoxemic respiratory failure, which may occur with cardiogenic shock, pulmonary edema (cardiogenic or noncardiogenic), or pneumonia. Mechanical ventilation should also be considered for treatment of ventilatory failure, which can result from an increased load on the respiratory system—often manifested by lactic acidosis or decreased lung compliance. Mechanical ventilation may decrease respiratory work, improve arterial oxygenation with improved tissue O₂ delivery, and reduce acidosis. Reduction in mean arterial pressure after institution of mechanical ventilation commonly occurs due to reduced venous return from positive

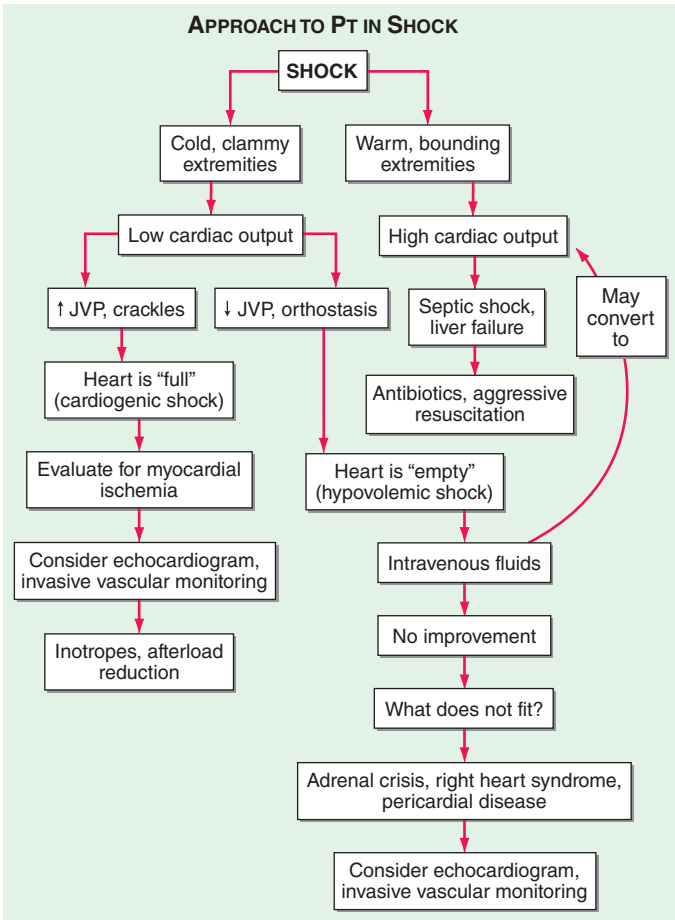


FIGURE 5-1 Approach to pt in shock. JVP, jugular venous pulse.

pressure ventilation, reduced endogenous catecholamine secretion, and administration of drugs used to facilitate intubation (such as propofol and opiates). Because hypovolemia often contributes to post-intubation hypotension, IV volume administration should be considered. The major types of respiratory failure as well as treatment of the mechanically ventilated pt are discussed in [Chap. 17](#).

■ MULTIORGAN SYSTEM FAILURE

Multiorgan system failure is a syndrome defined by the simultaneous dysfunction or failure of two or more organs in pts with critical illness. Multiorgan system failure is a common consequence of systemic inflammatory conditions (e.g., sepsis, pancreatitis, and trauma). To meet the criteria for multiorgan system failure, organ failure must persist for >24 h. Prognosis worsens with increased duration of organ failure and increased number of organ systems involved.

■ MONITORING IN THE ICU

With critical illness, close and often continuous monitoring of multiple organ systems is required. In addition to pulse oximetry, frequent arterial blood gas analysis can reveal evolving acid-base disturbances and assess the adequacy of ventilation. Intra-arterial pressure monitoring is frequently performed to follow blood pressure and to provide arterial blood gases and other blood samples. Pulmonary artery (Swan-Ganz) catheters can provide pulmonary artery pressure, cardiac output, systemic vascular resistance, and oxygen delivery measurements. However, no morbidity or mortality benefit from pulmonary artery catheter use has been demonstrated, and rare but significant complications from placement of central venous access (e.g., pneumothorax, infection) or the pulmonary artery catheter (e.g., cardiac arrhythmias, pulmonary artery rupture) can result. Thus, routine pulmonary artery catheterization in critically ill pts is not recommended. Monitoring pts on mechanical ventilation is reviewed in [Chap. 17](#).

■ PREVENTION OF CRITICAL ILLNESS COMPLICATIONS

Critically ill pts are prone to a number of complications, including the following:

- Sepsis: Often nosocomial infections related to the invasive monitoring devices used in critically ill pts.
- Anemia: Usually due to chronic inflammation as well as iatrogenic blood loss. A conservative approach to providing blood transfusions is recommended unless pts have active hemorrhage.
- Deep-vein thrombosis: May occur despite standard prophylaxis with subcutaneous (SC) heparin or lower extremity sequential compression devices and may occur at the site of central venous catheters. Low-molecular-weight heparins (e.g., enoxaparin) are more effective for high-risk pts than unfractionated heparin. Fondaparinux is highly effective in orthopedic pts at high risk for deep-vein thrombosis.
- GI bleeding: Stress ulcers of the gastric mucosa frequently develop in pts with bleeding diatheses or respiratory failure, necessitating prophylactic acid neutralization in such pts. Histamine receptor-2 antagonists are preferred for prophylactic treatment.
- Acute renal failure: A frequent occurrence in ICU pts, exacerbated by nephrotoxic medications and hypoperfusion. The most common etiology is acute tubular necrosis. Low-dose dopamine, fenoldopam, or vasopressin treatment does not protect against the development of acute renal failure.
- Inadequate nutrition and hyperglycemia: Enteral feeding, when possible, is preferred over parenteral nutrition, because the parenteral route is associated with multiple complications including hyperglycemia, cholestasis, and sepsis. The utility of tight glucose control in the ICU is controversial.
- ICU-acquired weakness: Neuropathies and myopathies have been described—typically after at least 1 week of ICU care. These complications are especially common in sepsis.

■ NEUROLOGIC DYSFUNCTION IN CRITICALLY ILL PTS

A variety of neurologic problems can develop in critically ill pts. Most ICU pts develop delirium, which is characterized by acute changes in mental status, inattention, disorganized thinking, and an altered level of consciousness. Use of dexmedetomidine was associated with less ICU delirium than midazolam, one of the conventional sedatives. Less common but important neurologic complications include anoxic brain injury, stroke, and status epilepticus.

■ LIMITATION OR WITHDRAWAL OF CARE

Withholding or withdrawing care commonly occurs in the ICU. Technological advances have allowed many pts to be maintained in the ICU with little or no

chance of recovery. Increasingly, pts, families, and caregivers have acknowledged the ethical validity to withhold or withdraw care when the pt or surrogate decision-maker determines that the pt's goals for care are no longer achievable with the clinical situation.

6

Pain and Its Management



APPROACH TO THE PATIENT

Pain

Pain is the most common symptom that brings a pt to a physician's attention. Management depends on determining its cause, alleviating triggering and potentiating factors, and providing rapid and effective pain relief whenever possible. Pain may be of somatic (skin, joints, muscles), visceral, or neuropathic (injury to nerves, spinal cord pathways, or thalamus) origin. Characteristics of each are summarized in [Table 6-1](#).

Neuropathic Pain Due to damage of peripheral or central nociceptive pathways. Definitions: *neuralgia*: pain in the distribution of a single nerve, as in trigeminal neuralgia; *dysesthesia*: spontaneous, unpleasant, abnormal sensation; *hyperalgesia* and *hyperesthesia*: exaggerated responses to nociceptive or touch stimulus, respectively; *allodynia*: perception of light mechanical stimuli as painful, as when vibration evokes painful sensation. Reduced pain perception is called *hypalgesia* or, when absent, *analgesia*. *Causalgia* is continuous severe burning pain with indistinct boundaries and accompanying sympathetic nervous system dysfunction (sweating; vascular, skin, and

TABLE 6-1 Characteristics of Somatic and Neuropathic Pain

Somatic pain

- Nociceptive stimulus usually evident
- Usually well localized
- Similar to other somatic pains in pt's experience
- Relieved by anti-inflammatory or narcotic analgesics

Visceral pain

- Most commonly activated by inflammation
- Pain poorly localized and usually referred
- Associated with diffuse discomfort, e.g., nausea, bloating
- Relieved by narcotic analgesics

Neuropathic pain

- No obvious nociceptive stimulus
- Associated evidence of nerve damage, e.g., sensory impairment, weakness
- Unusual, dissimilar from somatic pain, often shooting or electrical quality
- Only partially relieved by narcotic analgesics; may respond to antidepressants or anticonvulsants

hair changes—sympathetic dystrophy) that occurs after injury to a peripheral nerve.

Sensitization refers to a lowered threshold for activating primary nociceptors following repeated stimulation in damaged or inflamed tissues; inflammatory mediators play a role. Sensitization contributes to tenderness, soreness, and hyperalgesia (as in sunburn).

Referred pain results from the convergence of sensory inputs from skin and viscera on single spinal neurons that transmit pain signals to the brain. Because of this convergence, input from deep structures is mislocalized to a region of skin innervated by the same spinal segment.

Chronic Pain The problem is often difficult to diagnose with certainty, and pts may appear emotionally distraught. Several factors can cause, perpetuate, or exacerbate chronic pain: (1) painful disease for which there is no cure (e.g., arthritis, cancer, chronic daily headaches, diabetic neuropathy); (2) perpetuating factors initiated by a bodily disease that persist after the disease has resolved (e.g., damaged sensory or sympathetic nerves); (3) psychological conditions. Pay special attention to the medical history and to depression. Major depression is common, treatable, and potentially fatal (suicide).

PATHOPHYSIOLOGY: ORGANIZATION OF PAIN PATHWAYS

Pain-producing (nociceptive) sensory stimuli in skin and viscera activate peripheral nerve endings of primary afferent neurons, which synapse on second-order neurons in spinal cord or medulla (Fig. 6-1). These second-order neurons form crossed ascending pathways that reach the thalamus and project to the somatosensory cortex. Parallel ascending neurons, connecting with brainstem and thalamic nuclei, project to the limbic system and underlie the emotional aspect of pain. Pain transmission is regulated at the dorsal horn level by descending bulbospinal pathways that utilize serotonin, norepinephrine, and several neuropeptides as neurotransmitters.

Agents that modify pain perception may act by reducing tissue inflammation (NSAIDs, prostaglandin synthesis inhibitors), interfering with pain transmission (narcotics), or enhancing descending modulation (narcotics and antidepressants). Anticonvulsants (gabapentin, carbamazepine) may be effective for aberrant pain sensations arising from peripheral nerve injury.

TREATMENT

Pain (Table 6-2)

ACUTE SOMATIC PAIN

- Mild to moderate pain: Usually treated effectively with nonnarcotic analgesics, e.g., aspirin, acetaminophen, and NSAIDs, which inhibit cyclooxygenase (COX) and, except for acetaminophen, have anti-inflammatory actions, especially at high dosages. Particularly effective for headache and musculoskeletal pain.
- Parenteral NSAIDs: Ketorolac and diclofenac are sufficiently potent and rapid in onset to supplant opioids for many pts with acute severe pain.
- Narcotic analgesics in oral or parenteral form can be used for more severe pain. These are the most effective drugs available; the opioid antagonist naloxone should be readily available when narcotics are used in high doses or in unstable pts.
- Pt-controlled analgesia (PCA) permits infusion of a baseline dose plus self-administered boluses (activated by press of a button) as needed to control pain.

CHRONIC PAIN

- Develop an explicit treatment plan including specific and realistic goals for therapy, e.g., getting a good night's sleep, being able to go shopping, or returning to work.
- A multidisciplinary approach that utilizes medications, counseling, physical therapy, nerve blocks, and even surgery may be required to improve quality of life.
- Psychological evaluation is key; behaviorally based treatment paradigms are frequently helpful.
- Some pts may require referral to a pain clinic; for others, pharmacologic management alone can provide significant help.
- Tricyclic antidepressants are useful in management of chronic pain from many causes, including headache, diabetic neuropathy, postherpetic neuralgia, chronic low back pain, cancer, and central post-stroke pain.
- Anticonvulsants or antiarrhythmics benefit pts with neuropathic pain (e.g., diabetic neuropathy, trigeminal neuralgia).
- The long-term use of opioids is accepted for pain due to malignant disease, but is controversial for chronic pain of nonmalignant origin.

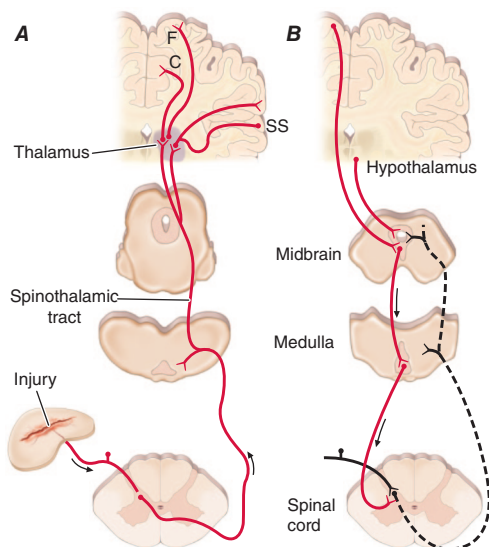


FIGURE 6-1 Pain transmission and modulatory pathways. **A.** Transmission system for nociceptive messages. Noxious stimuli activate the sensitive peripheral ending of the primary afferent nociceptor by the process of transduction. The message is then transmitted over the peripheral nerve to the spinal cord, where it synapses with cells of origin of the major ascending pain pathway, the spinothalamic tract. The message is relayed in the thalamus to the anterior cingulate (C), frontal insular (F), and somatosensory cortex (SS). **B.** Pain-modulation network. Inputs from frontal cortex and hypothalamus activate cells in the midbrain that control spinal pain-transmission cells via cells in the medulla.

TABLE 6-2 Drugs for Relief of Pain

GENERIC NAME	DOSE, mg	INTERVAL	COMMENTS
Nonnarcotic analgesics: Usual doses and intervals			
Acetylsalicylic acid	650 PO	q4h	Enteric-coated preparations available
Acetaminophen	650 PO	q4h	Side effects uncommon
Ibuprofen	400 PO	q4–6h	Available without prescription
Naproxen	250–500 PO	q12h	Naproxen is the common NSAID that poses the least cardiovascular risk; but it has a somewhat higher incidence of gastrointestinal bleeding
Fenoprofen	200 PO	q4–6h	Contraindicated in renal disease
Indomethacin	25–50 PO	q8h	Gastrointestinal side effects common
Ketorolac	15–60 IM/IV	q4–6h	Available for parenteral use
Celecoxib	100–200 PO	q12–24h	Useful for arthritis
Valdecoxib	10–20 PO	q12–24h	Removed from U.S. market in 2005
GENERIC NAME	PARENTERAL DOSE, mg	PO DOSE, mg	COMMENTS
Narcotic analgesics: Usual doses and intervals			
Codeine	30–60 q4h	30–60 q4h	Nausea common
Oxycodone	—	5–10 q4–6h	Usually available with acetaminophen or aspirin
Oxycodone extended-release	—	10–40 q12h	Oral extended-release tablet; high potential for misuse
Morphine	5 q4h	30 q4h	
Morphine sustained release	—	15–60 bid to tid	Oral slow-release preparation
Hydromorphone	1–2 q4h	2–4 q4h	Shorter acting than morphine sulfate
Levorphanol	2 q6–8h	4 q6–8h	Longer acting than morphine sulfate; absorbed well PO
Methadone	5–10 q6–8h	5–20 q6–8h	Due to long half-life, respiratory depression and sedation may persist after analgesic effect subsides; therapy should not be initiated with >40 mg/d, and dose escalation should be made no more frequently than every 3 days

Meperidine	50–100 q3–4h	300 q4h	Poorly absorbed PO; normeperidine is a toxic metabolite; routine use of this agent is not recommended
Butorphanol	—	1–2 q4h	Intranasal spray
Fentanyl	25–100 µg/h	—	72-h transdermal patch
Buprenorphine	5–20 µg/h	—	7-day transdermal patch
Buprenorphine	0.3 q6–8h	—	Parenteral administration
Tramadol	—	50–100 q4–6h	Mixed opioid/adrenergic action

GENERIC NAME	UPTAKE BLOCKADE		SEDATIVE POTENCY	ANTICHOLINERGIC POTENCY	ORTHOSTATIC HYPOTENSION	CARDIAC ARRHYTHMIA	AVE. DOSE, mg/d	RANGE, mg/d
	5-HT	NE						
Antidepressants^a								
Doxepin	++	+	High	Moderate	Moderate	Less	200	75–400
Amitriptyline	++++	++	High	Highest	Moderate	Yes	150	25–300
Imipramine	++++	++	Moderate	Moderate	High	Yes	200	75–400
Nortriptyline	+++	++	Moderate	Moderate	Low	Yes	100	40–150
Desipramine	+++	++++	Low	Low	Low	Yes	150	50–300
Venlafaxine	+++	++	Low	None	None	No	150	75–400
Duloxetine	+++	+++	Low	None	None	No	40	30–60
GENERIC NAME	PO DOSE, mg		INTERVAL	GENERIC NAME	PO DOSE, mg	INTERVAL		
Anticonvulsants and antiarrhythmics^a								
Phenytoin	300		daily/qhs	Clonazepam	1	q6h		
Carbamazepine	200–300		q6h	Gabapentin ^b	600–1200	q8h		
Oxcarbazepine	300		bid	Pregabalin	150–600	bid		

^aAntidepressants, anticonvulsants, and antiarrhythmics have not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of pain.

^bGabapentin in doses up to 1800 mg/d is FDA approved for postherpetic neuralgia.

Abbreviations: 5-HT, serotonin; NE, norepinephrine; NSAID, nonsteroidal anti-inflammatory drug.

7

Assessment of Nutritional Status



Stability of body weight requires that energy intake and expenditures are balanced over time. The major categories of energy output are resting energy expenditure (REE) and physical activity; minor sources include the energy cost of metabolizing food (thermic effect of food or specific dynamic action) and shivering thermogenesis. The average energy intake is about 2600 kcal/d for men and about 1800 kcal/d for women, though these estimates vary with age, body size, and activity level. Malnutrition occurs in 30–50% of hospitalized pts, depending upon the setting and severity of illness. The presence of inflammation, including after surgical procedures, can increase energy expenditure and alter nutritional assessment indicators such as albumin.

Dietary reference intakes (DRIs) and recommended dietary allowances (RDAs) have been defined for many nutrients, including 9 essential amino acids, 4 fat-soluble and 10 water-soluble vitamins, several minerals, fatty acids, choline, and water (see [Tables 325-1, 325-2, and 325-3](#) in HPIM-20). The usual water requirements are 1.0–1.5 mL/kcal energy expenditure in adults, with adjustments for excessive losses. The RDA for protein is 0.6-g/kg ideal body weight, representing 10–15% of total caloric intake. Fat should constitute $\leq 30\%$ of calories, and saturated fat should be $<10\%$ of calories. At least 55% of calories should be derived from carbohydrates.

MALNUTRITION

Malnutrition results from inadequate intake or abnormal GI assimilation of dietary calories, excessive energy expenditure, or altered metabolism of energy supplies by an intrinsic disease process.

Both outpatients and inpatients are at risk for malnutrition if they meet one or more of the following criteria:

- Unintentional loss of $>10\%$ of usual body weight in the preceding 3 months
- Body weight $<90\%$ of ideal for height
- Body mass index (BMI: $\text{weight}/\text{height}^2$ in kg/m^2) <18.5

ETIOLOGY

The major etiologies of malnutrition are starvation, stress from surgery or severe illness, and mixed mechanisms. Starvation results from decreased dietary intake (from poverty, chronic alcoholism, anorexia nervosa, fad diets, severe depression, neurodegenerative disorders, dementia, or strict vegetarianism; abdominal pain from intestinal ischemia or pancreatitis; or anorexia associated with AIDS, disseminated cancer, heart failure, or renal failure) or decreased assimilation of the diet (from pancreatic insufficiency; short bowel syndrome; celiac disease; or esophageal, gastric, or intestinal obstruction). Contributors to physical stress include fever, acute trauma, major surgery, burns, acute sepsis, hyperthyroidism, and inflammation as occurs in pancreatitis, collagen vascular diseases, and chronic infectious diseases such as tuberculosis or AIDS opportunistic infections. Mixed mechanisms occur in AIDS, disseminated cancer, chronic obstructive pulmonary disease, chronic liver disease, Crohn's disease, ulcerative colitis, and renal failure.

CLINICAL FEATURES

The historical features, clinical signs, and laboratory indicators of potential malnutrition are summarized in [Tables 7-1 and 7-2](#).

TABLE 7-1 History and Physical Examination Elements

ELEMENT	NOTES
Historical data	
Body weight	Ask about usual weight, peak weight, and deliberate weight loss. A 4.5 kg (10-lb) weight loss over 6 months is noteworthy and a weight loss of >10% of usual body weight is prognostic of clinical outcomes. Use medical records, family, and caregivers as information resources.
Medical and surgical conditions; chronic disease	<p>Look for medical or surgical conditions or chronic disease that can place one at nutritional risk secondary to increased requirements, or compromised intake or assimilation like: critical illness, severe burns, major abdominal surgery, multi-trauma, closed head injury, previous gastrointestinal surgery, severe gastrointestinal hemorrhage, enterocutaneous fistula, gastrointestinal obstruction, mesenteric ischemia, severe acute pancreatitis, chronic pancreatitis, inflammatory bowel disease, celiac disease, bacterial overgrowth, solid or hematologic malignancy, bone marrow transplant, acquired immune deficiency syndrome, and organ failure/transplant—kidney, liver, heart, lung, or gut.</p> <p>A number of conditions or diseases are characterized by severe acute inflammatory response including critical illness, major infection/sepsis, adult respiratory distress syndrome, systemic inflammatory response syndrome, severe burns, major abdominal surgery, multi-trauma, and closed head injury.</p> <p>Many conditions or diseases are more typically associated with mild to moderate chronic inflammatory response. Examples include cardiovascular disease, congestive heart failure, cystic fibrosis, inflammatory bowel disease, celiac disease, chronic pancreatitis, rheumatoid arthritis, solid tumors, hematologic malignancies, sarcopenic obesity, diabetes mellitus, metabolic syndrome, cerebrovascular accident, neuromuscular disease, dementia, organ failure/transplant—kidney, liver, heart, lung, or gut, periodontal disease, pressure wounds, and chronic obstructive pulmonary disease. Note that acute exacerbations, infections, or other complications may superimpose acute inflammatory response on such conditions or diseases.</p> <p>Examples of starvation-associated conditions that generally have little or no inflammatory component include anorexia nervosa or compromised intake in the setting of major depression.</p>
Constitutional signs/symptoms	Fever or hypothermia can indicate active inflammatory response. Tachycardia is also common. Anorexia is another manifestation of inflammatory response and is also often a side effect of treatments and medications.

(Continued)

TABLE 7-1 History and Physical Examination Elements (Continued)

ELEMENT	NOTES
Eating difficulties/gastrointestinal complaints	Poor dentition or problems swallowing can compromise oral intake. Vomiting, nausea, abdominal pain, abdominal distension, diarrhea, constipation, and gastrointestinal bleeding can be signs of gastrointestinal pathology that may place one at nutritional risk.
Eating disorders	Look for distorted body image, compulsive exercise, amenorrhea, vomiting, tooth loss, dental caries, and use of laxatives, diuretics or Ipecac.
Medication use	Many medications can adversely affect nutrient intake or assimilation. Review potential drug–drug and drug–nutrient interactions. A pharmacist consultant can be helpful.
Dietary practices and supplement use	Look for dietary practices including therapeutic, weight reduction, vegetarian, macrobiotic, and fad diets. Also record use of dietary supplements, including vitamins, minerals, and herbals. Ask about dietary intake. Recall, record, and food frequency tools are available. It is estimated that $\geq 50\%$ of adults take dietary supplements.
Influences on nutritional status	Ask about factors such as living environment, functional status (activities of daily living and instrumental activities of daily living), dependency, caregiver status, resources, dentition, alcohol or substance abuse, mental health (depression or dementia), and lifestyle.
Physical examination data	
Body mass index (BMI)	$\text{BMI} = \frac{\text{weight in kg}}{(\text{height in meters})^2}$ BMI $< 18.5 \text{ kg/m}^2$ proposed screen for malnutrition per National Institutes of Health guidelines. BMI $\leq 15 \text{ kg/m}^2$ is associated with increased mortality. Comparison with ideal body weight for stature can also be determined from reference tables. Note hydration status and edema at the time body weight is determined.
Weight loss	Look for loss of muscle mass and subcutaneous fat. Temporal and neck muscle wasting may be readily observed. Anthropometrics including skin-folds and circumferences can be useful but require training to achieve reliability.
Weakness/loss of strength	Decreased hand-grip and leg extensor strength have been related to loss of muscle mass in malnourished states. Lower extremity weakness may be observed in thiamine deficiency.
Peripheral edema	Peripheral edema may confound weight measurements and is often observed with reduced visceral proteins as well as inflammatory states. Edema may also be observed with thiamine deficiency.

(Continued)

TABLE 7-1 History and Physical Examination Elements (Continued)

ELEMENT	NOTES
Hair examination	<p>Hair findings are indicative of certain nutrient deficiencies.</p> <p>Loss: protein, B₁₂, folate</p> <p>Brittle: biotin</p> <p>Color change: zinc</p> <p>Dry: vitamins A and E</p> <p>Easy pluckability: protein, biotin, zinc</p> <p>Coiled, corkscrew: vitamins A and C</p> <p>Alopecia is common in severely malnourished persons.</p> <p>Ask about excessive hair loss on pillow or when combing hair.</p>
Skin examination	<p>Skin findings are indicative of certain nutrient deficiencies.</p> <p>Desquamation: riboflavin</p> <p>Petechiae: vitamins A and C</p> <p>Perifollicular hemorrhage: vitamin C</p> <p>Ecchymosis: vitamins C and K</p> <p>Xerosis, bran-like desquamation: essential fatty acid</p> <p>Pigmentation, cracking, crusting: niacin</p> <p>Acneiform lesions, follicular keratosis, xerosis: vitamin A</p> <p>Acro-oral dermatitis, erythematous, vesiculobullous, and pustular: zinc</p> <p>Characteristic nutritional dermatitis and skin findings may be observed with a number of nutrient deficiencies.</p> <p>Wounds and pressure sores should also be noted as indicators of compromised nutritional status.</p>
Eye examination	<p>Ocular findings are indicative of certain nutrient deficiencies.</p> <p>Bitot's spots: vitamin A</p> <p>Xerosis: vitamin A</p> <p>Angular palpebritis: riboflavin</p> <p>Also ask about difficulties with night vision/night blindness; indicates vitamin A deficiency.</p>
Perioral examination	<p>Perioral findings are indicative of certain nutrient deficiencies.</p> <p>Angular stomatitis and cheilosis: B complex, iron, and protein</p> <p>Glossitis: niacin, folate, and vitamin B₁₂</p> <p>Magenta tongue: riboflavin</p> <p>Bleeding gums, gingivitis, tooth loss: vitamin C</p> <p>Angular stomatitis, cheilosis, and glossitis are associated with vitamin and mineral deficiencies.</p> <p>Note poor dentition, caries, and tooth loss. Difficulty swallowing and impairment of gag should also be recognized.</p>

(Continued)

TABLE 7-1 History and Physical Examination Elements (Continued)

ELEMENT	NOTES
Extremity examination	Extremity findings indicate certain nutrient deficiencies. Arthralgia: vitamin C Calf pain: thiamine Extremities may also exhibit loss of muscle mass and/or peripheral edema. Neurological findings in the extremities may also result from deficiencies described below.
Mental status/ nervous system examination	Mental and nervous system findings indicate certain nutrient deficiencies. Ophthalmoplegia and foot drop: thiamine Paresthesia: thiamine, vitamin B ₁₂ , and biotin Depressed vibratory and position senses: vitamin B ₁₂ Anxiety, depression, and hallucinations: niacin Memory disturbance: vitamin B ₁₂ Hyporeflexia, loss of lower extremity deep tendon reflexes: thiamine and vitamin B ₁₂ Conduct formal cognitive and depression assessments as appropriate. Dementia and depression are common causes of malnutrition among older persons. Wernicke-Korsakoff syndrome may be observed with severe thiamine deficiency.
Functional assessment	Observe and test physical performance as indicated: gait, chair stands, stair steps, and balance. These provide complex measures of integrated neurological status, coordination, and strength.

Source: Adapted with permission from G Jensen: *Nutritional Syndromes*. *Smart Medicine/PIER*. Philadelphia, American College of Physicians, 2013.

TABLE 7-2 Body Composition, Laboratories, and Other Studies

TEST	NOTES
Body composition studies	
Anthropometrics	Skinfolds and circumferences require training for reliability. Typical coefficient of variation is $\geq 10\%$.
Bioelectrical impedance	Based upon differential resistance of body tissues. Equipment easily portable. Good measure of body water. Requires population-specific validation of regression equations.
Water displacement	Impractical for most clinical settings. Weighed in water tank. Historic reference measure.
Whole body counting and isotope dilution techniques	Research methodologies. Naturally occurring ⁴⁰ K isotope to measure body cell mass by whole body counting. Total body water measurement by dilution volume of tritium, deuterium, or ¹⁸ O-labeled water.
Air plethysmography	Research methodology. Subject sits inside moderately sized BodPod chamber. Validated against water displacement and impedance.
Dual energy x-ray absorptiometry (DEXA)	Often used for bone density but can be used for soft tissue measurements with appropriate software. Can compare truncal and appendicular components. Modest x-ray exposure.

(Continued)

TABLE 7-2 Body Composition, Laboratories, and Other Studies (Continued)

TEST	NOTES
Imaging with computed tomography (CT) or magnetic resonance imaging (MRI)	State-of-the-art research methods for visualizing body tissue compartments. Can quantify visceral fat. Costly and CT entails x-ray exposure.
Laboratories and other studies	
Albumin	Lacks sensitivity and specificity for malnutrition. Potent risk indicator for morbidity and mortality. Proxy measure for underlying injury, disease, or inflammation. Half-life is 14–20 days. Also consider liver disease, nephrotic syndrome, and protein-wasting enteropathy.
Prealbumin	Sensitive to short-term changes in inflammation and protein nutrition with half-life of 2–3 days. Otherwise suffers the same limitations of albumin with limited sensitivity and specificity for malnutrition. Levels may be decreased in liver failure and increased in renal failure.
Transferrin	Acute phase reactant also altered by perturbation in iron status. Half-life is 8–10 days. Lacks sensitivity and specificity for malnutrition.
Retinol-binding protein	Responds to very short-term changes in nutritional status but utility is also limited by response to stress and inflammation. Half-life is 12 h. Also affected by vitamin A deficiency and renal disease.
C-reactive protein	C-reactive protein is a positive acute phase reactant. It is generally elevated if an active inflammatory process is manifest.
Cholesterol	Low cholesterol (<160 mg/dL) is often observed in malnourished persons with serious underlying disease. It is unrelated to dietary intake in many clinical settings. Increased complications and mortality are observed. It appears that low cholesterol is again a nonspecific feature of poor health status that reflects cytokine-mediated inflammatory condition. Vegans and pts with hyperthyroidism may also exhibit low cholesterol.
Carotene	Nonspecific indicator of malabsorption and poor nutritional intake.
Cytokines	Research is exploring prognostic use of cytokine measurements as indicators of inflammatory status.
Electrolytes, blood urea nitrogen (BUN), creatinine, and glucose	Monitor for abnormalities consistent with under- or over-hydration status and purging (contraction alkalosis). BUN may also be low in the setting of markedly reduced body cell mass. BUN and creatinine are elevated in renal failure. Hyperglycemia may be nonspecific indicator of inflammatory response.
Complete blood count with differential	Screen for nutritional anemias (iron, B ₁₂ , and folate), lymphopenia (malnutrition) and thrombocytopenia (vitamin C and folate). Leukocytosis may be observed with inflammatory response.

(Continued)

TABLE 7-2 Body Composition, Laboratories, and Other Studies (Continued)

TEST	NOTES
Total lymphocyte count	Relative lymphopenia (total lymphocyte count $<1200/\text{mm}^3$) is a nonspecific marker for malnutrition.
Helper/suppressor T cell ratio	Ratio may be reduced in severely undernourished pts. Not specific for nutritional status.
Nitrogen balance	24-h urine can be analyzed for urine urea nitrogen (UUN) to determine nitrogen balance and give indication of degree of catabolism and adequacy of protein replacement. Requires accurate urine collection and normal renal function. Nitrogen balance = (protein/6.25) - (UUN + 4). Generally negative in the setting of acute severe inflammatory response.
Urine 3-methylhistidine	Indicator of muscle catabolism and protein sufficiency. Released upon breakdown of myofibrillar protein and excreted without reutilization. Urine measurement requires a meat-free diet for 3 days prior to collection.
Creatinine height index (CHI)	CHI = (24-h urinary creatinine excretion/ideal urinary creatinine for gender and height) \times 100. Indicator of muscle depletion. Requires accurate urine collection and normal renal function.
Prothrombin time/international normalized ratio (INR)	Nonspecific indicator of vitamin K status. Prolonged in liver failure.
Specific micronutrients	When suspected a variety of specific micronutrient levels may be measured: thiamine, riboflavin, niacin, folate, pyridoxine, vitamins A, C, D, E, B ₁₂ , zinc, iron, selenium, carnitine, and homocysteine—indicator of B ₁₂ , folate, and pyridoxine status.
Skin testing—recall antigens	Delayed hypersensitivity testing. While malnourished pts are often anergic, this is not specific for nutritional status.
Electrocardiogram	Severely malnourished pts with reduced body cell mass may exhibit low voltage and prolonged QT interval. These findings are not specific for malnutrition.
Video fluoroscopy	Helpful to evaluate suspected swallowing disorders.
Endoscopic and x-ray studies of gastrointestinal tract	Useful to evaluate impaired function, motility, and obstruction.
Fat absorption	72-h fecal fat can be used to quantitate degree of malabsorption.
Schilling test	Identify the cause for impaired vitamin B ₁₂ absorption.
Indirect calorimetry	Metabolic cart can be used to determine resting energy expenditure (REE) for accurate estimation of energy needs. Elevated REE is a sign of systemic inflammatory response.

Source: Adapted with permission from G Jensen: *Nutritional Syndromes*. *Smart Medicine/PIER*. Philadelphia, American College of Physicians, 2013.

8

Enteral and Parenteral Nutrition



Nutritional support should be initiated in pts with malnutrition or in those at risk for malnutrition (e.g., conditions that preclude adequate oral feeding or pts in catabolic states, such as sepsis, burns, major surgery, or trauma).

Enteral nutrition (EN) is provided through a feeding tube placed through the nose into the stomach or beyond it into the duodenum, via a mini-surgical procedure in which a feeding tube is inserted through the abdominal wall into the stomach or beyond it into the jejunum using an endoscope, or by an open surgical approach to access the stomach or small intestine. EN is the treatment of choice when optimized voluntary nutritional support is impossible or has failed. *Parenteral therapy* refers to the infusion of nutrient solutions into the bloodstream via a peripherally inserted central catheter (PICC), a centrally inserted externalized catheter, or a centrally inserted tunneled catheter or subcutaneous port. When feasible, EN is the preferred route because it sustains the digestive, absorptive, and immunologic functions of the GI tract, and because it minimizes the risk of fluid and electrolyte imbalance. Parenteral nutrition (PN) is often indicated in severe pancreatitis, necrotizing enterocolitis, prolonged ileus, and distal bowel obstruction.

ENTERAL NUTRITION

Standard Polymeric Formulas are the most widely used sources of EN. They are available in a wide variety of formats that generally meet the nutritional requirements of a normal, healthy person. Carbohydrates provide most of the energy. The proteins (from casein, whey, or soy) are intact and require normal pancreatic enzyme function for digestion and absorption. These products are isotonic or nearly so, and provide from 1000–2000 kcal and 50–70-g protein/L. Additional formula types include *Polymeric Formulas with Fiber*, *Elemental and Semi-elemental Formulas*, and *Immune-enhancing Formulas*, *Protein-enriched Formulas*, as well as disease-specific formulas used in pts with diabetic, hepatic, renal, or pulmonary disease.

After elevation of the head of the bed and confirmation of correct tube placement, continuous infusion is initiated using a half-strength diet at a rate of 25–50 mL/h. This can be advanced to full strength as tolerated to meet the energy target. The major risks of enteral tube feeding are aspiration, diarrhea, electrolyte imbalance, glucose intolerance, sinusitis, and esophagitis.

PARENTERAL NUTRITION

PN delivers a complete nutritional regimen directly into the bloodstream in the form of crystalline amino acids, dextrose, triglyceride emulsions, minerals (calcium, phosphate, magnesium, and zinc), electrolytes, and micronutrients. Because of its high osmolarity (>1200 mOsm/L) and often large volume, PN is infused into a central vein in adults. Ready-to-use PN admixtures typically containing 4–7% hydrous amino acids and 20–25% dextrose (with or without electrolytes) are available in two-chamber (amino acids and dextrose) or three-chamber (amino acids, dextrose, and lipid) bags that are intermixed, and vitamins, trace minerals, and additional electrolytes added just prior to infusion.

Although convenient and cost-effective, these products have fixed nutrient composition and thus are dosed according to the volume required to meet calorie requirements.

The risks of parenteral therapy include mechanical complications from insertion of the infusion catheter, catheter sepsis, fluid overload, hyperglycemia, electrolyte disorders, acid-base and electrolyte imbalance, cholestasis, metabolic bone disease, and micronutrient deficiencies.

The following parameters should be monitored in all pts receiving supplemental nutrition, whether enteral or parenteral:

- Fluid balance (weight, intake vs. output)
- Glucose, electrolytes, BUN (daily until stable, then 2× per week)
- Serum creatinine, albumin, phosphorus, calcium, magnesium, Hb/Hct, WBC (baseline, then 2× per week)
- International normalized ratio (INR) (baseline, then weekly)
- Micronutrient tests as indicated

SPECIFIC MICRONUTRIENT DEFICIENCY

Appropriate therapies for micronutrient deficiencies are outlined in [Table 8-1](#).

NUTRIENT	THERAPY
Vitamin A ^{a,b,c}	60 mg PO, repeated 1 and 14 days later if ocular changes; 30 mg for ages 6–11 months 15 mg PO qd × 1 month if chronic malabsorption
Vitamin C	200 mg PO qd
Vitamin D ^{a,d}	Encourage sun exposure if possible 50,000 units PO once weekly for 4–8 weeks, then 400–800 units PO qd Substantially higher dose may be required in chronic malabsorption
Folic acid	0.4 mg PO qd prenatally and during pregnancy Confirm normal B ₁₂ levels in pts with megaloblastic anemia
Vitamin B ₁₂	1000 µg IM × 6 doses to replenish stores, then 1000 µg IM monthly
Vitamin E ^a	800–1200 mg PO qd
Vitamin K ^a	10 mg IV × 1 1–2 mg PO qd or 1–2 mg IV weekly in chronic malabsorption
Thiamine ^b	300 mg IV qd × 3 days, followed by 10 mg PO qd until recovery
Niacin	100–200 mg PO tid for 5 days
Pyridoxine	50 mg PO qd, 100–200 mg PO qd if deficiency related to medications
Zinc ^{b,c}	60 mg PO bid

^aAssociated with fat malabsorption.

^bAssociated with chronic alcoholism; always replete thiamine before carbohydrates in alcoholics to avoid precipitation of acute thiamine deficiency.

^cAssociated with protein-calorie malnutrition.

^dTherapy must be monitored by serum calcium measurements.

9

Transfusion and Pheresis Therapy

**TRANSFUSIONS****WHOLE BLOOD TRANSFUSION**

Indicated when acute blood loss is sufficient to produce hypovolemia, whole blood provides both oxygen-carrying capacity and volume expansion. In acute blood loss, hematocrit may not accurately reflect degree of blood loss for 48 h until fluid shifts occur.

RED BLOOD CELL TRANSFUSION

Indicated for symptomatic anemia unresponsive to specific therapy or requiring urgent correction. Packed red blood cell (RBC) transfusions may be indicated in pts who are symptomatic from cardiovascular or pulmonary disease when Hb is between 70 and 90 g/L (7 and 9 g/dL). Transfusion is usually necessary when Hb is <70 g/L (<7 g/dL). One unit of packed RBCs raises the Hb by ~10 g/L (1 g/dL). In the setting of acute hemorrhage, packed RBCs, fresh frozen plasma (FFP), and platelets in an approximate ratio of 3:1:10 units are an adequate replacement for whole blood. Removal of leukocytes reduces risk of alloimmunization and transmission of cytomegalovirus. Washing to remove donor plasma reduces risk of allergic reactions. Irradiation prevents graft-versus-host disease in immunocompromised recipients by killing alloreactive donor lymphocytes. Avoid related donors.

Other Indications

(1) *Hypertransfusion therapy* to block production of defective cells, e.g., thalassemia, sickle cell anemia; (2) *exchange transfusion*—hemolytic disease of newborn, sickle cell crisis; (3) *transplant recipients*—decreases rejection of cadaveric kidney transplants.

Complications (Table 9-1)

(1) *Transfusion reaction*—immediate or delayed, seen in 1–4% of transfusions; IgA-deficient pts at particular risk for severe reaction; (2) *infection*—bacterial (rare); hepatitis C, <0.1–1 in 1,000,000 transfusions; HIV transmission, 0.1–1 in 1,000,000; (3) *circulatory overload*; (4) *iron overload*—each unit contains 200- to 250-mg iron; hemochromatosis may develop after 100 U of RBCs (less in children), in absence of blood loss; iron chelation therapy with deferoxamine indicated for ferritin >1000 ng/mL; (5) *graft-versus-host disease*; (6) *alloimmunization*.

AUTOLOGOUS TRANSFUSION

Use of pt's own stored blood avoids hazards of donor blood; also useful in pts with multiple RBC antibodies. Pace of autologous donation may be accelerated using erythropoietin (50–150 U/kg SC three times a week) in the setting of normal iron stores.

RED CELL EXCHANGE

The main goal of red cell exchange transfusions is to remove sickle cells and replace them with normal red cells to interrupt the vicious cycle of sickling, stasis, vasoocclusion, and hypoxemia that propagate sickle cell crises. The usual target is 70% hemoglobin A.

PLATELET TRANSFUSION

Prophylactic transfusions are usually reserved for platelet count <10,000/ μ L (<20,000/ μ L in acute leukemia). One unit elevates the count by about 10,000/ μ L

TABLE 9-1 Risks of Transfusion Complications**FREQUENCY, EPISODES: UNIT****Main reactions**

Circulatory overload (TACO)	• 10.9:100,000
Febrile (FNHTR)	• 100–1000:100,000, frequently under reported
Allergic	• 100–400:100,000, product-dependent
TRALI	• 0.4–1:100,000, with mitigation, product-dependent
Delayed hemolytic	• 40:100,000
Acute hemolytic	• 2.5–7.9:100,000

Infections^a

Bacteria (septic transfusion reaction)	• 0.3–25:1,000,000 (product and detection- or pathogen-reduction-dependent)
Hepatitis B	• 1:300,000 (<1:1,000,000 ^b)
Hepatitis C ^b	• <0.1–1:1,000,000
HIV-1, ^b -2	• 0.1–1:1,000,000
HTLV-I and -II	• 1:3,000,000
Malaria	• 1:4,000,000

Other complications

RBC allosensitization	• 1:100
HLA allosensitization	• 1:10 (in the absence of leukodepletion)
Graft-versus-host disease	• Extremely rare (with blood product irradiation in immunosuppressed pts)

^aOther infectious agents associated with transfusion include arbovirus (West Nile virus, Dengue virus, Zika virus) hepatitis A and E virus, parvovirus B-19, *Babesia microti* and *Babesia duncani* (babesiosis), *Anaplasma phagocytophilum* (human granulocytic ehrlichiosis), *Trypanosoma cruzi* (Chagas disease), *Treponema pallidum*, and human herpesvirus-8. Frequency of infectious risks differs significantly worldwide.

^bWith nucleic acid testing (NAT) screening.

Abbreviations: FNHTR, febrile nonhemolytic transfusion reaction; HTLV, human T lymphotropic virus; RBC, red blood cell; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury.

if no platelet antibodies are present as a result of prior transfusions. Efficacy assessed by 1- and 24-h posttransfusion platelet counts. HLA-matched single-donor platelets may be required in pts with platelet alloantibodies.

■ TRANSFUSION OF PLASMA COMPONENTS

FFP is a source of coagulation factors, fibrinogen, antithrombin, and proteins C and S. It is used to correct coagulation factor deficiencies, rapidly reverse warfarin effects, and treat thrombotic thrombocytopenic purpura (TTP). Cryoprecipitate is a source of fibrinogen, factor VIII, and von Willebrand factor; it may be used when recombinant factor VIII or factor VIII concentrates are not available.

THERAPEUTIC HEMAPHERESIS

Hemapheresis is removal of a cellular or plasma constituent of blood; the specific procedure is referred to by the blood fraction removed.

■ LEUKAPHERESIS

Leukapheresis is the removal of WBCs; it is most often used in acute leukemia, especially acute myeloid leukemia (AML) in cases complicated by marked

elevation ($>100,000/\mu\text{L}$) of the peripheral blast count, to lower risk of leukostasis (blast-mediated vasoocclusive events resulting in central nervous system or pulmonary infarction, hemorrhage). Leukapheresis is replacing bone marrow aspiration to obtain hematopoietic stem cells. After treatment with a chemotherapeutic agent and granulocyte-macrophage colony-stimulating factor, hematopoietic stem cells are mobilized from marrow to the peripheral blood; such cells are leukapheresed and then used for hematopoietic reconstitution after high-dose myeloablative therapy. A third emerging medical use of leukapheresis is to harvest lymphocytes to use as adoptive immunotherapy.

■ PLATELETPHERESIS

Used in some pts with thrombocytosis associated with myeloproliferative disorders with bleeding and/or thrombotic complications. Other treatments are generally used first. Plateletpheresis also enhances platelet yield from blood donors.

■ PLASMAPHERESIS

Indications

(1) *Hyperviscosity states*—e.g., Waldenström's macroglobulinemia; (2) *TTP*; (3) *immune-complex and autoantibody disorders*—e.g., Goodpasture's syndrome, rapidly progressive glomerulonephritis, myasthenia gravis; possibly Guillain-Barré, systemic lupus erythematosus, idiopathic thrombocytopenic purpura; (4) cold agglutinin disease, cryoglobulinemia. In plasma exchange, abnormal proteins are removed and normal plasma or plasma components are replaced; useful in TTP to remove anti-ADAMTS13 antibody and provide normal ADAMTS13 levels.

10

Palliative and End-of-Life Care



In 2016, 2,744,248 people died in the United States; death rates are declining. Nearly three-fourth of all deaths occur in people >65 years old. Heart disease and cancer are the two leading causes of death and together account for nearly half of all deaths. About 70% of deaths occur in people who have a condition that is known to be leading to their death; thus, planning for terminal care is relevant and important. An increasing fraction of deaths are occurring in hospices or at home rather than in the hospital.

Optimal care depends on a comprehensive assessment of pt needs in all four domains affected by illness: physical, psychological, social, and spiritual. A variety of assessment tools are available to assist in the process.

Communication and continuous assessment of management goals are key components to addressing end-of-life care. Physicians must be clear about the likely outcome of the illness(es) and provide an anticipated schedule with goals and landmarks in the care process. When the goals of care have changed from cure to palliation, that transition must be clearly explained and defended. Seven steps are involved in establishing goals:

1. Ensure that the medical information is as complete as possible and understood by all relevant parties.
2. Explore the pt's goals while making sure the goals are achievable.
3. Explain the options.
4. Show empathy as the pt and the family adjust to changing expectations.

5. Make a plan with realistic goals.
6. Follow-through with the plan.
7. Review and revise the plan periodically as the pt's situation changes.

■ ADVANCE DIRECTIVES

About 70% of pts lack decision-making capacity in their final days. Advance directives define ahead of time the level of intervention the pt is willing to accept. Two types of legal documents can be used: the advance directive, in which specific instructions from the pt may be made known; and the durable attorney for health care, in which a person is designated as having the pt's authority to make health decisions on pt's behalf. Forms are available free of charge from the National Hospice and Palliative Care Organization (www.nhpco.org). Physicians also should complete these forms for themselves.

■ PHYSICAL SYMPTOMS AND THEIR MANAGEMENT

The most common physical and psychological symptoms among terminally ill pts are shown in [Table 10-1](#). Studies of pts with advanced cancer have shown that pts experience an average of 11.5 symptoms.

Pain

Pain is noted in 36–90% of terminally ill pts. The various types of pain and their management are discussed in [Chap. 6](#).

Constipation

Constipation is noted in up to 87% of terminally ill pts. Medications that commonly contribute to constipation include opioids used to manage pain and dyspnea and tricyclic antidepressants with their anticholinergic effects. Inactivity, poor diet, and hypercalcemia may contribute. GI tract obstruction also may play a role in some settings.

INTERVENTIONS Improved physical activity (if possible), adequate hydration; opioid effects can be antagonized by the μ -opioid receptor blocker methylbuprenorphine (8–12 mg SC daily); rule out surgically correctable obstruction; laxatives and stool softeners ([Table 10-2](#)).

TABLE 10-1 Common Physical and Psychological Symptoms of Terminally Ill Pts

PHYSICAL SYMPTOMS	PSYCHOLOGICAL SYMPTOMS
Pain	Anxiety
Fatigue and weakness	Depression
Dyspnea	Hopelessness
Insomnia	Meaninglessness
Dry mouth	Irritability
Anorexia	Impaired concentration
Nausea and vomiting	Confusion
Constipation	Delirium
Cough	Loss of libido
Swelling of arms or legs	
Itching	
Diarrhea	
Dysphagia	
Dizziness	
Fecal and urinary incontinence	
Numbness/tingling in hands/feet	

TABLE 10-2 Medications for the Management of Constipation

INTERVENTION	DOSE	COMMENT
Stimulant laxatives Prune juice Senna (Senokot) Bisacodyl	120–240 mL/d 2–8 tablets PO bid 5–15 mg/d PO, PR	These agents directly stimulate peristalsis and may reduce colonic absorption of water. Work in 6–12 h.
Osmotic laxatives Lactulose Magnesium hydroxide (Milk of Magnesia) Magnesium citrate	 15–30 mL PO q4–8h 15–30 mL/d PO 125–250 mL/d PO	These agents are not absorbed. They attract and retain water in the gastrointestinal tract. Lactulose may cause flatulence and bloating. Lactulose works in 1 day, magnesium products in 6 h.
Stool softeners Sodium docusate (Colace) Calcium docusate	300–600 mg/d PO 300–600 mg/d PO	These agents work by increasing water secretion and as detergents, increasing water penetration into the stool. Work in 1–3 days.
Suppositories and enemas Bisacodyl Sodium phosphate enema	10–15 PR qd PR qd	Fixed dose, 4.5 oz, Fleet's.

Nausea

Up to 70% of pts with advanced cancer have nausea. Nausea may result from uremia, liver failure, hypercalcemia, bowel obstruction, severe constipation, infection, gastroesophageal reflux disease, vestibular disease, brain metastases, medications (cancer chemotherapy, antibiotics, nonsteroidal anti-inflammatory drugs, opioids, proton pump inhibitors), and radiation therapy.

INTERVENTIONS Treatment should be tailored to the cause. Offending medications should be stopped. Underlying conditions should be alleviated, if possible. If decreased bowel motility is suspected, metoclopramide may help. Nausea from cancer chemotherapy agents can generally be prevented with glucocorticoids and serotonin receptor blockers like ondansetron or dolasetron. Aprepitant is useful in controlling nausea from highly emetogenic agents like cisplatin. Vestibular nausea may respond to antihistamines (meclizine) or anticholinergics (scopolamine). Anticipatory nausea may be prevented with a benzodiazepine such as lorazepam. Haloperidol is sometimes useful when the nausea does not have a single specific cause.

Dyspnea

Up to 75% of dying pts experience dyspnea. Dyspnea exerts perhaps the greatest adverse effect on the pt, often even more distressing than pain. It may be caused by parenchymal lung disease, infection, effusions, pulmonary emboli,

TABLE 10-3 Medications for the Management of Dyspnea

INTERVENTION	DOSE	COMMENTS
Weak opioids		For pts with mild dyspnea
Codeine (or codeine with 325-mg acetaminophen)	30 mg PO q4h	For opioid-naïve pts
Hydrocodone	5 mg PO q4h	
Strong opioids		For opioid-naïve pts with moderate to severe dyspnea
Morphine	5–10 mg PO q4h 30–50% of baseline opioid dose q4h	For pts already taking opioids for pain or other symptoms
Oxycodone	5–10 mg PO q4h	
Hydromorphone	1–2 mg PO q4h	
Anxiolytics		Give a dose every hour until the pt is relaxed, then provide a dose for maintenance
Lorazepam	0.5–2.0 mg PO/SL/IV qh then q4–6h	
Clonazepam	0.25–2.0 mg PO q12h	
Midazolam	0.5 mg IV q15 min	

pulmonary edema, asthma, or compressed airway. While many of the causes may be treated, often the underlying cause cannot be reversed.

INTERVENTIONS Underlying causes should be reversed, where possible, as long as the intervention is not more unpleasant (e.g., repeated thoracenteses) than the dyspnea. Most often the treatment is symptomatic (Table 10-3).

Fatigue

Fatigue is nearly a universal symptom in terminally ill pts. It is often a direct consequence of the disease process (and the cytokines produced in response to that process) and may be complicated by inanition, dehydration, anemia, infection, hypothyroidism, and drug effects. Depression may also contribute to fatigue. Functional assessments include the Karnofsky performance status or the Eastern Cooperative Oncology Group system based on how much time the pt spends in bed each day: 0, normal activity; 1, symptomatic without being bedridden; 2, in bed <50% of the day; 3, in bed >50% of the day; 4, bedbound.

INTERVENTIONS Modest exercise and physical therapy may reduce muscle wasting and depression and improve mood; discontinue medications that worsen fatigue, if possible; glucocorticoids may increase energy and enhance mood; dextroamphetamine (5–10 mg/d) or methylphenidate (2.5–5 mg/d) in the morning may enhance energy levels but should be avoided at night because they may produce insomnia; modafinil and L-carnitine have shown some promise.

Depression

Up to 75% of terminally ill pts experience depression. The inexperienced physician may feel that depression is an appropriate response to terminal illness; however, in a substantial fraction of pts the depression is more intense and disabling than usual. Pts with a previous history of depression are at greater risk. A number of treatable conditions can cause depression-like symptoms including hypothyroidism, Cushing's syndrome, electrolyte abnormalities (e.g., hypercalcemia), and drugs including dopamine blockers, interferon, tamoxifen, interleukin 2, vincristine, and glucocorticoids.

TABLE 10-4 Medications for the Management of Delirium

INTERVENTIONS	DOSE
Neuroleptics	
Haloperidol	0.5–5 mg q2–12h, PO/IV/SC/IM
Thioridazine	10–75 mg q4–8h, PO
Chlorpromazine	12.5–50 mg q4–12h, PO/IV/IM
Atypical neuroleptics	
Olanzapine	2.5–5 mg qd or bid, PO
Risperidone	1–3 mg q12h, PO
Quetiapine	25–50 mg qd, PO
Anxiolytics	
Lorazepam	0.5–2 mg q1–4h, PO/IV/IM
Midazolam	1–5 mg/h continuous infusion, IV/SC
Anesthetics	
Propofol	0.3–2.0 mg/h continuous infusion, IV

INTERVENTIONS Dextroamphetamine or methylphenidate (see above); serotonin reuptake inhibitors such as fluoxetine, paroxetine, and citalopram; modafinil 100 mg/d; pemoline 18.75 mg in the A.M. and at noon.

Delirium

Delirium is a global cerebral dysfunction associated with altered cognition and consciousness; it is frequently preceded by anxiety. Unlike dementia, it is of sudden onset, is characterized by fluctuating consciousness and inattention, and may be reversible. It is generally manifested in the hours before death. It may be caused by metabolic encephalopathy in renal or liver failure, hypoxemia, infection, hypercalcemia, paraneoplastic syndromes, dehydration, constipation, urinary retention, and central nervous system spread of cancer. It is also a common medication side effect; offending agents include those commonly used in dying pts including opioids, glucocorticoids, anticholinergics, antihistamines, antiemetics, and benzodiazepines. Early recognition is key because the pt should be encouraged to use the periods of lucidity for final communication with loved ones. Day-night reversal with changes in mentation may be an early sign.

INTERVENTIONS Stop any and all unnecessary medications that may have this side effect; provide a calendar, clock, newspaper, or other orienting signals; gently correct hallucinations or cognitive mistakes; pharmacologic interventions are shown in [Table 10-4](#).

CARE DURING THE LAST HOURS

The clinical course of a dying pt may largely be predictable. Informing families that these changes might occur can help minimize the distress that they cause. In particular, the physician needs to be sensitive to the sense of guilt and helplessness that family members feel. They should be reassured that the illness is taking its course and their care of the pt is not at fault in any way. The pt stops eating because they are dying; they are not dying because they have stopped eating. Families and caregivers should be encouraged to communicate directly with the dying pt whether or not the pt is unconscious. Holding the pt's hand may be a source of comfort to both the pt and the family member/caregiver. [Table 10-5](#) provides a listing of some changes in the pt's condition in the final hours and advice on how to manage the changes.

Additional resources for managing terminally ill pts may be found at the following websites: www.epec.net, www.capc.org, and www.nhpco.org.

TABLE 10-5 Managing Changes in the Pt's Condition during the Final Days and Hours

CHANGES IN THE PT'S CONDITION	POTENTIAL COMPLICATION	FAMILY'S POSSIBLE REACTION AND CONCERN	ADVICE AND INTERVENTION
Profound fatigue	Bedbound with development of pressure ulcers that are prone to infection, malodor, and pain, and joint pain	Pt is lazy and giving up.	Reassure family and caregivers that terminal fatigue will not respond to interventions and should not be resisted. Use an air mattress if necessary.
Anorexia	None	Pt is giving up; pt will suffer from hunger and will starve to death.	Reassure family and caregivers that the pt is not eating because he or she is dying; not eating at the end of life does not cause suffering or death. Forced feeding, whether oral, parenteral, or enteral, does not reduce symptoms or prolong life.
Dehydration	Dry mucosal membranes (see below)	Pt will suffer from thirst and die of dehydration.	Reassure family and caregivers that dehydration at the end of life does not cause suffering because pts lose consciousness before any symptom distress. IV hydration can worsen symptoms of dyspnea by pulmonary edema and peripheral edema as well as prolong dying process.
Dysphagia	Inability to swallow oral medications needed for palliative care		Do not force oral intake. Discontinue unnecessary medications that may have been continued, including antibiotics, diuretics, antidepressants, and laxatives. If swallowing pills is difficult, convert essential medications (analgesics, antiemetics, anxiolytics, and psychotropics) to oral solutions, buccal, sublingual, or rectal administration.
"Death rattle"—noisy breathing		Pt is choking and suffocating.	Reassure the family and caregivers that this is caused by secretions in the oropharynx and the pt is not choking. Reduce secretions with scopolamine (0.2–0.4 mg SC q4h or 1–3 patches q3d). Reposition pt to permit drainage of secretions. Do not suction. Suction can cause pt and family discomfort and is usually ineffective.

Apnea, Cheyne-Stokes respirations, dyspnea		Pt is suffocating.	Reassure family and caregivers that unconscious pts do not experience suffocation or air hunger. Apneic episodes are frequently a premonitory change. Opioids or anxiolytics may be used for dyspnea. Oxygen is unlikely to relieve dyspneic symptoms and may prolong the dying process.
Urinary or fecal incontinence	Skin breakdown if days until death Potential transmission of infectious agents to caregivers	Pt is dirty, malodorous, and physically repellent.	Remind family and caregivers to use universal precautions. Frequent changes of bedclothes and bedding. Use diapers, urinary catheter, or rectal tube if diarrhea or high urine output.
Agitation or delirium	Day/night reversal Hurt self or caregivers	Pt is in horrible pain and going to have a horrible death.	Reassure family and caregivers that agitation and delirium do not necessarily connote physical pain. Depending on the prognosis and goals of treatment, consider evaluating for causes of delirium and modify medications. Manage symptoms with haloperidol, chlorpromazine, diazepam, or midazolam.
Dry mucosal membranes	Cracked lips, mouth sores, and candidiasis can also cause pain. Odor	Pt may be malodorous, physically repellent.	Use baking soda mouthwash or saliva preparation q15–30 min. Use topical nystatin for candidiasis. Coat lips and nasal mucosa with petroleum jelly q60–90 min. Use ophthalmic lubricants q4h or artificial tears q30 min.

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11

Cardiovascular Collapse and Sudden Death



Unexpected cardiovascular collapse and death most often result from ventricular fibrillation in pts with atherosclerotic coronary artery disease or underlying structural heart conditions. The most common etiologies are listed in [Table 11-1](#). Arrhythmic causes may be provoked by electrolyte disorders (especially hypokalemia), hypoxemia, acidosis, or massive sympathetic discharge, as may occur in CNS injury. Immediate institution of cardiopulmonary resuscitation (CPR) followed by advanced life support measures (see below) is mandatory. Without institution of CPR within 4–6 min, ventricular fibrillation or asystole is usually fatal.

■ MANAGEMENT OF CARDIAC ARREST

Basic life support (BLS) must commence immediately ([Fig. 11-1](#)):

1. Phone emergency line (e.g., 911 in the United States); retrieve automated external defibrillator (AED) if available.
2. If respiratory stridor is present, assess for aspiration of a foreign body and perform Heimlich maneuver.

TABLE 11-1 Cardiac Arrest and Sudden Cardiac Death

Structural Associations and Causes

1. Coronary artery disease (chronic, or acute coronary syndromes)
2. Cardiomyopathies (dilated, hypertrophic, arrhythmogenic right ventricular cardiomyopathy, infiltrative disorders [e.g., amyloid])
3. Inflammatory (e.g., myocarditis)
4. Valvular heart disease (e.g., aortic stenosis, mitral valve prolapse)
5. Electrophysiologic abnormalities (e.g., Wolff-Parkinson-White syndrome)
6. Inherited disorders associated with electrophysiological abnormalities (e.g., congenital long QT syndromes, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia)

Functional Contributing Factors

1. Transient ischemia
2. Low cardiac output states (heart failure, shock)
3. Systemic metabolic abnormalities
 - a. Electrolyte imbalance (e.g., hypokalemia)
 - b. Hypoxemia, acidosis
4. Neurologic disturbances (e.g., CNS injury)
5. Toxic responses
 - a. Proarrhythmic drug effects
 - b. Cardiac toxins (e.g., cocaine, digitalis intoxication)

Causes of Pulseless Electrical Activity Leading to Sudden Death

1. Massive pulmonary embolism
2. Aortic dissection
3. Tension pneumothorax
4. Cardiac tamponade
5. Exsanguination

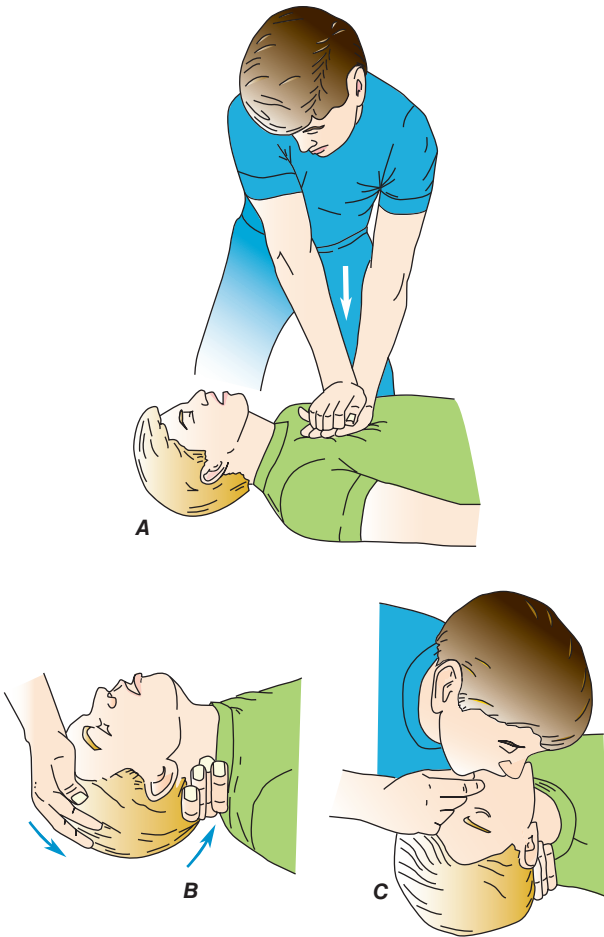


FIGURE 11-1 Major steps in cardiopulmonary resuscitation. **A.** Begin cardiac compressions at 100–120 compressions/min. **B.** Confirm that victim has an open airway. **C.** Trained rescuers begin ventilation if advanced life support equipment is not available (pocket mask preferred if available). (Modified from J Henderson: *Emergency Medical Guide*, 4th ed. New York, McGraw-Hill, 1978.)

3. Perform chest compressions (depressing sternum 5 cm) at rate of 100–120 per min without interruption. A second rescuer should attach and utilize AED.
4. If second rescuer is present and *trained*, tilt pt's head backward, lift chin, and begin rescue breathing (pocket mask is preferable to mouth-to-mouth respiration to prevent transmission of infection), while chest compressions continue. The lungs should be inflated twice in rapid succession for every 30 chest compressions. For *untrained* lay rescuers, chest compression only, without ventilation, is recommended until advanced life support capability arrives.
5. As soon as resuscitation equipment is available, begin **advanced life support** with continued chest compressions and ventilation. Although performed as simultaneously as possible, defibrillation (150–200 J biphasic) takes highest

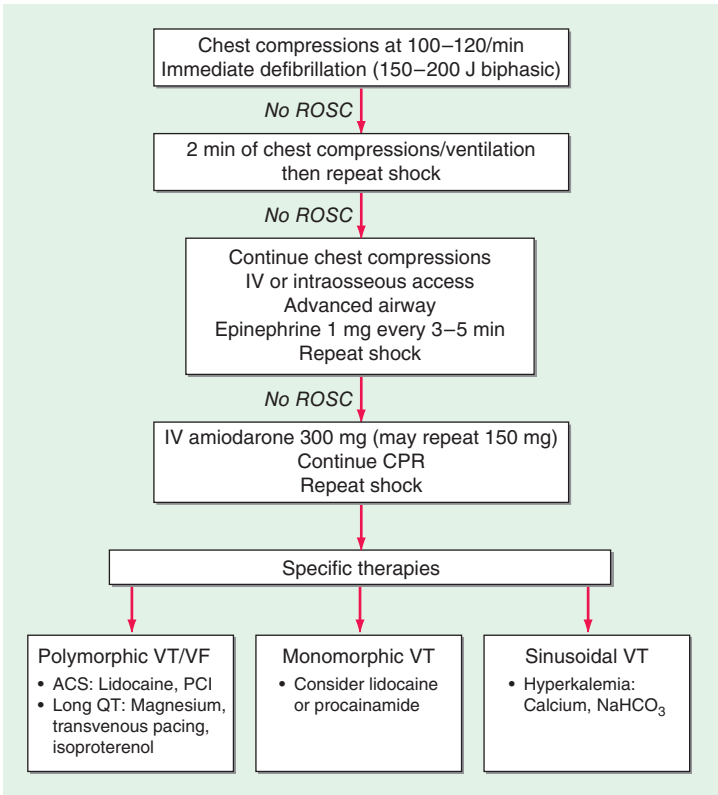


FIGURE 11-2 Management of cardiac arrest due to VF or VT. If metabolic acidosis persists after successful defibrillation and with adequate ventilation, also consider administration of 1 meq/kg NaHCO_3 . CPR, cardiopulmonary resuscitation; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia. (Modified from HPIM-20, Figure 299-3A.)

priority (Fig. 11-2), followed by establishment of IV access and insertion of an advanced airway (endotracheal tube or supraglottic) or bag-valve-mask device if an advanced airway cannot be achieved. One hundred percent O_2 should be administered initially. Once an advanced airway is placed, ventilate at rate of 1 breath every 6–8 s without interrupting chest compressions.

- Initial IV access should be through the antecubital vein, but if drug administration is ineffective, an intraosseous or central line (internal jugular or subclavian) should be placed. IV NaHCO_3 should be administered only if there is persistent severe acidosis ($\text{pH} < 7.15$) despite adequate ventilation. Calcium is not routinely administered but should be given to pts with known hypocalcemia, to those who have received toxic doses of calcium channel antagonists, or if hyperkalemia is thought to be the triggering event for resistant ventricular fibrillation.
- The approach to cardiovascular collapse caused by asystole, other bradyarrhythmic, or pulseless electrical activity is shown in Fig. 11-3.
- Therapeutic hypothermia (cooling to 32–36°C [89.6–96.8°F] for at least 24 h) should be considered for unconscious survivors of cardiac arrest.

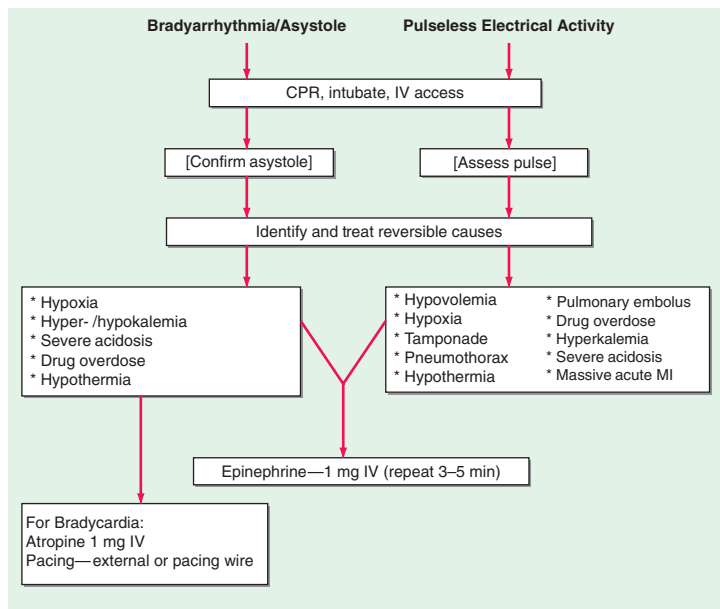


FIGURE 11-3 Algorithms for bradycardia/asystole (left) or pulseless electrical activity (right) are dominated by cardiopulmonary resuscitation (CPR) and a search for reversible causes. MI, myocardial infarction. (From Albert CM, Stevenson WG: *Cardiovascular collapse, cardiac arrest, and sudden cardiac death*, in Jameson JL et al (eds). *Harrison's Principles of Internal Medicine*, 20th ed. New York, NY: McGraw-Hill; 2018.)

■ FOLLOW-UP

If cardiac arrest resulted from ventricular fibrillation in initial hours of an acute MI, follow-up is standard post-MI care ([Chap. 121](#)). For other survivors of a ventricular fibrillation arrest, further assessment, including evaluation of coronary anatomy and left ventricular function is appropriate. In absence of a transient or reversible cause, placement of an implantable cardioverter defibrillator is usually indicated.

12

Shock



■ DEFINITION

Shock is a condition of severe impairment of tissue perfusion leading to cellular injury and dysfunction. Rapid recognition and treatment are essential to prevent irreversible organ damage and death. Common causes are listed in [Table 12-1](#).

■ CLINICAL MANIFESTATIONS

- Hypotension (mean arterial bp <60 mmHg), tachycardia, tachypnea, pallor, restlessness, and altered sensorium.

TABLE 12-1 Categories of Shock

Distributive shock (profound decrease in systemic vascular tone)
Sepsis
Pancreatitis
Anaphylaxis
Neurogenic (e.g., spinal cord injury)
Endocrine-related (Addison's disease, myxedema)
Cardiogenic shock
Myopathic (acute MI, fulminant myocarditis)
Mechanical (acute severe mitral regurgitation, acute severe aortic insufficiency [e.g., aortic dissection], severe aortic stenosis, acute VSD)
Arrhythmic
Obstructive shock
Pericardial tamponade
Massive pulmonary embolism
Tension pneumothorax
Hypovolemic shock
Hemorrhage
GI losses (vomiting, diarrhea)
Burns
Polyuria (diabetic ketoacidosis, diabetes insipidus)

Abbreviation: VSD, ventricular septal defect.

- Signs of intense peripheral vasoconstriction, with weak pulses and cold clammy extremities. In distributive (e.g., septic) shock, vasodilation predominates and extremities are warm.
- Oliguria (<20 mL/h) and metabolic acidosis common.
- Acute lung injury and acute respiratory distress syndrome (ARDS; see [Chap. 16](#)) with noncardiogenic pulmonary edema, hypoxemia, and diffuse pulmonary infiltrates.

APPROACH TO THE PATIENT

Shock

Obtain history for underlying causes, including cardiac disease (coronary disease, heart failure, pericardial disease), recent fever or infection leading to sepsis, drug effects (e.g., excess diuretics or antihypertensives), conditions leading to pulmonary embolism ([Chap. 135](#)), and potential sources of bleeding.

PHYSICAL EXAMINATION

Jugular veins are flat in oligemic or distributive (septic) shock; jugular venous distention (JVD) is typical in cardiogenic shock; JVD in presence of paradoxical pulse ([Chap. 112](#)) suggests cardiac tamponade ([Chap. 118](#)). Check for asymmetry of pulses (aortic dissection—[Chap. 127](#)). Assess for evidence of heart failure ([Chap. 126](#)), murmurs of aortic stenosis, acute mitral or aortic regurgitation, and

TABLE 12-2 Characteristics of Forms of Shock

TYPE OF SHOCK	CVP	PCWP	CARDIAC OUTPUT	SYSTEMIC VASCULAR RESISTANCE
Distributive	↓	↓	↑	↓
Cardiogenic	↑	↑	↓	↑
Obstructive	↑	↓↑	↓	↑
Hypovolemic	↓	↓	↓	↑

Abbreviations: CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure.

ventricular septal defect. Tenderness or rebound in abdomen may indicate peritonitis or pancreatitis; high-pitched bowel sounds suggest intestinal obstruction. Assess stool for GI bleeding.

Fever and chills typically accompany septic shock. Sepsis may not cause fever in elderly, uremic, or alcoholic pts. Skin lesions may suggest specific pathogens in septic shock (see [Chap. 14](#)).

LABORATORY

Obtain lactate, CBC, renal and liver function tests, PT, PTT, and cardiac troponin if myocardial ischemia, myocarditis, or pulmonary embolism is suspected. Arterial blood gas usually shows metabolic acidosis (in septic shock, respiratory alkalosis precedes metabolic acidosis). If sepsis is suspected, draw blood cultures, perform urinalysis, and obtain cultures of sputum, urine, and other suspected sites.

Obtain ECG (myocardial ischemia/infarction or acute arrhythmia) and chest x-ray (heart failure, tension pneumothorax, pneumonia). Echocardiography is often diagnostic of underlying cause (e.g., cardiac tamponade, left/right ventricular dysfunction, aortic dissection, right ventricular strain due to pulmonary embolism).

CVP or pulmonary capillary wedge (PCW) pressure measurements may be necessary to distinguish between different categories of shock ([Table 12-2](#)): Mean PCW <6 mmHg suggests hypovolemic or distributive shock; PCW >20 mmHg suggests left ventricular failure/cardiogenic shock. Cardiac output is decreased in cardiogenic, hypovolemic, and obstructive shock, and increased in distributive shock.

INITIAL TREATMENT OF SHOCK ([FIG. 12-1](#))

Aimed at rapid improvement of tissue hypoperfusion and respiratory impairment while underlying cause of shock is investigated:

- Serial measurements of bp (intraarterial line preferred), heart rate, continuous ECG monitor, urine output, pulse oximetry, blood studies: Hct, electrolytes, creatinine, BUN, ABGs, pH, calcium, phosphate, lactate, urine Na concentration (<20 mmol/L suggests volume depletion). Consider monitoring of CVP and/or pulmonary artery pressure/PCW pressures in pts with ongoing blood loss, marked fluid shifts, or suspected cardiac dysfunction (majority of pts do *not* require pulmonary artery catheter monitoring).
- Insert urinary catheter to monitor urine output.
- Assess mental status frequently.
- Augment systolic bp to >100 mmHg: (1) Temporarily place in reverse Trendelenburg position; (2) IV volume infusion (500- to 1000-mL bolus), unless cardiogenic shock suspected (begin with crystalloid [normal saline or Ringer's

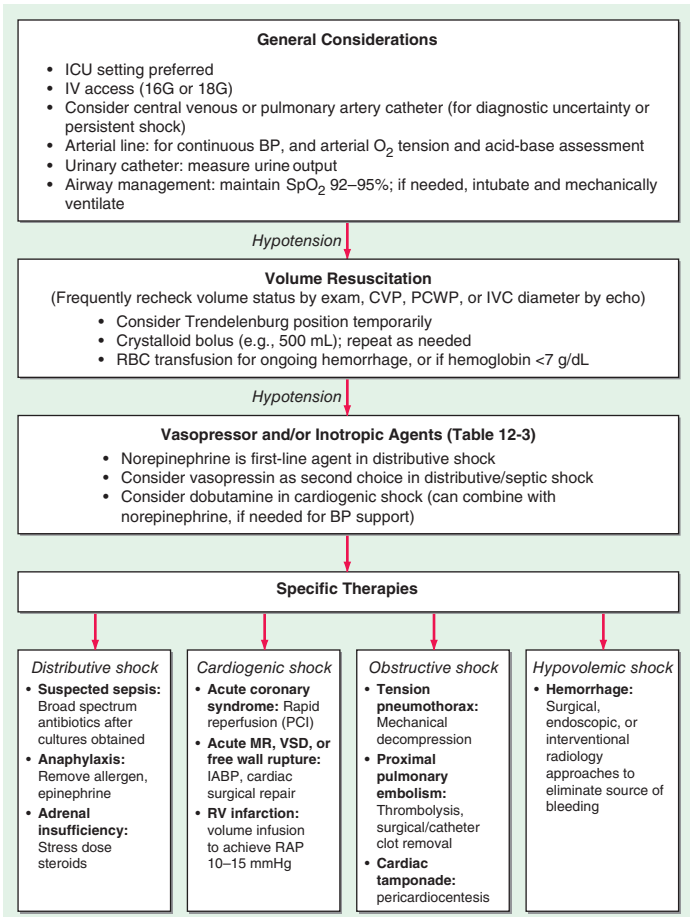


FIGURE 12-1 Initial treatment algorithm in shock states. BP, blood pressure; Echo, echocardiogram; IABP, intraaortic balloon pump; ICU, intensive care unit; PCI, percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure; RBC, red blood cell; RV, right ventricular.

lactate]; consider transfusion as part of fluid resuscitation, especially if Hgb <7 g/dL); continue volume replacement as needed to restore vascular volume.

- Add vasoactive drugs after intravascular volume is optimized; administer vasopressors (Table 12-3) if systemic vascular resistance (SVR) is decreased (norepinephrine preferred; for persistent hypotension, add vasopressin or phenylephrine).
- For cardiogenic shock, add inotropic agent (usually dobutamine) (Table 12-3); aim to maintain cardiac index >2.2 (L/m²)/min [>4.0 (L/m²)/min in septic shock].
- Administer supplemental O₂ to maintain SpO₂ 92–95%; intubate with mechanical ventilation if necessary.

TABLE 12-3 Vasopressors Used in Shock States^a

DRUG	DOSE	NOTES
Dopamine	1–2 µg/kg per min 2–10 µg/kg per min 10–20 µg/kg per min	Facilitates diuresis Positive inotropic and chronotropic effects; may increase O ₂ consumption as well as O ₂ delivery; use may be limited by tachycardia Generalized vasoconstriction (decreased renal perfusion)
Norepinephrine	0.5–30 µg/min	Potent vasoconstrictor; moderate inotropic effect; may be chosen over dopamine in sepsis due to less chronotropic and adverse effects; may be useful in cardiogenic shock with reduced SVR but should generally be reserved for refractory hypotension
Dobutamine	2–20 µg/kg per min	Primarily for cardiogenic shock (Chap. 121): positive inotrope; lacks vasoconstrictor activity; most useful when only mild hypotension present and avoidance of tachycardia desired
Phenylephrine	40–180 µg/min	Potent vasoconstrictor without inotropic effect; may be useful in distributive shock
Vasopressin	0.01–0.04 U/min	Occasionally used in refractory septic (distributive) shock

^aIsoproterenol not recommended in shock states because of potential hypotension and arrhythmogenic effects.

Abbreviation: SVR, systemic vascular resistance.

- If severe metabolic acidosis is present (pH <7.15), administer NaHCO₃.
- Identify and treat underlying cause of shock. Cardiogenic shock in acute MI is discussed in **Chap. 121**. Emergent coronary revascularization may be lifesaving if persistent ischemia is present.

SEPTIC SHOCK

See **Chap. 14**.

13

Narcotic Overdose

Lethal overdose is a relatively common complication of opioid use disorder (**Chap. 203**). Nearly 50,000 overdose deaths involving opioids occur annually in the United States, and these numbers continue to increase and have accelerated due to mixing high potency fentanyl derivatives with heroin. The accelerating death rates are partially because reversal of fentanyl overdoses can require

several-fold larger doses of naloxone than the doses in the intranasal devices used for nonmedical street resuscitations. Diagnosis is based on recognition of characteristic signs and symptoms, including shallow and slow respirations, pupillary miosis (mydriasis does not occur until significant brain anoxia supervenes), bradycardia, hypothermia, and stupor or coma; adulterants can also produce an “allergic-like” reaction characterized by decreased alertness, frothy pulmonary edema, and an elevated blood eosinophil count. Opioids generally do not produce seizures except for unusual cases of polydrug use with the opioid meperidine or with high doses of tramadol. Blood or urine toxicology studies can confirm a diagnosis, but immediate management must be based on clinical criteria.

Rapid recognition and treatment with naloxone, a highly specific reversal agent that is relatively free of complications, is essential. If naloxone is not administered, progression to respiratory and cardiovascular collapse leading to death occurs.

TREATMENT

Narcotic Abuse

Managing overdose requires support of vital functions, including intubation if needed, plus naloxone (Table 13-1). The goal is to reverse the respiratory depression and not to administer so much naloxone that it precipitates opiate withdrawal. Because naloxone only lasts a few hours and most opioids last considerably longer, an IV naloxone drip with close monitoring is frequently employed to provide a continuous level of antagonism for 24–72 h depending on the opioid used in the overdose (e.g., morphine vs methadone).

If the overdose is due to buprenorphine, naloxone might be required at total doses of 10 mg or greater, but primary buprenorphine overdose is nearly impossible because this agent is a partial opioid agonist; as the dose of buprenorphine is increased it has greater opioid antagonist than agonist activity. Thus, a 0.2-mg buprenorphine dose leads to analgesia and sedation, while a hundred times greater 20-mg dose produces profound opioid antagonism, precipitating opioid withdrawal in a person who had opioid use disorder on morphine or methadone.

When naloxone has only a limited effect, consider other sedative drugs, especially benzodiazepines which have produced overdoses and deaths in combination with buprenorphine. A specific antagonist for benzodiazepines—flumazenil at 0.2 mg/min—can be given to a maximum of 3 g/h, but it may precipitate seizures and increase intracranial pressure. Like naloxone, administration for a prolonged period is usually required because most benzodiazepines remain active for considerably longer than flumazenil.

TABLE 13-1 Management of Opioid Overdose

Establish airway. Intubation and mechanical ventilation may be necessary.

Naloxone 0.4–2.0 mg (IV, IM, or endotracheal tube). Onset of action with IV is ~1–2 min.

Repeat doses of naloxone if needed to restore adequate respiration or a continuous infusion of naloxone can be used.

One-half to two-thirds of the initial naloxone dose that reversed the respiratory depression is administered on an hourly basis (note: naloxone dosing is not necessary if the pt has been intubated).

Support of vital functions may include oxygen and positive-pressure breathing, IV fluids, pressor agents for hypotension, and cardiac monitoring to detect QT prolongation, which might require specific treatment. Activated charcoal and gastric lavage may be helpful for oral ingestions, but intubation will be needed if the pt is stuporous.

14

Sepsis and Septic Shock



DEFINITIONS

- *Sepsis*: a life-threatening organ dysfunction caused by a dysregulated host response to infection.
- *Septic shock*: a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities lead to substantially increased mortality risk. Pts need vasopressor therapy to elevate mean arterial pressure to ≥ 65 mmHg with a serum lactate concentration >2.0 mmol/L despite adequate fluid resuscitation.

ETIOLOGY

- Pneumonia is the most common antecedent infection, accounting for ~50% of cases of sepsis; intraabdominal and genitourinary infections are the next most common sources.
- Blood cultures are positive in approximately one-third of cases.
- Microbiologic results have revealed that 62% of isolates are gram-negative bacteria (most commonly *Pseudomonas aeruginosa*, *Klebsiella* spp., and *Escherichia coli*), 47% are gram-positive bacteria (most commonly *Staphylococcus aureus* and *Streptococcus pneumoniae*), and 19% are fungi, with some cultures being polymicrobial.

EPIDEMIOLOGY

- The incidence of sepsis in the United States is >2 million cases each year, with shock documented in ~30% of cases (19 per 1000 hospitalized encounters). This figure represents a rise of nearly 50% in the past decade; the reasons for this increase may include nonmedical issues.
- The rates of sepsis and septic shock are likely to be much higher in low- and middle-income countries, with mortality rates $>40\%$.

PATHOPHYSIOLOGY

- The host response evolves throughout the pt's course, with early proinflammatory reactions directed at eliminating pathogens responsible for "collateral" tissue damage and subsequent anti-inflammatory responses implicated in increased susceptibility to secondary infections.
- Hosts have numerous pattern recognition receptors whose recognition of highly conserved pathogen-associated molecular patterns (PAMPs; e.g., lipopolysaccharide) and damage-associated molecular patterns (DAMPs; e.g., extracellular RNA, DNA, and histones) triggers the release of inflammatory cytokines and activation of the complement system and platelet-activating factor.
- Impaired tissue oxygenation plays a key role in sepsis-associated organ failure.

CLINICAL FEATURES

- The two most commonly affected organ systems are the respiratory system, in which dysfunction classically manifests as the acute respiratory distress syndrome, and the cardiovascular system, in which dysfunction typically presents as hypotension.
- Acute kidney injury, which is found in >50% of septic pts, increases the risk of in-hospital death by six- to eightfold.
- Typical CNS dysfunction presents as coma or delirium.
- Many other abnormalities occur in sepsis, including ileus, DIC, and sick euthyroid syndrome. Adrenal dysfunction, the diagnosis of which is difficult to establish in these pts, is more commonly due to reversible dysfunction of the hypothalamic-pituitary axis or tissue glucocorticoid resistance than to direct damage to the adrenal gland.

DIAGNOSIS

There is no gold-standard method for determining whether a pt is septic.

- In pts with a suspected infection, the SOFA (sepsis-related organ failure assessment) score synthesizes vital signs and lab tests across six organ systems to help define whether the pt is septic. The score ranges from 0 to 24; pts with ≥ 2 new SOFA points are considered septic and are at $\geq 10\%$ risk of in-hospital death.
- The quickSOFA (qSOFA) score is a simpler algorithm that can be computed at the bedside. Pts are given 1 point each for systolic hypotension (≤ 100 mmHg), tachypnea (≥ 22 breaths/min), or altered mentation. A qSOFA score of ≥ 2 has a predictive value for sepsis similar to that of the SOFA score.
- Lactate levels are typically elevated in sepsis (≥ 2.5 mmol/L) but should not be used as a stand-alone biomarker for sepsis as they can occur in many other clinical conditions or may simply represent impaired clearance.

TREATMENT

Sepsis and Septic Shock

- Early treatment of sepsis and septic shock is best summarized by two “bundles” of care:
 1. Within 3 h of presentation (ideally within the first hour), the pt should be given appropriate broad-spectrum antibiotics (see [Table 14-1](#) for regimens), with collection of blood for culture before antibiotic administration and measurement of serum lactate levels.
 - For every 1-h delay in the initiation of antibiotic administration to pts with sepsis, there is a 3–7% increase in the odds of in-hospital death.
 2. Within 6 h of presentation, the pt should receive an IV fluid bolus and treatment with vasopressors for persistent hypotension or shock, and serum lactate levels should be re-measured.
 - More than 30% of pts with severe sepsis require source control, mainly for abdominal, urinary, and soft-tissue infections.
- Subsequent treatment of sepsis requires ongoing hemodynamic monitoring, support of organ function (e.g., provision of IV fluids, administration of blood products, and respiratory support, as needed), and—once the pt’s condition stabilizes—de-escalation of care.

TABLE 14-1 Initial Antimicrobial Therapy for Severe Sepsis with No Obvious Source in Adults with Normal Renal Function

CLINICAL CONDITION	ANTIMICROBIAL REGIMENS ^a
Septic shock (immunocompetent adult)	The many acceptable regimens include (1) piperacillin-tazobactam (3.375–4.5 g q6h), (2) cefepime (2 g q12h), or (3) meropenem (1 g q8h) or imipenem-cilastatin (0.5 g q6h). If the pt is allergic to β -lactam antibiotics, use (1) aztreonam (2 g q8h) or (2) ciprofloxacin (400 mg q12h) or levofloxacin (750 mg q24h). Add vancomycin (loading dose of 25–30 mg/kg, then 15–20 mg/kg q8–12h) to each of the above regimens.
Neutropenia (<500 neutrophils/ μ L)	Regimens include (1) cefepime (2 g q8h), (2) meropenem (1 g q8h) or imipenem-cilastatin (0.5 g q6h) or doripenem (500 mg q8h), or (3) piperacillin-tazobactam (3.375 g q4h). Add vancomycin (as above) if the pt has a suspected central line–associated bloodstream infection, severe mucositis, skin/soft tissue infection, or hypotension. Add tobramycin (5–7 mg/kg q24h) plus vancomycin (as above) plus caspofungin (one dose of 70 mg, then 50 mg q24h) if the pt has severe sepsis/septic shock.
Splenectomy	Use ceftriaxone (2 g q24h, or—in meningitis—2 g q12h). If the local prevalence of cephalosporin-resistant pneumococci is high, add vancomycin (as above). If the pt is allergic to β -lactam antibiotics, use levofloxacin (750 mg q24h) or moxifloxacin (400 mg q24h) plus vancomycin (as above).

^aAll agents are administered by the intravenous route.

Source: Adapted in part from DN Gilbert et al: *The Sanford Guide to Antimicrobial Therapy*, 47th ed, 2017; and from RS Munford: Sepsis and septic shock, in DL Kasper et al (eds). *Harrison's Principles of Internal Medicine*, 19th ed. New York, McGraw-Hill, 2015, p. 1757.

■ PROGNOSIS

The mortality rate from sepsis and septic shock is ~20%. Survivors remain at increased risk of death in the following months and years, and they often suffer from impaired physical or neurocognitive dysfunction, mood disorders, and low quality of life.

■ PREVENTION

The number of sepsis cases could be reduced by avoiding unnecessary antibiotic use, limiting the use of indwelling devices and catheters, minimizing unnecessary immune suppression, and increasing adherence to infection control programs at hospitals and clinics.

15 Acute Pulmonary Edema

Life-threatening, acute development of alveolar lung edema due to one or more of the following:

1. Elevation of hydrostatic pressure in the pulmonary capillaries (left heart failure, mitral valve disease).
2. Specific precipitants (Table 15-1), resulting in cardiogenic pulmonary edema in pts with previously compensated heart failure or without previous cardiac history.
3. Increased permeability of pulmonary alveolar-capillary membrane (noncardiogenic pulmonary edema). For common causes, see Table 15-2.

■ PHYSICAL FINDINGS

Pt appears severely ill, often diaphoretic, sitting bolt upright, tachypneic, and cyanosis may be present. Bilateral pulmonary rales; third heart sound may be present. Frothy, blood-tinged sputum may occur.

■ LABORATORY

Early arterial blood gases show reductions of both PaO_2 and PaCO_2 . With progressive respiratory failure, hypercapnia develops with acidemia. CXR shows pulmonary vascular redistribution, diffuse haziness in lung fields with perihilar "butterfly" appearance.

TREATMENT

Acute Pulmonary Edema

Immediate, aggressive therapy is mandatory for survival. The following measures should be instituted as simultaneously as possible for cardiogenic pulmonary edema:

1. Administer supplemental oxygen to achieve O_2 saturation $\geq 92\%$; if inadequate, use positive-pressure ventilation by face or nasal mask, and if necessary, endotracheal intubation.
2. Reduce preload:
 - a. Seat pt upright to reduce venous return, if not hypotensive.
 - b. Intravenous loop diuretic (e.g., furosemide, initially 0.5–1.0 mg/kg); use lower dose if pt does not take diuretics chronically.

TABLE 15-1 Precipitants of Acute Pulmonary Edema

Acute tachy- or bradyarrhythmia
Infection, fever
Acute MI
Severe hypertension
Acute mitral or aortic regurgitation
Increased circulating volume (Na^+ ingestion, blood transfusion, pregnancy)
Increased metabolic demands (exercise, hyperthyroidism)
Pulmonary embolism
Noncompliance (sudden discontinuation) of chronic heart failure medications

TABLE 15-2 Common Causes of Noncardiogenic Pulmonary Edema**Direct Injury to Lung**

Chest trauma, pulmonary contusion	Pneumonia
Aspiration	Oxygen toxicity
Smoke inhalation	Pulmonary embolism, reperfusion

Hematogenous Injury to Lung

Sepsis	Multiple transfusions
Pancreatitis	IV drug use, e.g., heroin
Nonthoracic trauma	Cardiopulmonary bypass

Possible Lung Injury Plus Elevated Hydrostatic Pressures

High-altitude pulmonary edema	Reexpansion pulmonary edema
Neurogenic pulmonary edema	

- c. Nitroglycerin (sublingual 0.4 mg \times 3 q5min) followed by 5–20 μ g/min IV if needed.
 - d. Morphine 2–4 mg IV acts as a venodilator and may relieve dyspnea and anxiety; use with caution and assess frequently for hypotension or respiratory depression; naloxone should be available to reverse effects if necessary.
 - e. Consider ACE inhibitor if pt is hypertensive, or in setting of acute MI with heart failure.
 - f. Consider nesiritide (recombinant brain natriuretic peptide; 2- μ g/kg bolus IV followed by 0.01 μ g/kg per min) for refractory symptoms—do not use in acute MI or cardiogenic shock.
3. Inotropic agents are indicated in cardiogenic pulmonary edema and severe LV dysfunction: dopamine, dobutamine, milrinone (**Chap. 12**).
 4. The precipitating cause of cardiogenic pulmonary edema (Table 15-1) should be sought and treated, particularly acute arrhythmias or infection. For refractory pulmonary edema associated with persistent cardiac ischemia, early coronary revascularization may be life-saving. For noncardiac pulmonary edema, identify and treat/remove cause (Table 15-2).

16

Acute Respiratory Distress Syndrome


DEFINITION AND ETIOLOGY

Acute respiratory distress syndrome (ARDS) develops rapidly and includes severe dyspnea, diffuse pulmonary infiltrates, and hypoxemia; it typically causes respiratory failure. Key diagnostic criteria for ARDS include (1) diffuse bilateral pulmonary infiltrates on CXR; (2) PaO₂ (arterial partial pressure of oxygen in mmHg)/FIO₂ (inspired O₂ fraction) \leq 300 mmHg; (3) absence of elevated left atrial pressure; and (4) acute onset within 1 week of a clinical insult or new or worsening respiratory symptoms. Although many medical and surgical conditions can cause ARDS, most cases (>80%) result from sepsis, pneumonia, trauma, multiple blood transfusions, gastric acid aspiration, and drug overdose. Individuals with more than one predisposing factor have a greater risk of developing

ARDS. Other risk factors include older age, chronic alcohol abuse, metabolic acidosis, pancreatitis, and overall severity of critical illness.

■ CLINICAL COURSE AND PATHOPHYSIOLOGY

There are three phases in the natural history of ARDS:

1. *Exudative phase*: Characterized by alveolar edema and neutrophil inflammation, with subsequent development of hyaline membranes from diffuse alveolar damage. The alveolar edema, which is most prominent in the dependent portions of the lung, causes atelectasis and reduced lung compliance. Hypoxemia, tachypnea, and progressive dyspnea develop, and increased pulmonary dead space can also lead to hypercarbia. Respiratory failure frequently develops during this phase. CXR reveals bilateral opacities consistent with pulmonary edema. The differential diagnosis is broad, but common alternative etiologies to consider are cardiogenic pulmonary edema, bilateral pneumonia, and alveolar hemorrhage. Unlike cardiogenic pulmonary edema, the CXR in ARDS rarely shows cardiomegaly, pleural effusions, or pulmonary vascular redistribution. The exudative phase duration is typically up to 7 days in length and usually begins within 12–36 h after the inciting insult.
2. *Proliferative phase*: This phase typically lasts from approximately days 7 to 21 after the inciting insult. Although most pts recover, some will develop progressive lung injury and evidence of pulmonary fibrosis. Even among pts who show rapid improvement allowing removal of mechanical ventilatory support, dyspnea and hypoxemia often persist during this phase.
3. *Fibrotic phase*: Although the majority of pts recover within 3–4 weeks of the initial pulmonary injury, some experience progressive fibrosis, necessitating prolonged ventilatory support and/or supplemental O₂. Increased risk of pneumothorax, reductions in lung compliance, and increased pulmonary dead space are observed during this phase.

TREATMENT

ARDS

Progress in recent therapy has emphasized the importance of general critical care of pts with ARDS in addition to lung protective ventilatory strategies. General care requires treatment of the underlying medical or surgical problem that caused lung injury, minimizing iatrogenic complications, prophylaxis to prevent venous thromboembolism and GI hemorrhage, prompt treatment of nosocomial infections, and adequate nutritional support. An algorithm for the initial management of ARDS is presented in [Fig. 16-1](#).

MECHANICAL VENTILATORY SUPPORT

Pts with ARDS typically require mechanical ventilatory support due to hypoxemia and increased work of breathing. A substantial improvement in outcomes from ARDS occurred with the recognition that mechanical ventilator–related overdistention of normal lung units with positive pressure can produce or exacerbate lung injury, causing or worsening ARDS. Currently recommended ventilator strategies limit alveolar distention but maintain adequate tissue oxygenation.

It has been clearly shown that low tidal volumes (≤ 6 -mL/kg predicted body weight) provide reduced mortality compared with higher tidal volumes (12-mL/kg predicted body weight). In ARDS, alveolar collapse can occur due to alveolar/interstitial fluid accumulation and loss of surfactant, thus worsening hypoxemia. Therefore, low tidal volumes are combined with the use of positive end-expiratory pressure (PEEP) at levels that strive to minimize alveolar

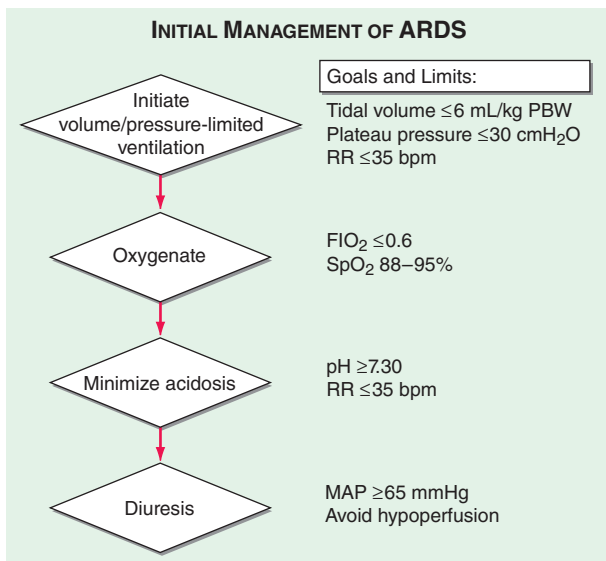


FIGURE 16-1 Algorithm for the initial management of ARDS. Clinical trials have provided evidence-based therapeutic goals for a stepwise approach to the early mechanical ventilation, oxygenation, and correction of acidosis and diuresis of critically ill pts with ARDS. FIO₂, inspired O₂ percentage; MAP, mean arterial pressure; PBW, predicted body weight; RR, respiratory rate; SpO₂, arterial oxyhemoglobin saturation measured by pulse oximetry.

collapse and achieve adequate oxygenation with the lowest required FIO₂. Use of PEEP levels higher than necessary to optimize oxygenation has not been proven to reduce ARDS mortality. Measurement of esophageal pressures to estimate transpulmonary pressure may help to identify an optimal level of PEEP. Other techniques that may improve oxygenation include placing the pt in the prone position; however, experience in repositioning critically ill pts is required.

ANCILLARY THERAPIES

Pts with ARDS have increased pulmonary vascular permeability leading to interstitial and alveolar edema. Therefore, they should receive IV fluids only as needed to achieve adequate cardiac output and tissue O₂ delivery as assessed by urine output, acid-base status, and arterial pressure. A randomized, placebo-controlled clinical trial suggested that neuromuscular blockage with cisatracurium for 48 h could potentially reduce mortality in severe ARDS. Lung-replacement therapy with extracorporeal membrane oxygenation (ECMO) may have utility in selected adult pts with severe ARDS. There is not convincing evidence currently to support the use of glucocorticoids or nitric oxide in ARDS.

OUTCOMES

Mortality from ARDS has declined with improvements in general critical care treatment and with the introduction of low tidal volume ventilation. Current mortality from ARDS is 35–46%, with most deaths due to sepsis and nonpulmonary organ failure. Increased risk of mortality from ARDS is associated with advanced age, preexisting organ dysfunction (e.g., chronic conditions of liver

disease, alcohol abuse, immunosuppression, or renal disease). Increased mortality has also been associated with ARDS related to direct lung injury (e.g., pneumonia, pulmonary contusion, and aspiration) compared with indirect lung injury (e.g., sepsis, trauma, and pancreatitis). Most surviving ARDS pts do not have significant long-term pulmonary disability.

17 Respiratory Failure



■ DEFINITION AND CLASSIFICATION OF RESPIRATORY FAILURE

Respiratory failure is defined as inadequate gas exchange due to malfunction of one or more components of the respiratory system. There are two main types of acute respiratory failure: hypoxemic and hypercarbic. Hypoxemic respiratory failure is defined by arterial O_2 saturation $<90\%$ while receiving an increased inspired O_2 fraction. Acute hypoxemic respiratory failure can result from pneumonia, pulmonary edema (due to elevated pulmonary microvascular pressures in heart failure and intravascular volume overload, or with normal pulmonary microvascular pressures in acute respiratory distress syndrome [ARDS]), and alveolar hemorrhage. Hypoxemia results from ventilation-perfusion mismatch and intrapulmonary shunting. Lung injury in ARDS can be worsened by mechanical ventilation, and lower tidal volumes can reduce lung injury.

Hypercarbic respiratory failure is characterized by alveolar hypoventilation and respiratory acidosis. Hypercarbic respiratory failure results from decreased minute ventilation and/or increased physiologic dead space. Conditions associated with hypercarbic respiratory failure include neuromuscular diseases (e.g., myasthenia gravis), disease processes causing diminished respiratory drive (e.g., drug overdose, brainstem injury), and respiratory diseases associated with respiratory muscle fatigue (e.g., exacerbations of asthma and chronic obstructive pulmonary disease [COPD]). The primary therapeutic goal in hypercarbic respiratory failure is to reverse the underlying cause of respiratory failure. Noninvasive positive-pressure ventilation may be effective, especially in COPD exacerbations.

Two other types of respiratory failure are commonly considered: (1) perioperative respiratory failure related to lung atelectasis, which can be treated with physiotherapy, positional changes, and/or noninvasive positive-pressure ventilation; and (2) hypoperfusion of respiratory muscles related to shock, which typically improves with intubation and mechanical ventilation.

■ MONITORING PTS ON MECHANICAL VENTILATION

For intubated pts receiving volume-controlled modes of mechanical ventilation, respiratory mechanics can be followed easily. The peak airway pressure is regularly measured by mechanical ventilators, and the plateau pressure can be assessed by including an end-inspiratory pause. The inspiratory airway resistance is calculated as the difference between the peak and plateau airway pressures (with adjustment for flow rate). Increased airway resistance can result from bronchospasm, respiratory secretions, or a kinked endotracheal tube. Static compliance of the respiratory system is calculated as the tidal volume divided by the gradient in airway pressure (plateau pressure minus PEEP). Reduced respiratory system compliance can result from pleural effusions, pneumothorax, pneumonia, pulmonary edema, or auto-PEEP (elevated end-expiratory pressure related to insufficient time for alveolar emptying before the next inspiration).

TREATMENT**The Mechanically Ventilated Pt**

Many pts receiving mechanical ventilation require treatment for pain (typically with opiates) and for anxiety (non-benzodiazepine sedatives are preferred since benzodiazepines are associated with worse pt outcomes). Protocol-driven approaches to sedation or daily interruption of sedative infusions can prevent excessive sedative drug accumulation. Less commonly, neuromuscular blocking agents (e.g., cisatracurium) are required to facilitate ventilation when there is extreme dyssynchrony between the pt's respiratory efforts and the ventilator that cannot be corrected with manipulation of the ventilator settings; aggressive sedation is required during treatment with neuromuscular blockers. Neuromuscular blocking agents should be used with caution because a myopathy associated with prolonged weakness can result.

Weaning from mechanical ventilation should be considered when the disease process prompting intubation has improved. Daily screening of intubated pts for weaning potential should be performed. Stable oxygenation (with oxygen supplementation levels that are achievable off of mechanical ventilation and at low positive end-expiratory pressure [PEEP] levels), intact cough and airway reflexes, and lack of requirement for vasopressor agents are required before considering a trial of weaning from mechanical ventilation. The most effective approach for weaning is usually a spontaneous breathing trial, which involves 30–120 min of breathing without significant ventilatory support. Either an open T-piece breathing system or minimal amounts of ventilatory support (pressure support to overcome resistance of the endotracheal tube and/or low levels of continuous positive airway pressure [CPAP]) can be used. Failure of a spontaneous breathing trial has occurred if tachypnea (respiratory rate <35 breaths/min for >5 min), hypoxemia (O_2 saturation $<90\%$), tachycardia (>140 beats/min or 20% increase from baseline), bradycardia (20% reduction from baseline), hypotension (systolic blood pressure <90 mmHg), hypertension (systolic blood pressure >180 mmHg), increased anxiety, or diaphoresis develops. At the end of the spontaneous breathing trial, the *rapid shallow breathing index* (RSBI or f/VT), which is calculated as respiratory rate in breaths/min divided by tidal volume in liters, can be used to predict weanability. An f/VT value <105 at the end of the spontaneous breathing test warrants a trial of extubation. Daily interruption of sedative infusions in conjunction with spontaneous breathing trials can limit excessive sedation and shorten the duration of mechanical ventilation. Despite careful weaning protocols, up to 10% of pts develop respiratory distress after extubation and may require reintubation.

18**Confusion, Stupor, and Coma****APPROACH TO THE PATIENT****Disorders of Consciousness**

Disorders of consciousness are common; these always signify a disorder of the nervous system. Assessment should determine the level of consciousness (drowsy, stuporous, comatose) and/or content of consciousness (confusion,

perseveration, hallucinations). *Confusion* is a lack of clarity in thinking with inattentiveness; *delirium* is used to describe an acute confusional state; *stupor*, a state in which vigorous stimuli are needed to elicit a response; *coma*, a condition of unresponsiveness. Pts in such states are usually seriously ill, and etiologic factors must be assessed (Tables 18-1 and 18-2).

■ DELIRIUM

Delirium is a clinical diagnosis made at the bedside; a careful history and physical examination are necessary, focusing on common etiologies of delirium, especially toxins and metabolic conditions. Observation will usually reveal an altered level of consciousness or a deficit of attention. Attention can be assessed through a simple bedside test of digits forward—pts are asked to repeat successively longer random strings of digits beginning with two digits in a row; a digit span of four digits or less usually indicates an attentional deficit unless hearing or language barriers are present. Delirium is vastly underrecognized, especially in pts presenting with a quiet, hypoactive state and those in the ICU.

A cost-effective approach to the evaluation of delirium allows the history and physical examination to guide tests. No single algorithm will fit all pts due to the large number of potential etiologies, but one step-wise approach is shown in Table 18-2.

Management begins with treatment of the underlying inciting factor (e.g., pts with systemic infections should be given appropriate antibiotics, and electrolyte disturbances judiciously corrected). Relatively simple methods of supportive care can be quite effective, such as frequent reorientation by staff, preservation of sleep-wake cycles, and attempting to mimic the home environment as much as possible. Chemical restraints exacerbate delirium and should be used as a last resort and only when necessary to protect pt or staff from possible injury; antipsychotics at very low dose are usually the treatment of choice, although evidence associates them with increased mortality in the elderly and limited efficacy in delirium.

■ COMA (TABLE 18-3)

Because coma demands immediate attention, the physician must employ an organized approach. Almost all instances of coma can be traced to either widespread abnormalities of the bilateral cerebral hemispheres or to reduced activity of the reticular activating system in the brainstem.

History

History should be obtained from witnesses or family members regarding use of insulin, narcotics, anticoagulants, other prescription drugs, suicidal intent, recent trauma, headache, epilepsy, significant medical problems, and antecedent symptoms. History of sudden headache followed by loss of consciousness suggests intracranial hemorrhage; preceding vertigo, nausea, diplopia, ataxia, hemisensory disorder suggest basilar artery involvement; chest pain, palpitations, and faintness suggest a cardiovascular cause.

Immediate Assessment

Acute respiratory and cardiovascular problems should be attended to prior to the neurologic assessment. Vital signs should be evaluated, and appropriate support initiated. Thiamine, glucose, and naloxone should be administered if the etiology of coma is not immediately apparent. Blood should be drawn for glucose, electrolytes, calcium, as well as renal (BUN, creatinine) and hepatic (ammonia, transaminases) function; also screen for presence of alcohol and other toxins, and obtain blood cultures if infection is suspected. Arterial blood-gas analysis is helpful in pts with lung disease and acid-base disorders. Fever, especially with

TABLE 18-1 Common Etiologies of Delirium**Toxins**

Prescription medications: especially those with anticholinergic properties, narcotics, and benzodiazepines

Drugs of abuse: alcohol intoxication and alcohol withdrawal, opiates, ecstasy, LSD, GHB, PCP, ketamine, cocaine, “bath salts,” marijuana and its synthetic forms

Poisons: inhalants, carbon monoxide, ethylene glycol, pesticides

Metabolic Conditions

Electrolyte disturbances: hypoglycemia, hyperglycemia, hyponatremia, hypernatremia, hypercalcemia, hypocalcemia, hypomagnesemia

Hypothermia and hyperthermia

Pulmonary failure: hypoxemia and hypercarbia

Liver failure/hepatic encephalopathy

Renal failure/uremia

Cardiac failure

Vitamin deficiencies: B₁₂, thiamine, folate, niacin

Dehydration and malnutrition

Anemia

Infections

Systemic infections: urinary tract infections, pneumonia, skin and soft tissue infections, sepsis

CNS infections: meningitis, encephalitis, brain abscess

Endocrine Conditions

Hyperthyroidism, hypothyroidism

Hyperparathyroidism

Adrenal insufficiency

Cerebrovascular Disorders

Global hypoperfusion states

Hypertensive encephalopathy

Focal ischemic strokes and hemorrhages (rare): especially nondominant parietal and thalamic lesions

Autoimmune Disorders

CNS vasculitis

Cerebral lupus

Neurologic paraneoplastic and autoimmune encephalitis

Seizure-Related Disorders

Nonconvulsive status epilepticus

Intermittent seizures with prolonged postictal states

Neoplastic Disorders

Diffuse metastases to the brain

Gliomatosis cerebri

Carcinomatous meningitis

CNS lymphoma

Hospitalization

Terminal end-of-life delirium

Abbreviations: CNS, central nervous system; GHB, γ -hydroxybutyrate; LSD, lysergic acid diethylamide; PCP, phencyclidine.

TABLE 18-2 Stepwise Evaluation of a Pt with Delirium**Initial Evaluation**

History with special attention to medications (including over-the-counter and herbals)
 General physical examination and neurologic examination
 Complete blood count
 Electrolyte panel including calcium, magnesium, phosphorus
 Liver function tests, including albumin
 Renal function tests

First-Tier Further Evaluation Guided by Initial Evaluation

Systemic infection screen
 Urinalysis and culture
 Chest radiograph
 Blood cultures
 Electrocardiogram
 Arterial blood gas
 Serum and/or urine toxicology screen (perform earlier in young persons)
 Brain imaging with MRI with diffusion and gadolinium (preferred) or CT
 Suspected CNS infection or other inflammatory disorder: lumbar puncture after brain imaging
 Suspected seizure-related etiology: electroencephalogram (EEG) (if high suspicion, should be performed immediately)

Second-Tier Further Evaluation

Vitamin levels: B₁₂, folate, thiamine
 Endocrinologic laboratories: thyroid-stimulating hormone (TSH) and free T₄; cortisol
 Serum ammonia
 Sedimentation rate
 Autoimmune serologies: antinuclear antibodies (ANA), complement levels; p-ANCA, c-ANCA, consider paraneoplastic/autoimmune encephalitis serologies
 Infectious serologies: rapid plasmin reagin (RPR); fungal and viral serologies if high suspicion; HIV antibody
 Lumbar puncture (if not already performed)
 Brain MRI with and without gadolinium (if not already performed)

Abbreviations: c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; p-ANCA, perinuclear antineutrophil cytoplasmic antibody.

petechial rash, suggests meningitis. Examination of CSF is essential in diagnosis of meningitis and encephalitis; lumbar puncture should not be deferred if meningitis is a possibility, but CT scan should be obtained first if a mass lesion is suspected. Empirical antibiotic and glucocorticoid coverage for meningitis should be instituted until CSF results are available. Fever with dry skin suggests heat shock or intoxication with anticholinergics. Hypothermia suggests myxedema, intoxication, sepsis, exposure, or hypoglycemia. Marked hypertension occurs with increased intracranial pressure (ICP) and hypertensive encephalopathy.

Neurologic Examination

Focus on establishing pt's best level of function and uncovering signs that enable a specific diagnosis. Comatose pt's best motor and sensory function should be assessed by testing responses to noxious stimuli; carefully note any asymmetric

TABLE 18-3 Differential Diagnosis of Coma

1. Diseases that cause no focal brainstem or lateralizing neurologic signs (CT scan is often normal)
 - a. Intoxications: alcohol, sedative drugs, opiates, etc.
 - b. Metabolic disturbances: anoxia, hyponatremia, hypernatremia, hypercalcemia, diabetic acidosis, nonketotic hyperosmolar hyperglycemia, hypoglycemia, uremia, hepatic coma, hypercarbia, Addisonian crisis, hypo- and hyperthyroid states, profound nutritional deficiency
 - c. Severe systemic infections: pneumonia, septicemia, typhoid fever, malaria, Waterhouse-Friderichsen syndrome
 - d. Shock from any cause
 - e. Status epilepticus, nonconvulsive status epilepticus, postictal states
 - f. Hyperperfusion syndromes including hypertensive encephalopathy, eclampsia, posterior reversible encephalopathy syndrome (PRES)
 - g. Severe hyperthermia, hypothermia
 - h. Concussion
 - i. Acute hydrocephalus
2. Diseases that cause focal brainstem or lateralizing cerebral signs (CT scan is typically abnormal)
 - a. Hemispherical hemorrhage (basal ganglionic, thalamic) or infarction (large middle cerebral artery territory) with secondary brainstem compression
 - b. Brainstem infarction due to basilar artery thrombosis or embolism
 - c. Brain abscess, subdural empyema
 - d. Epidural and subdural hemorrhage, brain contusion
 - e. Brain tumor with surrounding edema
 - f. Cerebellar and pontine hemorrhage and infarction
 - g. Widespread traumatic brain injury
 - h. Metabolic coma (see above) in the setting of preexisting focal damage
3. Diseases that cause meningeal irritation with or without fever, and with an excess of WBCs or RBCs in the CSF
 - a. Subarachnoid hemorrhage from ruptured aneurysm, arteriovenous malformation, trauma
 - b. Infectious meningitis and meningoencephalitis
 - c. Paraneoplastic and autoimmune meningitis
 - d. Carcinomatous and lymphomatous meningitis

responses, which suggest a focal lesion. Multifocal myoclonus indicates that a metabolic disorder is likely; intermittent twitching or subtle eye movements may be the only sign of a seizure.

Responsiveness

Stimuli of increasing intensity are applied to gauge the degree of unresponsiveness and any asymmetry in sensory or motor function. Motor responses may be purposeful or reflexive. Spontaneous flexion of elbows with leg extension, termed *decorticate posturing*, accompanies severe damage to contralateral hemisphere above midbrain. Internal rotation of the arms with extension of elbows, wrists, and legs, termed *decerebrate posturing*, suggests damage to midbrain or caudal diencephalon. These postural reflexes occur in profound encephalopathic states.

Pupillary Signs

In comatose pts, equal, round, reactive pupils exclude midbrain damage as cause and suggest a metabolic abnormality. Pinpoint pupils occur in narcotic overdose, pontine damage, hydrocephalus, or thalamic hemorrhage; the response to naloxone and presence of reflex eye movements (usually intact with drug overdose) can distinguish these. A unilateral, enlarged, often oval, poorly reactive pupil is caused by midbrain lesions or compression of third cranial nerve, as occurs in transtentorial herniation. Bilaterally dilated, unreactive pupils indicate severe bilateral midbrain damage, anticholinergic overdose, or ocular trauma.

Ocular Movements

Examine spontaneous and reflex eye movements. Intermittent horizontal divergence is common in drowsiness. Slow, to-and-fro horizontal movements suggest bihemispheric dysfunction. Conjugate eye deviation to one side indicates damage to the pons on the opposite side or a destructive lesion in the frontal lobe on the same side (*"The eyes look toward a hemispherical lesion and away from a brainstem lesion"*). An adducted eye at rest with impaired ability to turn eye laterally indicates an abducens (VI) nerve palsy, common in raised ICP or pontine damage. The eye with a dilated, unreactive pupil is often abducted at rest and cannot adduct fully due to third nerve dysfunction, as occurs with transtentorial herniation. Vertical separation of ocular axes (skew deviation) occurs in pontine or cerebellar lesions. Doll's head maneuver (oculocephalic reflex) and cold caloric-induced eye movements allow diagnosis of gaze or cranial nerve palsies in pts who do not move their eyes purposefully. Doll's head maneuver is tested by observing eye movements in response to lateral rotation of head (this should not be performed in pts with possible neck injury); full conjugate movement of eyes occurs in bihemispheric dysfunction. In comatose pts with intact brainstem function, raising head to 60° above the horizontal and irrigating external auditory canal with cool water causes tonic deviation of gaze to side of irrigated ear (*"cold calorics"*). In conscious pts, it causes nystagmus, vertigo, and emesis.

Respiratory Patterns

Cheyne-Stokes (periodic) breathing occurs in bihemispheric dysfunction and is common in metabolic encephalopathies. Respiratory patterns composed of gasps or other irregular breathing patterns are indicative of lower brainstem damage; such pts usually require intubation and ventilatory assistance.

Radiologic Examination

Lesions causing raised ICP commonly cause impaired consciousness. CT or MRI scan of the brain is often abnormal in coma but may not be diagnostic; appropriate therapy should not be postponed while awaiting a CT or MRI scan. Pts with disordered consciousness due to high ICP can deteriorate rapidly; emergent CT study is necessary to confirm the presence of mass effect and guide surgical intervention. CT scan is normal in some pts with subarachnoid hemorrhage; the diagnosis then rests on clinical history combined with RBCs (in the first few hours) or xanthochromia (from 6–12 h up to 1–4 weeks) in spinal fluid. CT, MR, or conventional angiography may be necessary to establish basilar artery thrombosis as cause of coma in pts with brainstem signs. The electroencephalogram (EEG) is useful in metabolic or drug-induced states but is rarely diagnostic except in coma due to seizures or herpes simplex encephalitis.

■ BRAIN DEATH

This results from total cessation of cerebral function while somatic function is maintained by artificial means and the heart continues to pump. It is legally and ethically equivalent to cardiorespiratory death. The pt is unresponsive to all forms of stimulation (widespread cortical destruction), brainstem reflexes are

absent (global brainstem damage), and there is complete apnea (destruction of the medulla). Demonstration of apnea requires that the PCO_2 be high enough to stimulate respiration, while PO_2 and blood pressure are maintained. EEG is isoelectric at high gain. The absence of deep tendon reflexes is not required because the spinal cord may remain functional. Special care must be taken to exclude drug toxicity and hypothermia prior to making a diagnosis of brain death. Diagnosis should be made only if the state persists for some agreed-upon period, usually 6–24 h; the diagnosis should be delayed for at least 24 h if the cause is unknown or due to cardiac arrest.

19

Stroke



Sudden onset of a neurologic deficit from a vascular mechanism: ~85% are ischemic; ~15% are primary hemorrhages (subarachnoid [Chap. 20] and intraparenchymal). An ischemic deficit that resolves rapidly without radiologic evidence of an infarction is termed a *transient ischemic attack* (TIA); 24 h is a commonly used boundary between TIA and stroke, although most TIAs last between 5 and 15 min. Stroke is a leading cause of neurologic disability in adults; ~150,000 deaths annually in the United States. Much can be done to limit morbidity and mortality through prevention and acute intervention.

■ PATHOPHYSIOLOGY

Ischemic stroke can be due to embolic occlusion of large cerebral vessels; source of emboli may be heart, aortic arch, or other arteries such as the internal carotids. Small, deep ischemic lesions are most often related to intrinsic small-vessel disease (lacunar strokes). Low-flow strokes are occasionally seen with severe proximal stenosis and inadequate collaterals challenged by systemic hypotensive episodes. Hemorrhages most frequently result from rupture of aneurysms or small vessels within brain tissue. Variability in stroke recovery is influenced by collateral vessels, blood pressure, and the specific site and mechanism of vessel occlusion; if blood flow is restored prior to significant cell death, the pt may experience only transient symptoms, i.e., a TIA.

■ CLINICAL FEATURES

Ischemic Stroke

Abrupt and dramatic onset of focal neurologic symptoms is typical. Pts may not seek assistance on their own because they are rarely in pain and may lose appreciation that something is wrong (*anosognosia*). Symptoms reflect the vascular territory involved (Table 19-1). Transient monocular blindness (*amaurosis fugax*) is a particular form of TIA due to retinal ischemia; pts describe a shade descending over the visual field and the ipsilateral carotid artery is often implicated.

Lacunar Syndromes (Small-Vessel Strokes)

Most common are:

- Pure motor hemiparesis of face, arm, and leg (internal capsule or pons)
- Pure sensory stroke (ventral thalamus)
- Ataxic hemiparesis (pons or internal capsule)
- Dysarthria—clumsy hand (pons or genu of internal capsule)

TABLE 19-1 Anatomic Localization in Stroke**Signs and Symptoms****Cerebral Hemisphere, Lateral Aspect (Middle Cerebral A.)**

Hemiparesis

Hemisensory deficit

Motor aphasia (Broca's)—hesitant speech with word-finding difficulty and preserved comprehension

Sensory aphasia (Wernicke's)—anomia, poor comprehension, jargon speech

Unilateral neglect, apraxias

Homonymous hemianopia or quadrantanopia

Gaze preference with eyes deviated toward side of lesion

Cerebral Hemisphere, Medial Aspect (Anterior Cerebral A.)

Paralysis of foot and leg with or without paresis of arm

Cortical sensory loss over leg

Grasp and sucking reflexes

Urinary incontinence

Gait apraxia

Cerebral Hemisphere, Posterior Aspect (Posterior Cerebral A.)

Homonymous hemianopia

Cortical blindness

Memory deficit

Dense sensory loss, spontaneous pain, dysesthesias, choreoathetosis

Brainstem, Midbrain (Posterior Cerebral A.)

Third nerve palsy and contralateral hemiplegia

Paralysis/paresis of vertical eye movement

Convergence nystagmus, disorientation

Brainstem, Pontomedullary Junction (Basilar A.)

Facial paralysis

Paresis of abduction of eye

Paresis of conjugate gaze

Hemifacial sensory deficit

Horner's syndrome

Diminished pain and thermal sense over half body (with or without face)

Ataxia

Brainstem, Lateral Medulla (Vertebral A.)

Vertigo, nystagmus

Horner's syndrome (miosis, ptosis, decreased sweating)

Ataxia, falling toward side of lesion

Impaired pain and thermal sense over half body with or without face

Intracranial Hemorrhage

Vomiting and drowsiness occur in some cases with increased intracranial pressure (ICP), and headache is common. Signs and symptoms are often not confined to a single vascular territory. Etiologies are diverse but hypertension is the most common cause (Table 19-2). Hypertensive hemorrhages typically occur in the following locations:

TABLE 19-2 Causes of Intracranial Hemorrhage

CAUSE	LOCATION	COMMENTS
Head trauma	Intraparenchymal: frontal lobes, anterior temporal lobes; subarachnoid; extra-axial (subdural, epidural)	Coup and contrecoup injury during brain deceleration
Hypertensive hemorrhage	Putamen, globus pallidus, thalamus, cerebellar hemisphere, pons	Chronic hypertension produces hemorrhage from small (~30–100 μ m) vessels in these regions
Transformation of prior ischemic infarction	Basal ganglion, subcortical regions, lobar	Occurs in 1–6% of ischemic strokes with predilection for large hemispheric infarctions
Metastatic brain tumor	Lobar	Lung, choriocarcinoma, melanoma, renal cell carcinoma, thyroid, atrial myxoma
Coagulopathy	Any	Risk for ongoing hematoma expansion
Drug	Any, lobar, subarachnoid	Cocaine, amphetamine
Arteriovenous malformation	Lobar, intraventricular, subarachnoid	Risk is ~2–3% per year for bleeding if previously unruptured
Aneurysm	Subarachnoid, intraparenchymal, rarely subdural	Mycotic and nonmycotic forms of aneurysms
Amyloid angiopathy	Lobar	Degenerative disease of intracranial vessels; associated with dementia, rare in pts <60 years
Cavernous angioma	Intraparenchymal	Multiple cavernous angiomas linked to mutations in <i>KRIT1</i> , <i>CCM2</i> , and <i>PDCD10</i> genes
Dural arteriovenous fistula	Lobar, subarachnoid	Produces bleeding by venous hypertension
Capillary telangiectasias	Usually brainstem	Rare cause of hemorrhage

- Putamen: contralateral hemiparesis often with homonymous hemianopia
- Thalamus: hemiparesis with prominent sensory deficit
- Pons: quadriplegia, “pinpoint” pupils, impaired horizontal eye movements
- Cerebellum: headache, vomiting, gait ataxia

A neurologic deficit that evolves gradually over 30–90 min strongly suggests intracerebral bleeding.

TREATMENT

Stroke

Principles of management are outlined in [Fig. 19-1](#). Stroke needs to be distinguished from potential mimics, including seizure, migraine, tumor, and metabolic derangements.

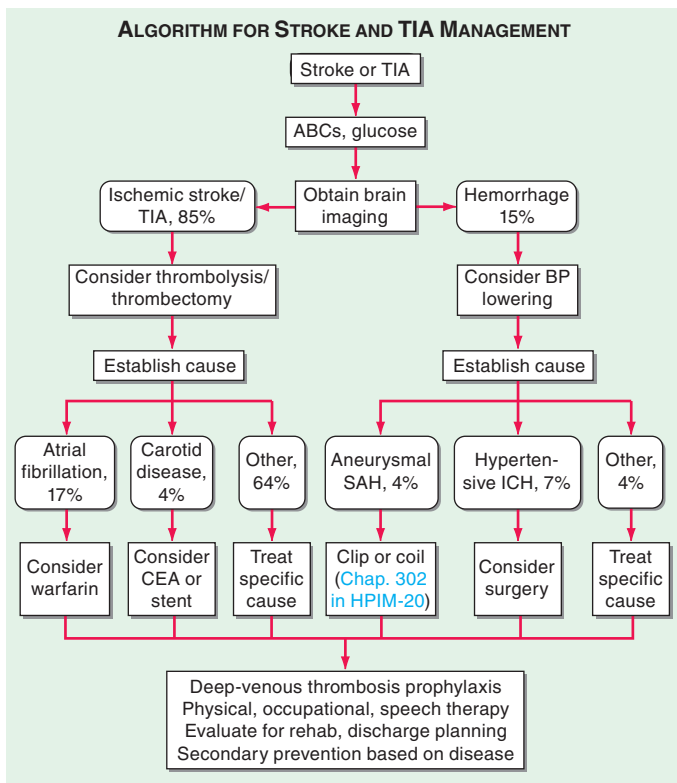


FIGURE 19-1 Medical management of stroke and TIA. *Rounded boxes* are diagnoses; *rectangles* are interventions. Numbers are percentages of stroke overall. ABCs, airway, breathing, circulation; BP, blood pressure; CEA, carotid endarterectomy; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack.

- **Imaging.** After initial stabilization, an emergency noncontrast head CT scan is necessary to differentiate ischemic from hemorrhagic stroke. With large ischemic strokes, CT abnormalities are usually evident within the first few hours, but small infarcts can be difficult to visualize by CT. CT or MR angiography (CTA/MRA) may help reveal vascular occlusions. Diffusion-weighted MRI has a high sensitivity for identifying ischemic stroke even minutes after onset.

ACUTE ISCHEMIC STROKE

Treatments designed to reverse or lessen tissue infarction include: (1) medical support, (2) intravenous thrombolysis, (3) endovascular revascularization, (4) antiplatelet agents, (5) anticoagulation, and (6) neuroprotection.

MEDICAL SUPPORT

Optimize perfusion in ischemic penumbra surrounding the infarct.

- Blood pressure should never be lowered precipitously (exacerbates the underlying ischemia), and only in the most extreme situations should gradual

lowering be undertaken (e.g., malignant hypertension with BP >220/120 mmHg or, if thrombolysis planned, BP >185/110 mmHg).

- Intravascular volume should be maintained with isotonic fluids because volume restriction is rarely helpful. Osmotic therapy with mannitol may be necessary to control edema in large infarcts, but isotonic volume must be replaced to avoid hypovolemia.
- In cerebellar infarction (or hemorrhage), rapid deterioration can occur from brainstem compression and hydrocephalus, requiring neurosurgical intervention.

INTRAVENOUS THROMBOLYSIS

- Ischemic deficits of <3 h duration, with no hemorrhage by CT criteria, may benefit from thrombolytic therapy with IV recombinant tissue plasminogen activator (Table 19-3).
- Based on trial data, IV rtPA is used in most centers for deficits of 3–4.5 h duration, but is not yet approved for this window in the United States (as it is in many other countries).

ENDOVASCULAR REVASCLARIZATION

- Ischemic stroke from large-vessel intracranial occlusion results in high rates of morbidity and mortality; pts with such occlusions benefit from embolectomy

TABLE 19-3 Administration of Intravenous Recombinant Tissue Plasminogen Activator (rtPA) for Acute Ischemic Stroke (AIS)^a

INDICATION	CONTRAINDICATION
Clinical diagnosis of stroke	Sustained BP >185/110 mmHg despite treatment
Onset of symptoms to time of drug administration ≤ 4.5 h ^b	Bleeding diathesis
CT scan showing no hemorrhage or edema of >1/3 of the MCA territory	Recent head injury or intracerebral hemorrhage
Age ≥ 18 years	Major surgery in preceding 14 days
	Gastrointestinal bleeding in preceding 21 days
	Recent myocardial infarction

Administration of rtPA

IV access with two peripheral IV lines (avoid arterial or central line placement)

Review eligibility for rtPA

Administer 0.9 mg/kg IV (maximum 90 mg) IV as 10% of total dose by bolus, followed by remainder of total dose over 1 h^c

Frequent cuff blood pressure monitoring

No other antithrombotic treatment for 24 h

For decline in neurologic status or uncontrolled blood pressure, stop infusion, give cryoprecipitate, and reimpose brain emergently

Avoid urethral catheterization for ≥ 2 h

^aSee Activase (tissue plasminogen activator) package insert for complete list of contraindications and dosing.

^bDepending on the country, IV rtPA may be approved for up to 4.5 h with additional restrictions.

^cA dose of 0.6 mg/kg is commonly used in Asia (Japan and China) based on randomized data indicating less hemorrhage and similar efficacy using this lower-dose.

Abbreviations: BP, blood pressure; CT, computed tomography; HCT, hematocrit; INR, international normalized ratio; MCA, middle cerebral artery; PTT, partial thromboplastin time.

(<6 h duration) administered at the time of an urgent cerebral angiogram at specialized centers. CT angiography is becoming more commonly used as part of initial imaging protocols to identify these pts rapidly. CT (or MR) perfusion can identify a subset of these pts who benefit from embolectomy up to 24 h.

ANTIPLATELET AGENTS

- Aspirin (up to 325 mg/d) is safe and has a small but definite benefit in acute ischemic stroke.

ANTICOAGULATION

- Trials do not support the use of heparin or other anticoagulants acutely for acute stroke.

NEUROPROTECTION

- Hypothermia is effective in coma following cardiac arrest but has not been shown to benefit stroke pts. Other neuroprotective agents have shown no efficacy in human trials despite promising animal data.

STROKE CENTERS AND REHABILITATION

- Care in comprehensive stroke units followed by rehabilitation services improves neurologic outcomes and reduces mortality.

ACUTE INTRACEREBRAL HEMORRHAGE

- Noncontrast head CT will confirm diagnosis.
- Rapidly identify and correct any coagulopathy.
- Control systolic BP to at least below 180 mmHg.
- 40% of pts die; prognosis is determined by volume and location of hematoma.
- Stuporous or comatose pts generally are treated presumptively for elevated ICP. Treatment for edema and mass effect with osmotic agents may be necessary; glucocorticoids not helpful.
- Neurosurgical consultation should be sought for possible urgent evacuation of cerebellar hematoma; in other locations, data do not support surgical intervention.

■ EVALUATION: DETERMINING THE CAUSE OF STROKE

Although initial management of acute ischemic stroke or TIA does not depend on the etiology, establishing a cause is essential to reduce risk of recurrence (Table 19-4); particular attention should be on atrial fibrillation and carotid atherosclerosis because these etiologies have proven secondary prevention strategies. Nearly 30% of strokes remain unexplained despite extensive evaluation.

Clinical examination should be focused on the peripheral and cervical vascular system. Routine studies include CXR and ECG, urinalysis, CBC/platelets, electrolytes, glucose, ESR, lipid profile, PT, and PTT. If a hypercoagulable state is suspected, further studies of coagulation are indicated.

Imaging evaluation may include brain MRI (compared with CT, increased sensitivity for small infarcts of cortex and brainstem); MR or CT angiography (evaluate patency of intracranial vessels and extracranial carotid and vertebral vessels); noninvasive carotid ultrasound; or cerebral angiography ("gold standard" for evaluation of intracranial and extracranial vascular disease). For suspected cardiogenic source, cardiac echocardiogram with attention to right-to-left shunts, and cardiac telemetry (including long-term cardiac event monitoring) indicated.

TABLE 19-4 Causes of Ischemic Stroke

COMMON CAUSES	UNCOMMON CAUSES
Thrombosis	Hypercoagulable disorders
Lacunar stroke (small vessel)	Protein C deficiency ^a
Large-vessel thrombosis	Protein S deficiency ^a
Dehydration	Antithrombin III deficiency ^a
Embolic occlusion	Antiphospholipid syndrome
Artery-to-artery	Factor V Leiden mutation ^a
Carotid bifurcation	Prothrombin G20210 mutation ^a
Aortic arch	Systemic malignancy
Arterial dissection	Sickle cell anemia
Cardioembolic	β Thalassemia
Atrial fibrillation	Polycythemia vera
Mural thrombus	Systemic lupus erythematosus
Myocardial infarction	Homocysteinemia
Dilated cardiomyopathy	Thrombotic thrombocytopenic purpura
Valvular lesions	Disseminated intravascular coagulation
Mitral stenosis	Dysproteinemias ^a
Mechanical valve	Nephrotic syndrome ^a
Bacterial endocarditis	Inflammatory bowel disease ^a
Paradoxical embolus	Oral contraceptives
Atrial septal defect	Venous sinus thrombosis ^b
Patent foramen ovale	Fibromuscular dysplasia
Atrial septal aneurysm	Vasculitis
Spontaneous echo contrast	Systemic vasculitis (PAN, granulomatosis with polyangiitis [We gener's], Takayasu's, giant cell arteritis)
Stimulant drugs: cocaine, amphetamine	Primary CNS vasculitis
	Meningitis (syphilis, tuberculosis, fungal, bacterial, zoster)
	Noninflammatory vasculopathy
	Reversible vasoconstriction syndrome
	Fabry's disease
	Angiocentric lymphoma
	Cardiogenic
	Mitral valve calcification
	Atrial myxoma
	Intracardiac tumor
	Marantic endocarditis
	Libman-Sacks endocarditis
	Subarachnoid hemorrhage vasospasm
	Moyamoya disease
	Eclampsia

^aChiefly cause venous sinus thrombosis.

^bMay be associated with any hypercoagulable disorder.

Abbreviations: CNS, central nervous system; PAN, polyarteritis nodosa.

■ PRIMARY AND SECONDARY PREVENTION OF STROKE (TABLE 19-5)

Risk Factors

Atherosclerosis is a systemic disease affecting arteries throughout the body. Multiple factors including hypertension, diabetes, hyperlipidemia, and family history influence stroke and TIA risk. Cardioembolic risk factors include atrial fibrillation/flutter, MI, valvular heart disease, and cardiomyopathy. Hypertension and diabetes are also specific risk factors for lacunar stroke and intraparenchymal hemorrhage. Smoking is a potent risk factor for all vascular mechanisms of stroke. Identification of modifiable risk factors and prophylactic interventions to lower risk is probably the best approach to stroke overall.

Antiplatelet Agents

Platelet antiaggregation agents can prevent atherothrombotic events, including TIA and stroke, by inhibiting formation of intraarterial platelet aggregates. Aspirin (50–325 mg/d) inhibits thromboxane A₂, a platelet aggregating and vasoconstricting prostaglandin. Aspirin, clopidogrel (blocks the platelet adenosine

TABLE 19-5 Recommendations on Chronic Use of Antithrombotics for Various Cardiac Conditions

CONDITION	RECOMMENDATION
Nonvalvular atrial fibrillation <ul style="list-style-type: none"> • CHA₂DS₂-VASc score of 0 • CHA₂DS₂-VASc score of 1 • CHA₂DS₂-VASc score ≥2 	Calculate CHA ₂ DS ₂ -VASc score ^a Aspirin or no antithrombotic Aspirin or OAC OAC
Rheumatic mitral valve disease <ul style="list-style-type: none"> • With atrial fibrillation, previous embolization, or atrial appendage thrombus, or left atrial diameter >55 mm • Embolization or appendage clot despite OAC 	OAC OAC plus aspirin
Mitral valve prolapsed <ul style="list-style-type: none"> • Asymptomatic • With otherwise cryptogenic stroke or TIA • Atrial fibrillation 	No therapy Aspirin OAC
Mitral annular calcification <ul style="list-style-type: none"> • Without atrial fibrillation but systemic embolization, or otherwise cryptogenic stroke or TIA • Recurrent embolization despite aspirin • With atrial fibrillation 	Aspirin OAC OAC
Aortic valve calcification <ul style="list-style-type: none"> • Asymptomatic • Otherwise cryptogenic stroke or TIA 	No therapy Aspirin
Aortic arch mobile atheroma <ul style="list-style-type: none"> • Otherwise cryptogenic stroke or TIA 	Aspirin or OAC
Patent foramen ovale <ul style="list-style-type: none"> • Otherwise cryptogenic ischemic stroke or TIA • Indication for OAC (deep-venous thrombosis or hypercoagulable state) 	Aspirin or closure with device OAC

(Continued)

TABLE 19-5 Recommendations on Chronic Use of Antithrombotics for Various Cardiac Conditions (Continued)

CONDITION	RECOMMENDATION
Mechanical heart valve <ul style="list-style-type: none"> • Aortic position, bileaflet or Medtronic Hall tilting disk with normal left atrial size and sinus rhythm • Mitral position tilting disk or bileaflet valve • Mitral or aortic position, anterior-apical myocardial infarct or left atrial enlargement • Mitral or aortic position, with atrial fibrillation, or hypercoagulable state, or low ejection fraction, or atherosclerotic vascular disease • Systemic embolization despite target INR 	<p>VKA INR 2.5, range 2–3</p> <p>VKA INR 3.0, range 2.5–3.5</p> <p>VKA INR 3.0, range 2.5–3.5</p> <p>Aspirin plus VKA INR 3.0, range 2.5–3.5</p> <p>Add aspirin and/or increase INR: prior target was 2.5 increase to 3.0, range 2.5–3.5; prior target was 3.0 increase to 3.5, range 3–4</p>
Bioprosthetic valve <ul style="list-style-type: none"> • No other indication for VKA therapy 	Aspirin
Infective endocarditis	Avoid antithrombotic agents
Nonbacterial thrombotic endocarditis <ul style="list-style-type: none"> • With systemic embolization 	Full-dose unfractionated heparin or SC LMWH

^aCHA₂DS₂-VASc score is calculated as follows: 1 point for Congestive heart failure, 1 point for Hypertension, 2 points for Age ≥75 y, 1 point for diabetes mellitus, 2 points for stroke or TIA, 1 point for vascular disease (prior MI, peripheral vascular disease or aortic plaque), 1 point for age 65–74 y, 1 point for female sex category; sum of point is the total CHA₂DS₂-VASc score.

Note: Dose of aspirin is 50–325 mg/d; target INR for OAC is between 2 and 3 unless otherwise specified.

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin; OAC, oral anticoagulant (VKA, thrombin inhibitor, or oral factor Xa inhibitors); TIA, transient ischemic attack; VKA, vitamin K antagonist.

Sources: Modified from DE Singer et al: *Chest* 133:546S, 2008; DN Salem et al: *Chest* 133:593S, 2008; CT January et al: *JACC* 64:2246, 2014.

diphosphate [ADP] receptor), and the combination of aspirin plus extended-release dipyridamole (inhibits platelet uptake of adenosine) are the antiplatelet agents most commonly used. In general, antiplatelet agents reduce new stroke events by 25–30%. Every pt who has experienced an atherothrombotic stroke or TIA and has no contraindication should take an antiplatelet agent regularly because the average annual risk of another stroke is high. The choice of aspirin, clopidogrel, or dipyridamole plus aspirin must balance the fact that the latter are marginally more effective than aspirin but the cost is higher. In pts with minor stroke or TIA, a short course (21–90 d) of aspirin in combination with clopidogrel reduces events; long-term dual antiplatelet medications are ineffective and have higher rates of hemorrhagic complications.

Embolic Stroke

In pts with atrial fibrillation and stroke, anticoagulants are generally the treatment of choice.

Anticoagulation Therapy for Noncardiogenic Stroke

Data do not support the use of long-term warfarin for preventing atherothrombotic stroke for either intracranial or extracranial cerebrovascular disease.

Carotid Revascularization

Carotid endarterectomy benefits many pts with *symptomatic* severe (>70%) *carotid stenosis*; the relative risk reduction is ~65%. However, if the perioperative stroke rate is >6% for any surgeon, the benefit is questionable. Endovascular stenting is another option, especially in those aged <70 years. Surgical results in pts with *asymptomatic carotid stenosis* are less robust, and medical therapy for reduction of atherosclerosis risk factors plus antiplatelet medications is generally recommended in this group pending ongoing trial results.

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Subarachnoid Hemorrhage



Excluding head trauma, the most common cause of subarachnoid hemorrhage (SAH) is rupture of an intracranial saccular aneurysm; other etiologies include bleeding from a vascular malformation (arteriovenous malformation or dural arteriovenous fistula) and extension into the subarachnoid space from a primary intracerebral hemorrhage. Approximately 2% of the population harbor aneurysms, and 25,000–30,000 cases of aneurysmal rupture producing SAH occur each year in the United States; rupture risk for aneurysms <10 mm in size is ~0.1% per year; for unruptured aneurysms, the surgical morbidity rate far exceeds the percentage.

■ CLINICAL PRESENTATION

Sudden, severe headache, often with transient loss of consciousness at onset; vomiting is common. Bleeding may injure adjacent brain tissue and produce focal neurologic deficits. A progressive third nerve palsy, usually involving the pupil, along with headache, suggests posterior communicating artery aneurysm. In addition to dramatic presentations, aneurysms can undergo small ruptures with leaks of blood into the subarachnoid space (sentinel bleeds). The initial clinical manifestations of SAH can be graded using established scales ([Table 20-1](#)); prognosis for good outcome falls as the grade increases.

■ INITIAL EVALUATION

- Noncontrast CT is initial study of choice and usually demonstrates hemorrhage if obtained within 72 h. Lumbar puncture (LP) is required for diagnosis of suspected SAH if CT is nondiagnostic and the diagnosis is suspected; xanthochromia of the spinal fluid is seen within 6–12 h after rupture and lasts for 1–4 weeks.
- Cerebral angiography is necessary to localize and define the anatomic details of the aneurysm and to determine if other unruptured aneurysms exist; angiography should be performed as soon as possible after diagnosis of SAH.
- ECG may reveal ST-segment and T-wave changes similar to cardiac ischemia; caused by circulating catecholamines and excessive discharge of sympathetic neurons. A reversible cardiomyopathy producing shock or congestive heart failure may result.
- Studies of coagulation and platelet count should be obtained, with rapid correction indicated if SAH is documented.

TABLE 20-1 Grading Scales for Subarachnoid Hemorrhage

GRADE	HUNT-HESS SCALE	WORLD FEDERATION OF NEUROSURGICAL SOCIETIES (WFNS) SCALE
1	Mild headache, normal mental status, no cranial nerve or motor findings	GCS ^a score 15, no motor deficits
2	Severe headache, normal mental status, may have cranial nerve deficit	GCS score 13–14, no motor deficits
3	Somnolent, confused, may have cranial nerve or mild motor deficit	GCS score 13–14, with motor deficits
4	Stupor, moderate to severe motor deficit, may have intermittent reflex posturing	GCS score 7–12, with or without motor deficits
5	Coma, reflex posturing or flaccid	GCS score 3–6, with or without motor deficits

^aGlasgow Coma Scale; see [Table 21-2](#).

TREATMENT

Subarachnoid Hemorrhage

ANEURYSM REPAIR

- Early aneurysm repair prevents rerupture.
- The International Subarachnoid Aneurysm Trial (ISAT) demonstrated improved outcomes with endovascular therapy compared to surgery; however, some aneurysms have morphology not amenable to endovascular treatment, and therefore surgery is still an important treatment option for some pts.

MEDICAL MANAGEMENT

- Closely follow serum electrolytes and osmolality; hyponatremia (“cerebral salt wasting”) frequently develops several days after SAH, and supplemental oral salt plus IV normal saline or hypertonic saline may be needed to overcome renal losses.
- Anticonvulsants are sometimes begun until the aneurysm is treated; most experts reserve this therapy only for pts in whom a seizure has occurred.
- Blood pressure should be carefully controlled, while preserving cerebral blood flow, in order to decrease the risk of rerupture until the aneurysm is repaired.
- All pts should have pneumatic compression stockings applied to prevent pulmonary embolism; unfractionated heparin administered subcutaneously for deep-vein thrombosis prophylaxis can be initiated immediately following endovascular treatment and within days following craniotomy and surgical clipping.

HYDROCEPHALUS

- Severe hydrocephalus may require urgent placement of a ventricular catheter for external CSF drainage; some pts will require permanent shunt placement.
- Deterioration of a SAH pt in the first hours to days should prompt repeat CT scanning to evaluate ventricular size.

VASOSPASM

- The leading cause of mortality and morbidity following initial rupture; may appear 4–14 days after the initial hemorrhage, leading to focal ischemia and stroke.
 - Treatment with the calcium channel antagonist nimodipine (60 mg PO q4h) improves outcomes, perhaps by preventing ischemic injury rather than reducing risk of vasospasm.
 - Cerebral perfusion can be improved in symptomatic vasospasm by increasing mean arterial pressure with vasopressor agents such as phenylephrine or norepinephrine, and intravascular volume can be expanded with crystalloid, augmenting cardiac output and reducing blood viscosity by reducing the hematocrit; this so-called “triple-H” (hypertension, hemodilution, and hypervolemic) therapy is widely used.
 - If symptomatic vasospasm persists despite optimal medical therapy, intraarterial vasodilators and angioplasty of the cerebral vessels can be effective.
-

21

Increased Intracranial Pressure and Head Trauma**INCREASED INTRACRANIAL PRESSURE**

A limited volume of extra tissue, blood, CSF, or edema can be added to the intracranial contents without raising the intracranial pressure (ICP). Clinical deterioration or death may follow increases in ICP that shift intracranial contents, distort vital brainstem centers, or compromise cerebral perfusion. Cerebral perfusion pressure (CPP), defined as the mean arterial pressure (MAP) minus the ICP, is the driving force for circulation across capillary beds of the brain; decreased CPP is a fundamental mechanism of secondary ischemic brain injury and constitutes an emergency that requires immediate attention. In general, ICP should be maintained at <20 mmHg and CPP should be maintained at ≥ 60 mmHg.

CLINICAL FEATURES

Elevated ICP may occur in a wide range of disorders including head trauma, intracerebral hemorrhage, subarachnoid hemorrhage (SAH) with hydrocephalus, and fulminant hepatic failure.

Symptoms of high ICP include drowsiness, headache (especially a constant ache that is worse upon awakening), nausea, emesis, diplopia, and blurred vision. Papilledema and sixth nerve palsies are common. If not controlled, cerebral hypoperfusion, pupillary dilation, coma, focal neurologic deficits, posturing, abnormal respirations, systemic hypertension, and bradycardia may result.

Masses that cause raised ICP also distort midbrain and diencephalic anatomy, leading to stupor and coma. Brain tissue is pushed away from the mass against fixed intracranial structures and into spaces not normally occupied. Posterior fossa masses, which may initially cause ataxia, stiff neck, and nausea, are especially dangerous because they can both compress vital brainstem structures and cause obstructive hydrocephalus.

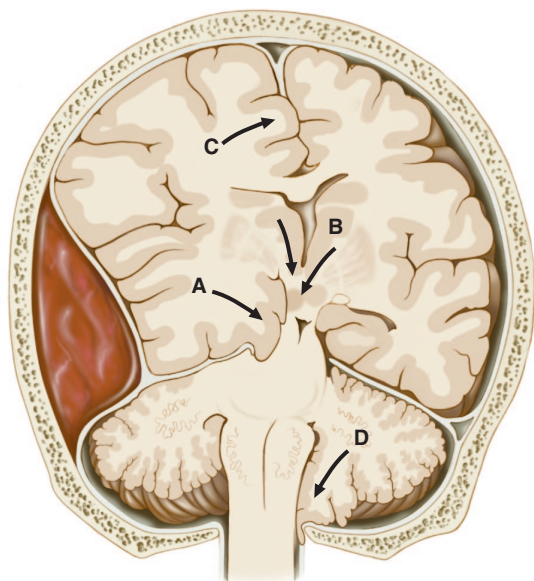


FIGURE 21-1 Types of cerebral herniation. **A.** Uncal; **B.** central; **C.** transfalcial; **D.** foraminal.

Herniation syndromes ([Fig. 21-1](#)) include:

- *Uncal*: Medial temporal lobe displaced through the tentorium, compressing the third cranial nerve and pushing the cerebral peduncle of the midbrain against the tentorium, leading to ipsilateral pupillary dilation, contralateral hemiparesis, and posterior cerebral artery compression.
- *Central*: Downward displacement of the thalamus through the tentorium; miotic pupils and drowsiness are early signs.
- *Transfalcial*: Cingulate gyrus displaced under the midline falx, leading to anterior cerebral artery compression.
- *Foraminal*: Cerebellar tonsils displaced into the foramen magnum, causing medullary compression and respiratory arrest.

TREATMENT

Increased Intracranial Pressure

- A number of different interventions may lower ICP, and ideally the selection of treatment will be based on the underlying mechanism responsible for the elevated ICP ([Table 21-1](#)).
- With hydrocephalus, the principal cause of elevated ICP is impaired CSF drainage; in this setting, ventricular drainage of CSF may be sufficient.
- If cytotoxic edema is responsible, as in head trauma or stroke, use of osmotic diuretics such as mannitol or hypertonic saline is an appropriate early step.
- Elevated ICP may cause tissue ischemia; resulting vasodilation can lead to a cycle of worsening ischemia. Paradoxically, administration of vasopressor

TABLE 21-1 Stepwise Approach to Treatment of Elevated Intracranial Pressure (ICP)^a

Insert ICP monitor—ventriculostomy versus parenchymal device

General goals: maintain ICP <20 mmHg and CPP ≥60 mmHg. For ICP >20–25 mmHg for >5 min:

1. Elevate head of the bed; midline head position
2. Drain CSF via ventriculostomy (if in place)
3. Osmotherapy—mannitol 25–100 g q4h as needed (maintain serum osmolality <320 mosmol) or hypertonic saline (30 mL, 23.4% NaCl bolus)
4. Glucocorticoids—dexamethasone 4 mg q6h for vasogenic edema from tumor, abscess (avoid glucocorticoids in head trauma, ischemic and hemorrhagic stroke)
5. Sedation (e.g., morphine, propofol, or midazolam); add neuromuscular paralysis if necessary (pt will require endotracheal intubation and mechanical ventilation at this point, if not before)
6. Hyperventilation—to PaCO₂ 30–35 mmHg (short-term use or skip this step)
7. Pressor therapy—phenylephrine, dopamine, or norepinephrine to maintain adequate MAP to ensure CPP ≥60 mmHg (maintain euolemia to minimize deleterious systemic effects of pressors). May adjust target CPP in individual pts based on autoregulation status.
8. Consider second-tier therapies for refractory elevated ICP
 - a. Decompressive craniectomy
 - b. High-dose barbiturate therapy (“pentobarb coma”)
 - c. Hypothermia to 33°C

^aThroughout ICP treatment algorithm, consider repeat head computed tomography to identify mass lesions amenable to surgical evacuation. May alter order of steps based on directed treatment to specific cause of elevated ICP.

Abbreviations: CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; MAP, mean arterial pressure; PaCO₂, arterial partial pressure of carbon dioxide.

agents to increase MAP may actually lower ICP by increasing perfusion; therefore, hypertension should be treated carefully, if at all.

- Free water should be restricted.
- Fever should be treated aggressively.
- Hyperventilation is best used for only short periods of time until a more definitive treatment can be instituted.
- ICP monitoring may help guide medical and surgical decisions in selected pts with cerebral edema (Fig. 21-2).

After stabilization and initiation of the above therapies, a CT scan (or MRI, if feasible) is performed to delineate the cause of the elevated ICP. Emergency surgery is sometimes necessary to decompress the intracranial contents in cerebellar stroke with edema, surgically accessible tumor, and subdural or epidural hemorrhage.

HEAD TRAUMA

Almost 10 million traumatic brain injuries (TBI) occur worldwide each year that are serious enough to result in death or hospitalization; in the United States, the estimated annual cost is >\$76 billion.

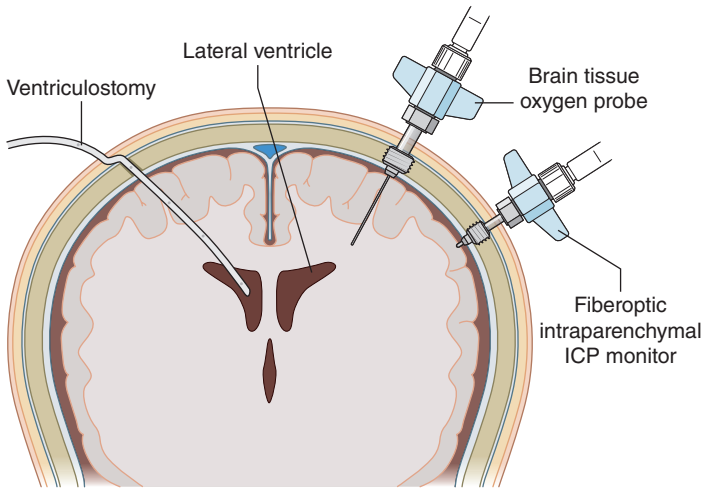


FIGURE 21-2 Intracranial pressure (ICP) and brain tissue oxygen monitoring. A ventriculostomy allows for drainage of cerebrospinal fluid to treat elevated ICP. Fiberoptic ICP and brain tissue oxygen monitors are usually secured using a screwlike skull bolt. Cerebral blood flow and microdialysis probes (not shown) may be placed in a manner similar to the brain tissue oxygen probe.

■ CLINICAL FEATURES

Head trauma can cause immediate loss of consciousness. Prolonged alterations in consciousness may be due to parenchymal, subdural, or epidural hematoma or to diffuse shearing of axons in the white matter. The term “*concussion*” is vague and is not based on widely accepted objective criteria. Skull fracture should be suspected in pts with CSF rhinorrhea, hemotympanum, and periorbital or mastoid ecchymoses. Glasgow Coma Scale ([Table 21-2](#)) is useful for grading severity of brain injury.

TABLE 21-2 Glasgow Coma Scale

Eye Opening (E)		Verbal Response (V)	
Spontaneous	4	Oriented	5
To speech	3	Confused	4
To pressure	2	Words	3
None	1	Sounds	2
		None	1
Best Motor Response (M)			
Obedying commands	6		
Localizing	5		
Normal flexion	4		
Abnormal flexion	3		
Extension	2		
None	1		

Note: Revised GCS (2014).

Source: From G Teasdale et al: The Glasgow Coma Scale at 40 years: Standing the test of time. *Lancet Neurol* 13:844, 2014.

APPROACH TO THE PATIENT**Head Injury**

Medical personnel caring for head injury pts should be aware that:

- Spinal injury often accompanies head injury and care must be taken to prevent compression of the spinal cord due to instability of the spinal column.
- Intoxication is a frequent accompaniment of traumatic brain injury; when appropriate, testing should be carried out for drugs and alcohol.
- Accompanying systemic injuries, including ruptures of abdominal organs, may produce vascular collapse or respiratory compromise requiring immediate attention.

Mild TBI/Concussion The pt with minor head injury who is alert and attentive after a short period of unconsciousness may have headache, dizziness, faintness, nausea, a single episode of emesis, difficulty with concentration, a brief amnesic period, or slight blurring of vision. Such pts have usually sustained a concussion and are expected to have a good prognosis.

Studies have indicated that older age (>65 years), two or more episodes of vomiting, >30 min of retrograde or persistent anterograde amnesia, seizure, and concurrent drug or alcohol intoxication are sensitive (but not specific) indicators of intracranial hemorrhage that justify CT scanning. It may be appropriate to be more liberal in obtaining CT scans in children, although the risks of radiation must be considered.

In the current absence of adequate data, a common sense approach to athletic concussion has been to remove the individual from play immediately and avoid contact sports for at least several days after a mild injury and for a longer period if there are more severe injuries or protracted neurologic symptoms such as headache and difficulty concentrating.

Injury of Intermediate Severity Pts who are not comatose but who have persistent confusion, behavioral changes, subnormal alertness, extreme dizziness, or focal neurologic signs such as hemiparesis should be hospitalized and have a cerebral imaging study. A cerebral contusion or hematoma is often found. Pts with intermediate head injury require medical observation to detect increasing drowsiness, respiratory dysfunction, pupillary enlargement, or other changes in the neurologic examination. Abnormalities of attention, intellect, spontaneity, and memory tend to return to normal weeks or months after the injury, although some cognitive deficits may be persistent.

Severe Injury Pts who are comatose from onset require immediate neurologic attention and resuscitation. After intubation, with care taken to immobilize the cervical spine, the depth of coma, pupillary size and reactivity, limb movements, and plantar responses are assessed. As soon as vital functions permit and cervical spine x-rays and a CT scan have been obtained, the pt should be transported to a critical care unit. CT scan may be normal in comatose pts with axonal shearing lesions in cerebral white matter.

The finding of an epidural or subdural hematoma or large intracerebral hemorrhage requires prompt decompressive surgery in otherwise salvageable pts. Measurement of ICP with a ventricular catheter or fiberoptic device in order to guide treatment has been favored by many units but has not improved outcome. Use of prophylactic anticonvulsants for 7 days has been recommended but there is little supportive data in the absence of multiple seizures.

22

Spinal Cord Compression



APPROACH TO THE PATIENT

Spinal Cord Compression

Initial symptoms of focal neck or back pain may evolve over days to weeks; followed by combinations of paresthesias, sensory loss, motor weakness, and sphincter disturbance evolving over hours to several days. Partial lesions may selectively involve one or more tracts and may be limited to one side of the cord. In severe or abrupt cases, areflexia reflecting spinal shock may be present, but hyperreflexia supervenes over days to weeks. With thoracic lesions, a sensory level to pain may be present on the trunk, indicating localization to the cord at that dermatomal level.

In pts with spinal cord symptoms, the first priority is to exclude treatable compression by a mass. Compression is more likely to be preceded by warning signs of neck or back pain, bladder disturbances, and sensory symptoms prior to development of weakness; noncompressive etiologies such as infarction and hemorrhage are more likely to produce myelopathy without antecedent symptoms.

MRI with gadolinium, centered on the clinically suspected level, is the initial diagnostic procedure. CT myelography can be helpful in pts who have contraindications to MRI. It is important to image the entire spine to search for additional clinically silent lesions. Infectious etiologies, unlike tumor, often cross the disc space to involve adjacent vertebral bodies.

■ NEOPLASTIC SPINAL CORD COMPRESSION

Occurs in 5–10% of pts with cancer; epidural tumor may be the initial manifestation of malignancy. Most neoplasms are epidural in origin and result from metastases to the adjacent spinal bones. Almost any malignant tumor can metastasize to the spinal column, with lung, breast, prostate, kidney, lymphoma, and plasma cell dyscrasia being particularly frequent. The thoracic cord is most commonly involved; exceptions include prostate and ovarian tumors, which preferentially involve the lumbar and sacral segments from spread through veins in the anterior epidural space. Urgent MRI is indicated when the diagnosis is suspected; up to 40% of pts with neoplastic cord compression at one level are found to have asymptomatic epidural disease elsewhere, thus, imaging of the entire length of the spine is important to define the extent of disease. Plain radiographs will miss 15–20% of metastatic vertebral lesions.

TREATMENT

Neoplastic Spinal Cord Compression

- Glucocorticoids to reduce edema (typically dexamethasone, 10 mg intravenously) can be administered before the imaging study if the clinical suspicion is high, and continued at a lower dose (4 mg every 6 h orally) until radiotherapy (generally 30–40 Gy administered in 8–10 fractions) and/or surgical decompression is completed.
- Early surgery, either decompression by laminectomy or vertebral body resection, followed by radiotherapy is more effective than radiotherapy alone for

pts with a single area of spinal cord compression by extradural tumor. Surgery also indicated when cord compression worsens despite radiotherapy, when maximum dose of radiotherapy has been delivered previously to the site, or when a vertebral fracture or spinal instability contributes to cord compression.

- Newer techniques such as stereotactic radiosurgery can deliver high doses of focused radiation with similar rates of response compared to traditional radiotherapy; these are increasingly being used, particularly for pts with radioresistant tumors or requiring re-irradiation.
- Time is of the essence; fixed motor deficits (paraplegia or quadriplegia) established for >12 h do not usually improve, and beyond 48 h the prognosis for substantial motor recovery is poor.
- Biopsy is needed if there is no history of underlying malignancy; a simple systemic workup including chest imaging, mammography, measurement of prostate-specific antigen (PSA), and abdominal CT usually reveals the diagnosis.

■ SPINAL EPIDURAL ABSCESS

Presents as a triad of pain, fever, and progressive limb weakness. Aching pain is almost always present, either over the spine or in a radicular pattern. The duration of pain prior to presentation is generally <2 weeks but may be several months or longer. Fever is usually present along with elevated white blood cell count, sedimentation rate, and C-reactive protein. Risk factors include an impaired immune status (diabetes mellitus, HIV, renal failure, alcoholism, malignancy), intravenous drug abuse, and infections of skin or other soft tissues. Most cases are due to *Staphylococcus aureus*; other causes include gram-negative bacilli, *Streptococcus*, anaerobes, fungi, and tuberculosis. Methicillin resistant *Staphylococcus aureus* (MRSA) is an additional consideration, and therapy should be tailored to this possibility.

MRI localizes the abscess. Lumbar puncture (LP) is required only if encephalopathy or other clinical signs raise question of associated meningitis, a feature found in <25% of cases. The level of the LP should be planned to minimize risk of meningitis due to passage of the needle through infected tissue.

TREATMENT

Spinal Epidural Abscess

- Decompressive laminectomy with debridement combined with long-term antibiotic treatment.
- Surgical evacuation is unlikely to improve deficits of more than several days duration.
- Broad-spectrum antibiotics (typically vancomycin 15–20 mg/kg q12h (staphylococcus including MRSA, streptococcus), ceftriaxone 2 gm q24h (gram-negative bacilli), and when indicated metronidazole 30 mg/kg/d divided into q6h intervals (anaerobes) should be started empirically before surgery, modified on the basis of culture results, and continued for 6–8 weeks.
- With prompt diagnosis and treatment, up to two-thirds of pts experience significant recovery.

■ SPINAL EPIDURAL HEMATOMA

Hemorrhage into the epidural (or subdural) space causes acute focal or radicular pain followed by variable signs of a spinal cord disorder. Therapeutic anticoagulation, trauma, tumor, or blood dyscrasia is a predisposing condition; rarely, hematomas complicate LP or epidural anesthesia. Treatment consists of prompt reversal of any underlying bleeding disorder and surgical decompression.

23

Hypoxic-Ischemic Encephalopathy



Results from lack of delivery of oxygen to the brain because of extreme hypotension or respiratory failure. Most common causes are myocardial infarction (MI), cardiac arrest, shock, asphyxiation, paralysis of respiration, and carbon monoxide or cyanide poisoning. In some circumstances, hypoxemia may predominate. Carbon monoxide and cyanide poisoning are termed *histotoxic hypoxemia* because they cause a direct impairment of the respiratory chain.

■ CLINICAL MANIFESTATIONS

Mild degrees of pure hypoxemia (e.g., at high altitude) cause impaired judgment, inattentiveness, motor incoordination, and, at times, euphoria. However, with hypoxia-ischemia, such as occurs with circulatory arrest, consciousness is lost within seconds. If circulation is restored within 3–5 min, full recovery may occur, but with longer periods permanent cerebral damage usually results. It may be difficult to judge the precise degree of hypoxia-ischemia, and some pts make a relatively full recovery even after 8–10 min of global ischemia. The distinction between pure hypoxemia and hypoxia-ischemia is important, because a PaO_2 as low as 2.7 kPa (20 mmHg) can be well tolerated if it develops gradually and normal blood pressure is maintained, but short durations of very low or absent cerebral circulation may result in permanent impairment.

Clinical examination at different time points after an insult (especially cardiac arrest) helps to assess prognosis. The prognosis is better for pts with intact brainstem function, as indicated by normal pupillary light responses, intact oculocephalic (doll's eyes), oculovestibular (caloric), and corneal reflexes. Absence of these reflexes and the presence of persistently dilated pupils that do not react to light are grave prognostic signs. A low likelihood of a favorable outcome is suggested by the absence of a pupillary light reflex or an extensor or absent motor response to pain on day 3 following the injury. Bilateral absence of the cortical somatosensory evoked potentials (SSEP) also conveys a poor prognosis, as does a very elevated serum level ($>33 \mu\text{g/L}$) of the biochemical marker neuron-specific enolase (NSE) within the first 3 days. The presence of a burst-suppression pattern of myoclonic status epilepticus on EEG or a nonreactive EEG is associated with a low likelihood of good functional outcome. Administration of mild hypothermia after cardiac arrest may change the time points when these clinical and electrophysiologic predictors become reliable in identifying pts with a very low likelihood of clinically meaningful recovery. Current approaches to prognostication after cardiac arrest encourage the use of a multimodal approach that includes these diagnostic tests, along with CT or MRI neuroimaging, in conjunction with clinical neurological assessment.

Long-term consequences include persistent coma or vegetative state, dementia, visual agnosia, parkinsonism, choreoathetosis, ataxia, myoclonus, seizures,

and an amnesic state. Delayed postanoxic encephalopathy is an uncommon phenomenon in which pts appear to make an initial recovery following an insult and then have a relapse with a progressive course often characterized by widespread demyelination on imaging studies.

TREATMENT

Hypoxic-Ischemic Encephalopathy

- Initial treatment is directed at restoring normal cardiorespiratory function. This includes securing a clear airway, ensuring adequate oxygenation and ventilation, and restoring cerebral perfusion, whether by cardiopulmonary resuscitation, fluids, pressors, or cardiac pacing.
- Mild hypothermia (33°C [91°F]), initiated as early as possible and continued for 12–24 h, improves outcome in pts who remain comatose after cardiac arrest, based on trials in pts whose initial rhythm was primarily ventricular fibrillation or pulseless ventricular tachycardia. Potential complications include coagulopathy and an increased risk of infection. In a more recent study, targeted temperature management (TTM) to 33°C or 36°C resulted in similar outcomes.
- Anticonvulsants are not usually given prophylactically but may be used to control seizures.
- Posthypoxic myoclonus can be controlled with clonazepam (1.5–10 mg/d) or valproate (300–1200 mg/d) in divided doses.
- Myoclonic status epilepticus within 24 h after a hypoxic-ischemic insult portends a very poor prognosis, even if seizures are controlled.

24

Status Epilepticus



Defined as continuous seizures or repetitive, discrete seizures with impaired consciousness in the interictal period. The duration of seizure activity to meet the definition has traditionally been 15–30 min. A more practical definition is any situation requiring the acute use of anticonvulsants; in generalized convulsive status epilepticus (GCSE), this is typically when seizures last >5 min.

■ CLINICAL FEATURES

Has numerous subtypes: GCSE (e.g., persistent, generalized electrographic seizures, coma, and tonic-clonic movements), and nonconvulsive status epilepticus (e.g., persistent absence seizures or focal seizures with confusion or partially impaired consciousness, and minimal motor abnormalities). GCSE is obvious when overt convulsions are present, but after 30–45 min of uninterrupted seizures, the signs may become increasingly subtle (mild clonic movements of the fingers; fine, rapid movements of the eyes; or paroxysmal episodes of tachycardia, pupillary dilatation, and hypertension). Electroencephalogram (EEG) may be the only method of diagnosis with these subtle signs; therefore, if a pt remains comatose after a seizure, EEG should be performed to exclude ongoing status epilepticus. GCSE is life-threatening when accompanied by cardiorespiratory dysfunction, hyperthermia, and metabolic derangements such as acidosis

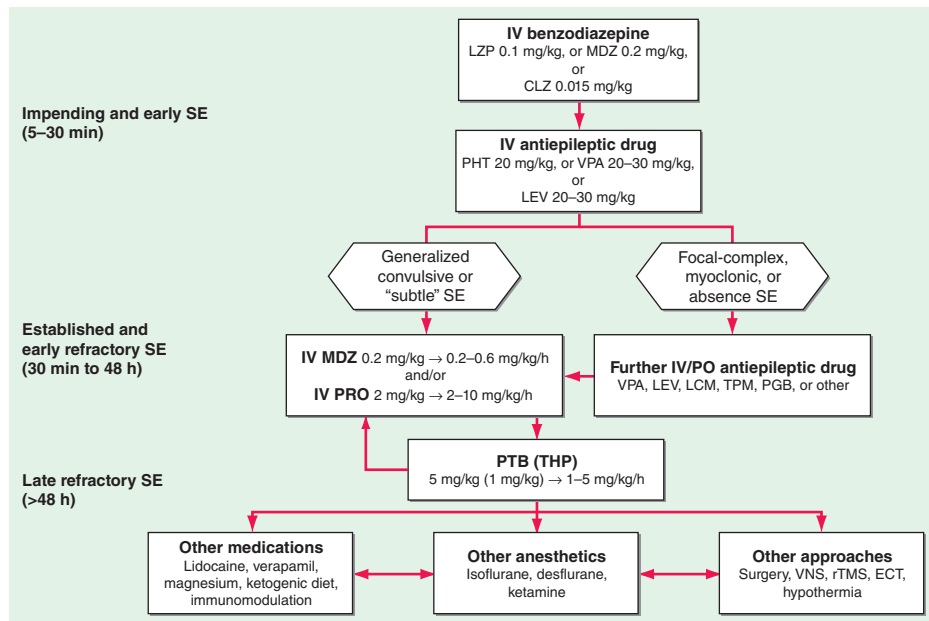


FIGURE 24-1 Pharmacologic treatment of generalized tonic-clonic status epilepticus (SE) in adults. CLZ, clonazepam; ECT, electroconvulsive therapy; LCM, lacosamide; LEV, levetiracetam; LZP, lorazepam; MDZ, midazolam; PGB, pregabalin; PHT, phenytoin or fos-phenytoin; PRO, propofol; PTB, pentobarbital; rTMS, repetitive transcranial magnetic stimulation; THP, thiopental; TPM, topiramate; VNS, vagus nerve stimulation; VPA, valproic acid. (From Rossetti AO, Lowenstein DH: *Management of refractory status epilepticus in adults: Still more questions than answers. Lancet Neurol* 10:922, 2011.)

(from prolonged muscle activity). Irreversible neuronal injury may occur from persistent seizures, even when a pt is paralyzed from neuromuscular blockade.

■ ETIOLOGY

Principal causes of GCSE are antiepileptic drug withdrawal or noncompliance, metabolic disturbances, drug toxicity, CNS infections, CNS tumors, refractory epilepsy, and head trauma.

TREATMENT

Status Epilepticus

GCSE is a medical emergency and must be treated immediately.

- First attend to any acute cardiorespiratory problems or hyperthermia.
- Perform a brief medical and neurologic examination, establish venous access, and send labs to screen for metabolic abnormalities including anticonvulsant levels if pt has a history of epilepsy.
- Anticonvulsant therapy should then begin without delay ([Fig. 24-1](#)).
- In parallel, it is essential to determine the cause of the seizures to prevent recurrence and treat any underlying abnormalities.

The treatment of nonconvulsive status epilepticus is somewhat less urgent since the ongoing seizures are not accompanied by the severe metabolic disturbances of GCSE; however, evidence suggests cellular injury in the region of the seizure focus, so the condition should be treated as promptly as possible using the general approach for GCSE.

■ PROGNOSIS

The mortality rate is 20% in GCSE, and the incidence of permanent neurologic sequelae is 10–50%.

25

Diabetic Ketoacidosis and Hyperosmolar Coma



Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are acute complications of diabetes mellitus (DM). DKA is seen primarily in individuals with type 1 DM and HHS in individuals with type 2 DM. Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and altered mental status. The metabolic similarities and differences in DKA and HHS are summarized in [Table 25-1](#).

DIABETIC KETOACIDOSIS

■ ETIOLOGY

DKA results from insulin deficiency with a relative or absolute increase in glucagon and may be precipitated by inadequate insulin administration, infection (pneumonia, urinary tract infection, gastroenteritis, sepsis), infarction (cerebral, coronary, mesenteric, peripheral), surgery, trauma, drugs (cocaine), or pregnancy. A common clinical scenario is the pt with type 1 DM who erroneously

TABLE 25-1 Laboratory Values in DKA and HHS (Representative Ranges at Presentation)

	DKA	HHS
Glucose, ^a mmol/L (mg/dL)	13.9–33.3 (250–600)	33.3–66.6 (600–1200) ^c
Sodium, meq/L	125–135	135–145
Potassium, ^a meq/L	Normal to ↑ ^b	Normal
Magnesium ^a	Normal ^b	Normal
Chloride ^a	Normal	Normal
Phosphate ^a	Normal to ↓ ^b	Normal
Creatinine, μmol/L (mg/dL)	Slightly ↑	Moderately ↑
Osmolality (mosmol/mL)	300–320	330–380
Plasma ketones ^a	++++	±
Serum bicarbonate, ^a meq/L	<15 meq/L	Normal to slightly ↓
Arterial pH	6.8–7.3	>7.3
Arterial PCO ₂ , ^a mmHg	20–30	Normal
Anion gap ^a [Na – (Cl + HCO ₃)], meq/L	↑	Normal to slightly ↑

^aLarge changes occur during treatment of DKA.

^bAlthough plasma levels may be normal or high at presentation, total-body stores are usually depleted.

^cLarge changes occur during treatment.

Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state.

stops administering insulin because of anorexia/lack of food intake caused by a minor illness, followed by lipolysis and progressive ketosis leading to DKA.

■ CLINICAL FEATURES

The initial symptoms of DKA include anorexia, nausea, vomiting, polyuria, and thirst. Abdominal pain, altered mental function, or frank coma may ensue. Classic signs of DKA include Kussmaul respirations and an acetone odor on the pt's breath. Volume depletion can lead to dry mucous membranes, tachycardia, and hypotension. Fever and abdominal tenderness may also be present. Laboratory evaluation reveals hyperglycemia, ketosis (β -hydroxybutyrate > acetoacetate), and metabolic acidosis (arterial pH 6.8–7.3) with an increased anion gap (Table 25-1). The fluid deficit is often 3–5 L and can be greater. Despite a total-body potassium deficit, the serum potassium at presentation may be normal or mildly high as a result of acidosis. Similarly, phosphate may be normal at presentation despite total-body phosphate depletion. Leukocytosis, hypertriglyceridemia, and hyperlipoproteinemia are common. Hyperamylasemia is usually of salivary origin but may suggest a diagnosis of pancreatitis. The measured serum sodium is reduced as a consequence of osmotic fluid shifts due to hyperglycemia (1.6-meq reduction for each 5.6-mmol/L [100-mg/dL] rise in the serum glucose).

TREATMENT

Diabetic Ketoacidosis

The management of DKA is outlined in [Table 25-2](#).

HYPERGLYCEMIC HYPEROSMOLAR STATE

■ ETIOLOGY

Relative insulin deficiency and inadequate fluid intake are the underlying causes of HHS. Hyperglycemia induces an osmotic diuresis that leads to profound

TABLE 25-2 Management of Diabetic Ketoacidosis

1. Confirm diagnosis (\uparrow plasma glucose, positive serum ketones, metabolic acidosis).
2. Admit to hospital; intensive care setting may be necessary for frequent monitoring or if pH <7.00 or unconscious.
3. Assess:
Serum electrolytes (K^+ , Na^+ , Mg^{2+} , Cl^- , bicarbonate, phosphate)
Acid-base status—pH, HCO_3^- , PCO_2 , β -hydroxybutyrate
Renal function (creatinine, urine output)
4. Replace fluids: 2–3 L of 0.9% saline over first 1–3 h (10–20 mL/kg per hour); subsequently, 0.45% saline at 250–500 mL/h; change to 5% glucose and 0.45% saline at 150–250 mL/h when plasma glucose reaches 250 mg/dL (13.9 mmol/L).
5. Administer short-acting regular insulin: IV (0.1 units/kg), then 0.1 units/kg per hour by continuous IV infusion; increase two- to threefold if no response by 2–4 h. If the initial serum potassium is <3.3 mmol/L (3.3 meq/L), do not administer insulin until the potassium is corrected.
6. Assess pt: What precipitated the episode (noncompliance, infection, trauma, pregnancy, infarction, cocaine)? Initiate appropriate workup for precipitating event (cultures, CXR, ECG).
7. Measure capillary glucose every 1–2 h; measure electrolytes (especially K^+ , bicarbonate, phosphate) and anion gap every 4 h for first 24 h.
8. Monitor blood pressure, pulse, respirations, mental status, fluid intake, and output every 1–4 h.
9. Replace K^+ : 10 meq/h when plasma K^+ <5.0–5.2 meq/L (or 20–30 meq/L of infusion fluid), ECG normal, urine flow and normal creatinine documented; administer 40–80 meq/h when plasma K^+ <3.5 meq/L or if bicarbonate is given. If initial serum potassium is >5.2 mmol/L (5.2 meq/L), do not supplement K^+ until the potassium is corrected.
10. See text about bicarbonate or phosphate supplementation.
11. Continue above until pt is stable, glucose goal is 8.3–11.1 mmol/L (150–200 mg/dL), and acidosis is resolved. Insulin infusion may be decreased to 0.02–0.1 units/kg per hour.
12. Administer long-acting insulin as soon as pt is eating. Allow for a 2–4 h overlap in insulin infusion and SC long-acting insulin injection.

Source: Adapted from Sperling M: *Therapy for Diabetes Mellitus and Related Disorders*. American Diabetes Association, Alexandria, VA, 1998; and Nyenwe EA, Kitabchi AE: *Metabolism* 65:507, 2016.

intravascular volume depletion. HHS is often precipitated by a serious, concurrent illness such as myocardial infarction or sepsis and is compounded by conditions that impede access to water.

■ CLINICAL FEATURES

Presenting symptoms include polyuria, thirst, and altered mental state, ranging from lethargy to coma. Notably absent are symptoms of nausea, vomiting, and abdominal pain and the Kussmaul respirations characteristic of DKA. The prototypical pt is an elderly individual with a history of polyuria, weight loss, and diminished oral intake. The laboratory features are summarized in Table 25-1. In contrast to DKA, acidosis and ketonemia are usually not found; however, a small anion gap may be due to lactic acidosis, and moderate ketonuria may occur from starvation. Prerenal azotemia is typically present. Although the measured serum

sodium may be normal or slightly low, the corrected serum sodium is usually increased (add 1.6 meq to measured sodium for each 5.6-mmol/L [100-mg/dL] rise in the serum glucose). HHS, even when adequately treated, has a significant mortality rate (up to 15%), which is in part explained by comorbidities and pt age.

TREATMENT

Hyperglycemic Hyperosmolar State

The precipitating problem should be sought and treated. Sufficient IV fluids (1–3 L of 0.9% normal saline over the first 2–3 h) should be given to stabilize the hemodynamic status. The calculated free water deficit (usually 9–10 L) should be reversed over the next 1–2 days, using 0.45% saline initially then 5% dextrose in water. Overly rapid fluid replacement should be avoided to prevent worsening of neurologic status. Potassium repletion is usually necessary. The plasma glucose may drop precipitously with hydration alone, though insulin therapy with an IV bolus of 0.1 units/kg followed by a constant infusion rate (0.1 units/kg per hour) is usually required. If the serum glucose does not fall, the insulin infusion rate should be doubled. Glucose should be added to IV fluid when the plasma glucose falls to 11.1–13.9 mmol/L (200–250 mg/dL), and the insulin infusion rate should be decreased to 0.02–0.1 unit/kg per hour. The insulin infusion should be continued until the pt has resumed eating and can be transitioned to a subcutaneous insulin regimen.

26

Hypoglycemia



Glucose is an obligate metabolic fuel for the brain. Hypoglycemia should be considered in any pt with confusion, altered level of consciousness, or seizures. Counterregulatory responses to hypoglycemia include insulin suppression and the release of catecholamines, glucagon, growth hormone, and cortisol.

The laboratory diagnosis of hypoglycemia is usually defined as a plasma glucose level <2.5 – 2.8 mmol/L (<45 – 50 mg/dL), although the absolute glucose level at which symptoms occur varies among individuals. For this reason, *Whipple's triad* should be present: (1) symptoms consistent with hypoglycemia, (2) a low plasma glucose concentration measured by a method capable of accurately measuring low glucose levels (not a glucose monitor), and (3) relief of symptoms after the plasma glucose level is raised.

ETIOLOGY

Hypoglycemia occurs most commonly as a result of treating pts with diabetes mellitus (Table 26-1). Additional factors to be considered in any pt with hypoglycemia are as follows:

1. Drugs: insulin, insulin secretagogues (especially chlorpropamide, repaglinide, nateglinide), alcohol, high doses of salicylates, sulfonamides, pentamidine, quinine, quinolones
2. Critical illness: hepatic, renal, or cardiac failure; sepsis; prolonged starvation
3. Hormone deficiencies: adrenal insufficiency, hypopituitarism (particularly in young children)

TABLE 26-1 Causes of Hypoglycemia in Adults**Ill or Medicated Individual**

1. Drugs
 - Insulin or insulin secretagogue
 - Alcohol
 - Others
2. Critical illness
 - Hepatic, renal, or cardiac failure
 - Sepsis
 - Inanition
3. Hormone deficiency
 - Cortisol
 - Growth hormone
 - Glucagon and epinephrine (in insulin-deficient diabetes)
4. Non- β -cell tumor (e.g., Mesenchymal tumors)

Seemingly Well Individual

5. Endogenous hyperinsulinism
 - Insulinoma
 - Functional β -cell disorders (nesidioblastosis)
 - Noninsulinoma pancreatogenous hypoglycemia
 - Post-gastric bypass hypoglycemia
 - Insulin autoimmune hypoglycemia
 - Antibody to insulin
 - Antibody to insulin receptor
 - Insulin secretagogue
 - Other
6. Disorders of gluconeogenesis and fatty acid oxidation
7. Exercise
8. Accidental, surreptitious, or malicious hypoglycemia

Source: Adapted from Cryer PE et al: Evaluation and management of adult hypoglycemic disorders: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 94:709, 2009. ©The Endocrine Society, 2009.

4. Insulinoma (pancreatic β cell tumor), β cell hyperplasia (nesidioblastosis; congenital or after gastric or bariatric surgery)
5. Other rare etiologies: non- β cell tumors (large mesenchymal or epithelial tumors producing an incompletely processed IGF-II, other nonpancreatic tumors), antibodies to insulin or the insulin receptor, inherited enzymatic defects such as hereditary fructose intolerance and galactosemia.

CLINICAL FEATURES

Symptoms of hypoglycemia can be divided into autonomic (adrenergic: palpitations, tremor, and anxiety; cholinergic: sweating, hunger, and paresthesia) and neuroglycopenic (behavioral changes, confusion, fatigue, seizure, loss of consciousness, and, if hypoglycemia is severe and prolonged, death). Signs of autonomic discharge, such as tachycardia, cardiac arrhythmia, elevated systolic blood pressure, pallor, and diaphoresis, are typically present in a pt with hypoglycemia awareness but may be absent in a pt with pure neuroglycopenia.

TABLE 26-2 Diagnostic Interpretation of Hypoglycemia

DIAGNOSIS	GLUCOSE, mmol/L (mg/dL)	INSULIN, μ U/mL	C-PEPTIDE, pmol/L	PROINSULIN, pmol/L	URINE OR PLASMA SULFONYLUREA
Nonhypoglycemic	≥ 2.2 (≥ 40)	< 3	< 200	< 5	No
Insulinoma	≤ 2.5 (≤ 45)	≥ 3	≥ 200	≥ 5	No
Exogenous insulin	≤ 2.5 (≤ 45)	$\geq 3^a$	< 200	< 5	No
Sulfonylurea	≤ 2.5 (≤ 45)	≥ 3	≥ 200	≥ 5	Yes
Non-insulin mediated	≤ 2.5 (≤ 45)	< 3	< 200	< 5	No

^aOften very high.

Recurrent hypoglycemia shifts thresholds for the autonomic symptoms and counterregulatory responses to lower glucose levels, leading to hypoglycemic unawareness. Under these circumstances, the first manifestation of hypoglycemia is neuroglycopenia, placing pts at risk of being unable to treat themselves.

■ DIAGNOSIS

Diagnosis of the hypoglycemic mechanism is critical for choosing a treatment that prevents recurrent hypoglycemia. Urgent treatment is often necessary in pts with suspected hypoglycemia. Nevertheless, blood should be drawn at the time of symptoms, whenever possible before the administration of glucose, to allow documentation of hypoglycemia as the cause of symptoms. If the glucose level is low and the cause of hypoglycemia is unknown, additional assays should be performed on blood obtained at the time of a low plasma glucose. These should include insulin, proinsulin, C-peptide, sulfonylurea levels, cortisol, and ethanol. In the absence of documented spontaneous hypoglycemia, overnight fasting or food deprivation during observation in the outpatient setting will sometimes elicit hypoglycemia and allow diagnostic evaluation. An extended (up to 72 h) fast under careful supervision in the hospital may be required—the test should be terminated if plasma glucose drops to <2.5 mmol/L (45 mg/dL) and the pt has symptoms.

Interpretation of fasting test results is shown in [Table 26-2](#).

TREATMENT

Hypoglycemia

The syndrome of hypoglycemic unawareness in pts with diabetes mellitus is reversible after as little as 2 weeks of scrupulous avoidance of hypoglycemia. This involves a shift of glycemic thresholds for sympathetic autonomic symptoms back to higher glucose concentrations.

Acute therapy of hypoglycemia requires administration of oral glucose or, if unavailable, rapidly absorbable sugar (e.g., fruit juice), or 25 g of a 50% solution IV followed by a constant infusion of 5% or 10% dextrose if parenteral therapy is necessary. Hypoglycemia from sulfonylureas is often prolonged, requiring treatment and monitoring for ≥ 24 h. SC or IM glucagon can be used in diabetics. Prevention of recurrent hypoglycemia requires treatment of the underlying cause of hypoglycemia, including discontinuation or dose reduction of offending drugs, treatment of critical illnesses, replacement of hormonal deficiencies, and surgery of insulinomas or other tumors. Diazoxide or octreotide therapy can be used to control hypoglycemia in inoperable metastatic insulinoma or nesidioblastosis. Treatment of other forms of hypoglycemia is dietary, with avoidance of fasting and ingestion of frequent small meals.

27

Oncologic Emergencies



Emergencies in the cancer pt may be classified into three categories: effects from tumor expansion, metabolic or hormonal effects mediated by tumor products, and treatment complications.

STRUCTURAL/OBSTRUCTIVE ONCOLOGIC EMERGENCIES

The most common problems are superior vena cava syndrome; pericardial effusion/tamponade; spinal cord compression; seizures (**Chap. 184**) and/or increased intracranial pressure; and intestinal, urinary, or biliary obstruction. The last three conditions are discussed in **Chap. 71** in HPIM-20.

■ SUPERIOR VENA CAVA SYNDROME (**FIG. 27-1**)

Obstruction of the superior vena cava reduces venous return from the head, neck, and upper extremities. About 85% of cases are due to lung cancer; lymphoma and thrombosis of central venous catheters are other causes. Pts often present with facial swelling, dyspnea, and cough. In severe cases, the mediastinal

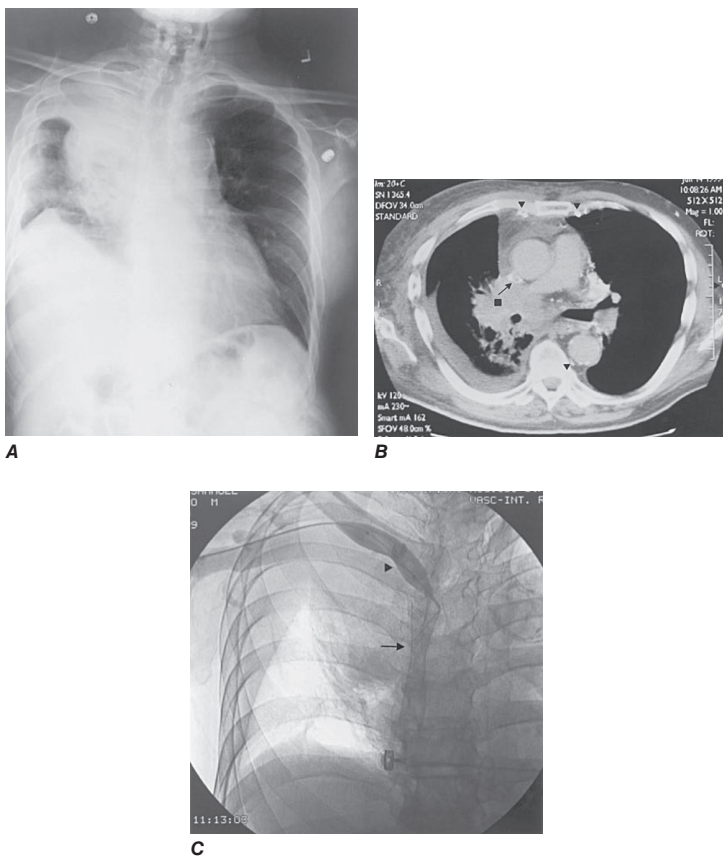


FIGURE 27-1 Superior vena cava syndrome (SVCS). **A.** Chest radiographs of a 59-year-old man with recurrent SVCS caused by non-small-cell lung cancer showing right paratracheal mass with right pleural effusion. **B.** Computed tomography of same pt demonstrating obstruction of the superior vena cava with thrombosis (arrow) by the lung cancer (square) and collaterals (arrowheads). **C.** Balloon angioplasty (arrowhead) with stent (arrow) in same pt.

mass lesion may cause tracheal obstruction. Dilated neck veins and increased collateral veins on anterior chest wall are noted on physical examination. Chest x-ray (CXR) documents widening of the superior mediastinum; 25% of pts have a right-sided pleural effusion.

TREATMENT

Superior Vena Cava Syndrome

Radiation therapy is the treatment of choice for non-small-cell lung cancer and other solid tumors; chemotherapy is effective in small-cell lung cancer, lymphoma, and germ cell tumors. Symptoms recur in 10–30% of pts and can be palliated by venous stenting. Clotted central catheters producing this syndrome should be removed and anticoagulation therapy initiated.

■ PERICARDIAL EFFUSION/TAMPONADE

Accumulation of fluid in the pericardium impairs filling of the heart and decreases cardiac output. Most commonly seen in pts with lung or breast cancers, leukemias, or lymphomas, pericardial tamponade may also develop as a late complication of mediastinal radiation therapy (constrictive pericarditis). Common symptoms are dyspnea, cough, chest pain, orthopnea, and weakness. Pleural effusion, sinus tachycardia, jugular venous distention, hepatomegaly, and cyanosis are frequent physical findings. Paradoxical pulse, decreased heart sounds, pulsus alternans, and friction rub are less common with malignant than nonmalignant pericardial disease. Echocardiography is diagnostic; pericardiocentesis may show serous or bloody exudate, and cytology usually shows malignant cells.

TREATMENT

Pericardial Effusion/Tamponade

Drainage of fluid from the pericardial sac may be lifesaving until a definitive surgical procedure (pericardial stripping or window) can be performed.

■ SPINAL CORD COMPRESSION

Primary spinal cord tumors occur rarely, and cord compression is most commonly due to epidural metastases from vertebral bodies involved with tumor, especially from prostate, lung, breast, lymphoma, and myeloma primaries. Pts present with back pain, worse when recumbent, with local tenderness. Loss of bowel and bladder control may occur. On physical examination, pts have a loss of sensation below a horizontal line on the trunk, called a *sensory level*, which usually corresponds to one or two vertebrae below the site of compression. Weakness and spasticity of the legs and hyperactive reflexes with upgoing toes on Babinski testing are often noted. Spine radiographs may reveal erosion of the pedicles (winking owl sign), lytic or sclerotic vertebral body lesions, and vertebral collapse. Collapse alone is not a reliable indicator of tumor; it is a common manifestation of a more common disease, osteoporosis. MRI can visualize the cord throughout its length and define the extent of tumor involvement.

TREATMENT

Spinal Cord Compression (See [Chap. 22](#))

■ EMERGENT PARANEOPLASTIC SYNDROMES

Most paraneoplastic syndromes have an insidious onset (Chap. 78). Hypercalcemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and adrenal insufficiency may present as emergencies.

■ HYPERCALCEMIA

The most common paraneoplastic syndrome, hypercalcemia occurs in about 10% of cancer pts, particularly those with lung, breast, head and neck, and kidney cancer and myeloma. Bone resorption mediated by parathyroid hormone-related protein is the most common mechanism; interleukin 1 (IL-1), IL-6, tumor necrosis factor, and transforming growth factor β may act locally in tumor-involved bone. Pts usually present with nonspecific symptoms: fatigue, anorexia, constipation, weakness. Hypoalbuminemia associated with malignancy may make symptoms worse for any given serum calcium level because more calcium will be free rather than protein bound.

TREATMENT

Hypercalcemia

Saline hydration, antiresorptive agents (e.g., pamidronate, 60–90 mg IV over 4 h, or zoledronate, 4–8 mg IV), and glucocorticoids usually lower calcium levels significantly within 1–3 days. Treatment effects usually last several weeks. Treatment of the underlying malignancy is also important.

■ SIADH

Induced by the action of arginine vasopressin produced by certain tumors (especially small cell cancer of the lung), SIADH is characterized by hyponatremia, inappropriately concentrated urine, and high urine sodium excretion in the absence of volume depletion. Most pts with SIADH are asymptomatic. When serum sodium falls to <115 meq/L, pts may experience anorexia, depression, lethargy, irritability, confusion, weakness, and personality changes.

TREATMENT

SIADH

Water restriction controls mild forms. Demeclocycline (150–300 mg PO tid or qid) inhibits the effects of vasopressin on the renal tubule but has a slow onset of action (1 week). Conivaptan can be given PO (20–120 mg bid) or IV (10–40 mg); tolvaptan (15 mg PO daily) is a vasopressin antagonist that can be used. Treatment of the underlying malignancy is also important. If the pt has mental status changes with sodium levels <115 meq/L, normal saline infusion plus furosemide to increase free water clearance may provide more rapid improvement. Rate of correction should not exceed 0.5–1 meq/L per hour. More rapid change can produce fluid shifts that lead to brain damage.

■ ADRENAL INSUFFICIENCY

The infiltration of the adrenals by tumor and their destruction by hemorrhage are the two most common causes. In addition, the immunologic checkpoint inhibiting antibodies, ipilimumab, nivolumab, and pembrolizumab can produce an autoimmune hypophysitis that leads to adrenal insufficiency. Symptoms such as nausea, vomiting, anorexia, and orthostatic hypotension may be attributed to progressive cancer or to treatment side effects. Certain treatments

(e.g., ketoconazole, aminoglutethimide) may directly interfere with steroid synthesis in the adrenal.

TREATMENT

Adrenal Insufficiency

In emergencies, a bolus of 100-mg IV hydrocortisone is followed by a continuous infusion of 10 mg/h. In nonemergent but stressful circumstances, 100–200 mg/d oral hydrocortisone is the beginning dose, tapered to maintenance of 15–37.5 mg/d. Fludrocortisone (0.1 mg/d) may be required in the presence of hyperkalemia.

TREATMENT COMPLICATIONS

Complications from treatment may occur acutely or emerge only many years after treatment. Toxicity may be either related to the agents used to treat the cancer or from the response of the cancer to the treatment (e.g., leaving a perforation in a hollow viscus or causing metabolic complications such as tumor lysis syndrome). Several treatment complications present as emergencies. Fever and neutropenia and tumor lysis syndrome will be discussed here; others are discussed in [Chap. 71](#) in HPIM-20.

■ FEVER AND NEUTROPENIA

Many cancer pts are treated with myelotoxic agents. When peripheral blood granulocyte counts are $<1000/\mu\text{L}$, the risk of infection is substantially increased (48 infections/100 pts). A neutropenic pt who develops a fever ($>38^\circ\text{C}$ [100.4°F]) should undergo physical examination with special attention to skin lesions, mucous membranes, IV catheter sites, and perirectal area. Two sets of blood cultures from different sites should be drawn and a CXR performed, and any additional tests should be guided by findings from the history and physical examination. Any fluid collections should be tapped, and urine and/or fluids should be examined under the microscope for evidence of infection.

TREATMENT

Fever and Neutropenia

After cultures are obtained, all pts should receive IV broad-spectrum antibiotics (e.g., ceftazidime, 1 g q8h). If an obvious infectious site is found, the antibiotic regimen is designed to cover organisms that may cause the infection. Usually therapy should be started with an agent or agents that cover both gram-positive and -negative organisms. If the fever resolves, treatment should continue until neutropenia resolves. Persistence of febrile neutropenia after 7 days should lead to addition of amphotericin B (or another broad-spectrum antifungal agent like posaconazole) to the antibiotic regimen.

■ TUMOR LYSIS SYNDROME

When rapidly growing tumors are treated with effective chemotherapy regimens, the dying tumor cells can release large amounts of nucleic acid breakdown products (chiefly uric acid), potassium, phosphate, and lactic acid. The phosphate elevations can lead to hypocalcemia. The increased uric acid, especially in the setting of acidosis, can precipitate in the renal tubules and lead to renal failure. The renal failure can exacerbate the hyperkalemia.

TREATMENT**Tumor Lysis Syndrome**

Prevention is the best approach. Maintain hydration with 3 L/d of saline, keep urine pH >7.0 with bicarbonate administration, and start allopurinol, 300 mg/m² per day, 24 h before starting chemotherapy. Once chemotherapy is given, monitor serum electrolytes every 6 h. If after 24 h, uric acid (>8 mg/dL) and serum creatinine (>1.6 mg/dL) are elevated, rasburicase (recombinant urate oxidase), 0.2 mg/kg IV daily, may lower uric acid levels. If serum potassium is >6.0 meq/L and renal failure ensues, hemodialysis may be required. Maintain normal calcium levels.

28

Anaphylaxis**DEFINITION**

A life-threatening systemic hypersensitivity reaction to contact with an allergen; it may appear within minutes of exposure to the offending substance. Manifestations include respiratory distress, pruritus, urticaria, mucous membrane swelling, GI disturbances (including nausea, vomiting, abdominal pain, and diarrhea), and vascular collapse. Virtually any allergen may trigger an anaphylactic reaction, but among the more common agents are proteins such as antisera, hormones, pollen extracts, Hymenoptera venom, and foods; drugs (especially antibiotics); and diagnostic agents such as IV contrast material. Atopy does not seem to predispose to anaphylaxis from drug reactions or venom exposures. Anaphylactic transfusion reactions are covered in [Chap. 9](#).

CLINICAL PRESENTATION

Time to onset is variable, but symptoms usually occur within seconds to minutes of exposure to the offending antigen. Eighty to ninety percent are uniphasic; however, 10–20% are biphasic where anaphylactic symptoms return about an hour after resolution of the initial symptoms:

- *Respiratory*: mucous membrane swelling, hoarseness, stridor, wheezing
- *Cardiovascular*: tachycardia, hypotension
- *Cutaneous*: pruritus, urticaria, angioedema

DIAGNOSIS

Diagnosis is made by obtaining history of exposure to offending substance with subsequent development of characteristic complex of symptoms.

TREATMENT**Anaphylaxis**

Treatment of first choice is 0.3–0.5 mL of 1:1000 (1.0 mg/mL) epinephrine IM, with repeated doses as required at 5- to 20-min intervals for a severe reaction. The pt should be placed in the supine position to support venous return and prevent “empty heart syndrome.”

Epinephrine provides both α - and β -adrenergic effects, resulting in vasoconstriction and bronchial smooth-muscle relaxation. Beta blockers are relatively contraindicated in persons at risk for anaphylactic reactions.

The following should also be used as necessary:

- Normal saline, and vasopressor agents, if intractable hypotension occurs.
- Antihistamines such as diphenhydramine 50–100 mg IM or IV.
- Nebulized bronchodilators for bronchospasm.
- Oxygen; endotracheal intubation or tracheostomy may be necessary for progressive hypoxemia.
- Glucocorticoids (methylprednisolone 0.5–1.0 mg/kg IV); not useful for acute manifestations but may help alleviate later recurrence of hypotension, bronchospasm, or urticaria.

■ PREVENTION

Avoidance of offending antigen, where possible; skin testing and desensitization to materials such as penicillin and Hymenoptera venom, if necessary. Individuals should wear an informational bracelet and have immediate access to an unexpired epinephrine kit.

29

Bites, Venoms, Stings, and Marine Poisonings



MAMMALIAN BITES

- Each year, there are ~300 dog and cat bites per 100,000 population in the United States, with most bites inflicted by pet animals.
- The microbiology of bite wounds typically reflects the oral flora of the biting animal.
- Bites from many different animals can transmit rabies and tularemia.

■ DOG BITES

- **Epidemiology:** Dogs bite ≥ 4.7 million people per year, causing 80% of all animal bites; 15–20% of dog bites become infected.
- **Bacteriology (Table 29-1):** Includes aerobic and anaerobic organisms, such as β -hemolytic streptococci; *Eikenella corrodens*; *Capnocytophaga canimorsus*; and *Pasteurella*, *Staphylococcus*, *Actinomyces*, *Prevotella*, *Neisseria*, and *Fusobacterium* species.
- **Clinical features:** Typically manifest within 8–24 h after the bite as local cellulitis with purulent, sometimes foul-smelling discharge. Systemic spread (e.g., bacteremia, endocarditis, brain abscess) can occur. *C. canimorsus* infection can present as sepsis syndrome, disseminated intravascular coagulation (DIC), and renal failure, particularly in pts who are splenectomized, have hepatic dysfunction, or are otherwise immunosuppressed.

■ CAT BITES

- **Epidemiology:** Cat bites and scratches result in infection in >50% of cases.
- **Bacteriology (Table 29-1):** Includes organisms similar to those involved in dog bites. *Pasteurella multocida* and *Bartonella henselae* (the agent of cat-scratch

TABLE 29-1 Management of Wound Infections Following Animal and Human Bites

BITING SPECIES	COMMONLY ISOLATED PATHOGENS	PREFERRED ANTIBIOTIC(S) ^a	ALTERNATIVE IN PENICILLIN-ALLERGIC PT	PROPHYLAXIS ADVISED FOR EARLY UNINFECTED WOUNDS	OTHER CONSIDERATIONS
Dog	<i>Staphylococcus aureus</i> , <i>Pasteurella multocida</i> , anaerobes, <i>Capnocytophaga canimorsus</i>	Amoxicillin/clavulanate (250–500 mg PO tid) or ampicillin/sulbactam (1.5–3.0 g IV q6h)	Clindamycin (150–300 mg PO qid) plus either TMP-SMX (1 DS tablet PO bid) or ciprofloxacin (500 mg PO bid)	Sometimes ^b	Consider rabies prophylaxis.
Cat	<i>P. multocida</i> , <i>S. aureus</i> , anaerobes	Amoxicillin/clavulanate or ampicillin/sulbactam as above	Clindamycin plus TMP-SMX as above or a fluoroquinolone	Usually	Consider rabies prophylaxis. Carefully evaluate for joint/bone penetration.
Human, occlusional	Viridans streptococci, <i>S. aureus</i> , <i>Haemophilus influenzae</i> , anaerobes	Amoxicillin/clavulanate or ampicillin/sulbactam as above	Erythromycin (500 mg PO qid) or a fluoroquinolone	Always	
Human, clenched-fist	As for occlusional, plus <i>Eikenella corrodens</i>	Ampicillin/sulbactam as above or imipenem (500 mg q6h)	Cefoxitin ^c	Always	Examine for tendon, nerve, or joint involvement.
Monkey	As for human bite	As for human bite	As for human bite	Always	For macaque monkeys, consider B virus prophylaxis with acyclovir.

Snake	<i>Pseudomonas aeruginosa</i> , <i>Proteus</i> spp., <i>Bacteroides fragilis</i> , <i>Clostridium</i> spp.	Ampicillin/sulbactam as above	Clindamycin plus TMP-SMX as above or a fluoroquinolone	Sometimes, especially with venomous snakes	Administer antivenin for venomous snakebite.
Rodent	<i>Streptobacillus moniliformis</i> , <i>Leptospira</i> spp., <i>P. multocida</i>	Penicillin VK (500 mg PO qid)	Doxycycline (100 mg PO bid)	Sometimes	
Aquatic animal (alligator, piranha, shark, moray eel, barracuda)	<i>Aeromonas hydrophila</i> , marine <i>Vibrio</i> spp. (<i>Vibrio vulnificus</i>)	Third-generation cephalosporin (e.g., ceftriaxone, 1 g IV q24h) plus doxycycline (100 mg PO bid)	Clindamycin plus levofloxacin (750 mg PO qd) plus doxycycline	Always	Obtain prompt surgical consultation, as risk for necrotizing infection is high with <i>Aeromonas</i> and <i>Vibrio</i> spp.

^aAntibiotic choices should be based on culture data when available. These suggestions for empirical therapy need to be tailored to individual circumstances and local conditions. IV regimens should be used for hospitalized pts. A single IV dose of antibiotics may be given to pts who will be discharged after initial management.

^bProphylactic antibiotics are suggested for severe or extensive wounds, facial wounds, and crush injuries; when bone or joint may be involved; and when comorbidity is present.

^cMay be hazardous in pts with immediate-type hypersensitivity to penicillin.

Abbreviations: DS, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole.

disease) are important cat-associated pathogens. Tularemia and sporotrichosis have been associated with cat bites.

- **Clinical features:** *P. multocida* infections can cause rapidly advancing inflammation and purulent discharge within a few hours after the bite. Because of deep tissue penetration by narrow, sharp feline incisors, cat bites are more likely than dog bites to cause septic arthritis or osteomyelitis.

■ OTHER NONHUMAN MAMMALIAN BITES

- *Old World monkeys (Macaca species):* Bites may transmit herpes B virus (*Herpesvirus simiae*), which can cause CNS infections with high mortality rates.
- *Seals, walruses, polar bears:* Bites may cause a chronic suppurative infection known as *seal finger*, which is probably due to *Mycoplasma* species.
- *Small rodents and their predators:* Bites may transmit *rat-bite fever*, caused by *Streptobacillus moniliformis* (in the United States) or *Spirillum minor* (in Asia).
 - *Rat-bite fever* occurs after the initial wound has healed, a feature distinguishing it from an acute bite-wound infection.
 - *S. moniliformis* infections manifest 3–10 days after the bite as fever, chills, myalgias, headache, and severe migratory arthralgias followed by a maculopapular rash involving the palms and soles. Disease can progress to metastatic abscesses, endocarditis, meningitis, and pneumonia.
- *Haverhill fever* is an *S. moniliformis* infection acquired from contaminated milk or drinking water and has manifestations similar to those described earlier.
 - *S. minor* infections cause local pain, purple swelling at the bite site, and associated lymphangitis and regional lymphadenopathy 1–4 weeks after the bite, with evolution into a nonspecific systemic illness.

■ HUMAN BITES

- **Epidemiology:** Human bites become infected 10–15% of the time.
 - *Occlusional* injuries are inflicted by actual biting; *clenched-fist* injuries result when the fist of one individual strikes the teeth of another.
 - Clenched-fist injuries are more common and typically result in more serious infections (e.g., septic arthritis, tenosynovitis).
- **Bacteriology:** See Table 29-1.

TREATMENT

Mammalian Bites

- **Wound management:** Wound closure is controversial in bite injuries. After thorough cleansing, facial wounds <24 h old are usually sutured for cosmetic reasons and because the abundant facial blood supply lessens the risk of infection. Elsewhere on the body, many authorities do not attempt primary closure of wounds that are or may become infected (e.g., wounds >12 h old), preferring instead to irrigate them copiously, debride devitalized tissue, remove foreign bodies, and approximate the margins. Delayed primary closure may be undertaken after the risk of infection has passed. Puncture wounds due to cat bites should be left unsutured because of the high rate at which they become infected.
- **Antibiotic therapy:** See Table 29-1. Antibiotics are typically given for 3–5 days (as prophylaxis in pts presenting within 8 h of the bite) or for 10–14 days (as treatment for established infections).
- **Other prophylaxis:** Rabies prophylaxis (passive immunization with rabies immune globulin and active immunization with rabies vaccine) should be given in consultation with local and regional public health authorities. A tetanus booster for pts immunized previously but not boosted within 5 years

should be considered, as should primary immunization and tetanus immune globulin administration for pts not previously immunized against tetanus.

VENOMOUS SNAKEBITES

- **Epidemiology:** Worldwide, 1.2–5.5 million snakebites are sustained each year, with 421,000–1,841,000 envenomations and 20,000–94,000 deaths.
 - Bite rates are highest in temperate and tropical climates where populations subsist by manual agriculture and fishing.
 - Differentiation of venomous from nonvenomous snake species can be difficult; color pattern is notoriously misleading.
- **Clinical features:** Snake venoms are complex mixtures of enzymes and other substances that promote vascular leaking, cause tissue necrosis, affect the coagulation cascade, and impair organ function.
 - Specific presentations differ somewhat with the particular snake species.
 - Systemic symptoms may include hypotension, pulmonary edema, hemorrhage, altered mental status, or paralysis (including muscles of respiration).
- **Prognosis:** The overall mortality rate for venomous snakebite is <1% among U.S. victims who receive antivenom; the incidence of permanent functional loss in a bitten extremity is substantial.

TREATMENT

Venomous Snakebites

FIELD MANAGEMENT

- Get the victim to definitive care as soon as possible.
- Splint a bitten extremity and keep it at heart level to lessen bleeding and discomfort.
- *Avoid* incisions into the bite wound, cooling, consultation with traditional healers, tourniquets, and electric shock because these measures are ineffective and may increase local tissue damage.
- If the offending snake is reliably identified and known to be primarily neurotoxic, pressure immobilization (wrapping of the entire limb in a bandage at a pressure of 40–70 mmHg for upper limbs or 55–70 mmHg for lower limbs) may be used. The victim must be carried to medical care, because walking will disperse venom from the bite site regardless of its anatomic location.

HOSPITAL MANAGEMENT

- Monitor vital signs, cardiac rhythm, urine output, and O₂ saturation closely. Watch for evidence of cranial nerve dysfunction (e.g., ptosis), which may precede difficulty swallowing or respiratory insufficiency.
- Note the level of swelling and the circumference of the affected limb every 15 min until swelling has stabilized.
- Treat shock initially with isotonic saline (20–40 mL/kg IV); if hypotension persists, try 5% albumin (10–20 mL/kg IV) and vasopressors.
- Begin the search for appropriate, specific antivenom early in all cases of known venomous snakebite. In the United States, round-the-clock assistance is available from regional poison control centers.
 1. Any evidence of systemic envenomation (systemic symptoms or signs, laboratory abnormalities) and significant, progressive local findings (e.g., swelling that crosses a joint, involves more than half of the bitten limb, or is

- rapidly spreading; extensive blistering or bruising; severe pain) are indications for antivenom administration.
2. Treating physicians should seek advice from snakebite experts regarding indications for and dosing of antivenom. The duration of antivenom administration depends on the offending snake species, but multiple doses are not effective in reversing bite responses that have already been established (e.g., renal failure, established paralysis, necrosis).
 3. Worldwide, antivenom quality varies. Rates of anaphylactoid reaction can exceed 50%, prompting some authorities to recommend pretreatment with low-dose SC epinephrine (0.25 mg of 1:1000 aqueous solution). Prophylactic use of antihistamines and glucocorticoids is not beneficial. CroFab, an antivenom used in the United States against North American pit viper species, poses a low risk of allergy elicitation.
 4. A trial of acetylcholinesterase inhibitors should be undertaken for pts with objective evidence of neurologic dysfunction because this treatment may cause neurologic improvement in pts bitten by snakes with postsynaptic neurotoxins.
- Elevate the bitten extremity above heart level once antivenom administration has been initiated.
 - Update tetanus immunization.
 - Observe pts for muscle-compartment syndrome.
 - Observe pts with signs of envenomation in the hospital for at least 24 h. Pts with “dry” bites should be watched for at least 8 h because symptoms are commonly delayed.

MARINE ENVENOMATIONS

- Much of the management of envenomation by marine creatures is supportive in nature. Specific marine antivenom can be used when appropriate.

■ INVERTEBRATES

- **Etiology:** Injuries from cnidocysts (stinging cells) of hydroids, fire coral, jellyfish, Portuguese man-of-wars, and sea anemones cause similar clinical symptoms that differ in severity. Other invertebrates (e.g., sea sponges, annelid worms, sea urchins) have spines that can inflict painful stings.
- **Clinical features:** Pain (prickling, burning, and throbbing), pruritus, and paresthesia develop immediately at the site of the bite. Neurologic, GI, renal, cardiovascular, respiratory, rheumatologic, and ocular symptoms have been described.

TREATMENT

Marine Invertebrate Envenomations

- Decontaminate the skin immediately with saline. Vinegar (5% acetic acid) is an all-purpose agent useful for pain caused by a number of different species. Rubbing alcohol (40–70% isopropanol) can be used as a substitute, although it may exacerbate nematocyst discharge in some species.
- After decontamination, topical anesthetics, antihistamines, or steroid lotions may be helpful.
- Narcotics may be necessary for persistent pain.
- Muscle spasms may respond to diazepam (2–5 mg titrated upward as needed) or IV 10% calcium gluconate (5–10 mL).

■ VERTEBRATES

- **Etiology:** Many marine vertebrates including stingrays, scorpionfish (e.g., lionfish and stonefish), marine catfish, and horned venomous sharks are capable of envenomating humans.
- **Clinical features:** Depend on the offending fish
 - *Stingrays:* Inflict both an envenomation and a traumatic wound. The venom causes immediate, intense pain that peaks at 30–60 min and may last up to 48 h. The wound often becomes ischemic and heals poorly. Systemic effects can include weakness, dysrhythmias, hypotension, paralysis, and rare deaths.
 - *Stonefish:* Because of the neuromuscular toxicity of the venom, stings may be life-threatening, and death may occur within 6–8 h. Local pain is immediate and intense and may last for days. Systemic effects are similar to those of stingray envenomations.

TREATMENT**Marine Vertebrate Envenomations**

- Immerse the affected part immediately in nonscalding hot water (113°F/45°C) for 30–90 min or until there is significant pain relief. Repeated hot-water therapy may help with recurrent pain.
- Explore, debride, and vigorously irrigate the wound after local/regional anesthetics are given.
- Antivenom is available for stonefish and serious scorpionfish envenomations. In the United States, contact the nearest regional poison control center for assistance.
- Leave wounds to heal by secondary intention or to be treated by delayed primary closure.
- Update tetanus immunization.
- Consider empirical antibiotics to cover *Staphylococcus* and *Streptococcus* species for serious wounds or envenomations in immunocompromised hosts. Coverage should be broadened to include *Vibrio* species if the wound is primarily closed.

MARINE POISONINGS**■ CIGUATERA**

- **Epidemiology:** The most common fish-associated nonbacterial food poisoning in the United States, with most cases occurring in Florida and Hawaii
 - In all, 20,000–50,000 people are affected annually, although 90% of cases may go unreported.
 - Three-quarters of cases involve barracuda, snapper, jack, or grouper found in the Indian Ocean, the South Pacific, and the Caribbean Sea.
- **Pathogenesis:** Ciguatera toxin acts on neuron voltage-gated sodium channels and is created by marine dinoflagellates, whose consumption by fish allows the toxin to accumulate in the food chain. Three major ciguateric toxins—CTX-1, -2, and -3—are found in the flesh and viscera of ciguateric fish, are typically unaffected by external factors (e.g., heat, cold, freeze-drying, gastric acid), and do not generally affect the fish (e.g., odor, color, or taste).
- **Clinical features:** Pts typically develop symptoms within 2–6 h, with virtually all pts affected within 24 h. The diagnosis is made on clinical grounds.

- Symptoms can be numerous (>150 reported) and include diarrhea, vomiting, abdominal pain, neurologic signs (e.g., paresthesias, weakness, fasciculations, ataxia), maculopapular or vesicular rash, and hemodynamic instability.
- A pathognomonic symptom—reversal of hot and cold tactile perception—develops within 3–5 days and can last for months.

TREATMENT

Ciguatera Poisoning

- Therapy is supportive and based on symptoms.
- Cool showers, hydroxyzine (25 mg PO q6–8h), or amitriptyline (25 mg PO bid) may ameliorate pruritus and dysesthesias.
- For 6 months after disease onset, the pt should avoid ingestion of fish (fresh or preserved), shellfish, fish oils, fish or shellfish sauces, alcohol, nuts, and nut oils.

■ PARALYTIC SHELLFISH POISONING

- **Etiology:** Induced by ingestion of contaminated filter-feeding organisms (e.g., clams, oysters, scallops, mussels) that concentrate water-soluble, heat- and acid-stable chemical toxins
 - The best-characterized and most frequently identified paralytic shellfish toxin is saxitoxin.
 - Paralytic shellfish toxins cannot be destroyed by ordinary cooking.
- **Clinical features:** Oral paresthesias (initially tingling and burning, later numbness) develop within minutes to hours after ingestion of contaminated shellfish and progress to involve the neck and distal extremities. Flaccid paralysis and respiratory insufficiency may follow 2–12 h later; 12% of pts die, most within 18 h.

TREATMENT

Paralytic Shellfish Poisoning

- If pts present within hours of ingestion, gastric lavage and stomach irrigation with 2 L of a 2% sodium bicarbonate solution may be of benefit, as may administration of activated charcoal (50–100 g) and non-magnesium-based cathartics (e.g., sorbitol, 20–50 g).
- The pt should be monitored for respiratory paralysis for at least 24 h.

■ SCOMBROID

- **Etiology:** Histamine intoxication due to bacterial decomposition of inadequately preserved or refrigerated scombroid fish (e.g., tuna, mackerel, saury, needlefish, wahoo, skipjack, and bonito)
 - This syndrome can also occur with nonscombroid fish (e.g., sardines, herring, dolphinfish, amberjack, and bluefish).
 - Affected fish typically have a sharply metallic or peppery taste but may be normal in appearance and flavor.
 - Because of uneven distribution of decay within the fish, not all people who eat an affected fish will become ill.
- **Clinical features:** Within 15–90 min of ingestion, pts present with oral tingling, mild abdominal pain, and nausea. Pts with severe cases develop flushing

(exacerbated by UV exposure), pruritus, urticaria, angioneurotic edema, bronchospasm, GI symptoms, and hypotension.

- Symptoms generally resolve within 8–12 h.
- May be worse in pts concurrently taking isoniazid because of inhibition of GI tract histaminases.

TREATMENT

Scombroid Poisoning

- Treatment consists of antihistamine (H_1 or H_2) administration.
- If bronchospasm is severe, an inhaled bronchodilator or injected epinephrine may be used.

ARTHROPOD BITES AND STINGS

■ TICK BITES AND TICK PARALYSIS

- **Epidemiology:** Ticks are important carriers of vector-borne diseases (e.g., Lyme disease, babesiosis, anaplasmosis, ehrlichiosis) in the United States.
- **Etiology:** While ticks feed on blood from their hosts, their secretions may produce local reactions, transmit diverse pathogens, induce a febrile illness, or cause paralysis. Soft ticks attach for <1 h; hard ticks can feed for >1 week.
- **Clinical features:** Except for tick-borne diseases, most manifestations of tick bites are self-limited following tick removal.
 - *Tick-induced fever*, in the absence of pathogen transmission, is associated with headache, nausea, and malaise and usually resolves ≤ 36 h after the tick is removed.
 - *Tick paralysis* is an ascending flaccid paralysis due to a toxin in tick saliva that causes neuromuscular block and decreased nerve conduction.
 - Weakness begins symmetrically in the lower extremities ≤ 6 days after the tick's attachment and ascends symmetrically, causing complete paralysis of the extremities and cranial nerves.
 - Deep tendon reflexes are decreased or absent, but sensory examination and lumbar puncture (LP) yield normal findings.
 - Tick removal results in improvement within hours; failure to remove the tick may lead ultimately to respiratory paralysis and death.

TREATMENT

Tick Bites and Tick Paralysis

- Ticks should be removed with forceps applied close to the point of attachment, which should then be disinfected.
- Pts bitten by a deer tick in Lyme disease–endemic regions can receive a prophylactic oral dose of doxycycline (200 mg) within 72 h of tick removal.
- Tick removal within 36 h of attachment usually prevents transmission of the agents of Lyme disease, babesiosis, anaplasmosis, and ehrlichiosis.

■ SPIDER BITES

Recluse Spider Bites

- **Epidemiology:** Brown recluse spiders occur mainly in the south-central United States, and their close relatives are found in the Americas, Africa, and the Middle East. These spiders only infrequently bite humans, typically if threatened or pressed against the skin.

- **Clinical features:**

- Most bites by the brown recluse spider result in only minor injury with edema and erythema, although severe necrosis of the skin and SC tissue and systemic hemolysis may occur.
- Within hours, the site of the bite becomes painful and pruritic, with central induration surrounded by zones of ischemia and erythema.
- Fever and other nonspecific systemic symptoms may develop within 3 days of the bite.
- Lesions typically resolve within a few days, but severe cases can leave a large ulcer and a depressed scar that take months or years to heal.

TREATMENT

Recluse Spider Bites

- Initial management includes RICE (rest, ice, compression, elevation). Administration of analgesics, antihistamines, antibiotics, and tetanus prophylaxis should be undertaken as indicated.
 - Early debridement or surgical excision of the wound without closure delays healing.
-

Widow Spider Bites

- **Epidemiology:** Black widow spiders, recognized by a red hourglass marking on a shiny black ventral abdomen, are most abundant in the southeastern United States. Other *Latrodectus* species are present in other temperate and subtropical parts of the world.
- **Pathogenesis:** Female widow spiders produce a potent neurotoxin that binds irreversibly to presynaptic nerve terminals and causes release and depletion of acetylcholine and other neurotransmitters.
- **Clinical features:**
 - Within 60 min, painful cramps spread from the bite site to large muscles of the extremities and trunk.
 - Extreme abdominal muscular rigidity and pain may mimic peritonitis, but the abdomen is nontender.
 - Other features are similar to that of acetylcholine overdose (e.g., excessive salivation, lacrimation, urination, and defecation; GI upset; and emesis).
 - Although pain may subside within the first 12 h, it can recur for weeks.
 - Respiratory arrest, cerebral hemorrhage, or cardiac failure may occur.

TREATMENT

Widow Spider Bites

- Treatment consists of RICE and tetanus prophylaxis.
 - The use of antivenom is limited by its questionable efficacy and concern about anaphylaxis and serum sickness.
-

SCORPION STINGS

- **Epidemiology:** Only ~30 of the ~1000 species of scorpions produce potentially lethal venoms, causing >5000 deaths worldwide each year. Among scorpions in the United States, only the bark scorpion (*Centruroides sculpturatus* or *C. exilicauda*) in the Southwest produces a potentially lethal venom.

- **Clinical features:** The severity of symptoms depends on the particular scorpion species. For the U.S. bark scorpion, symptoms progress to maximal severity in ~5 h and typically subside within 1–2 days, although pain and paresthesias can last for weeks.
 - *Bark scorpion:* Swelling generally is not apparent; tapping on the affected area (*the tap test*) can accentuate pain, paresthesia, and hyperesthesia. Cranial nerve dysfunction and skeletal muscle hyperexcitability develop within hours. Complications include tachycardia, arrhythmias, hypertension, hyperthermia, rhabdomyolysis, acidosis, and occasional fatal respiratory arrests.
 - Outside the United States, scorpion envenomations can cause massive release of endogenous catecholamines with hypertensive crises, arrhythmias, pulmonary edema, and myocardial damage.

TREATMENT

Scorpion Stings

- Stings of nonlethal species require at most ice packs, analgesics, or antihistamines.
- In severe envenomations, aggressive supportive care should include pressure dressings and cold packs to decrease the absorption of venom.
- A continuous IV infusion of midazolam helps control agitation and involuntary muscle movements.
- *C. sculpturatus* antivenom administered IV rapidly reverses cranial nerve dysfunction and muscular symptoms.

HYMENOPTERA STINGS

- **Epidemiology:** The hymenoptera include bees, wasps, hornets, yellow jackets, and ants. About 100 deaths from hymenoptera stings occur annually in the United States, nearly all due to allergic reactions to venoms. An estimated 0.4–4.0% of the U.S. population exhibits immediate-type hypersensitivity to insect stings.
- **Clinical features:**
 - Uncomplicated stings cause pain, a wheal-and-flare reaction, and local edema that subside within hours.
 - Multiple stings (e.g., from wasps, hornets, ants) can lead to vomiting, diarrhea, generalized edema, dyspnea, hypotension, rhabdomyolysis, renal failure, and death.
 - Large (>10-cm) local reactions (e.g., with erythema, edema, warmth, tenderness) progressing over 1–2 days are not uncommon; while they resemble cellulitis, they are in fact hypersensitivity reactions. Such reactions recur on subsequent exposure but are seldom accompanied by anaphylaxis.
 - Serious reactions occur within 10 min (and rarely >5 h) after the sting and include upper airway edema, bronchospasm, hypotension, shock, and death.

TREATMENT

Hymenoptera Stings

- Stingers embedded in skin should be removed promptly by grasping with forceps or scraping with a blade or fingernail.

- The site should be disinfected and ice packs applied to slow the spread of venom.
 - Elevation of the bite site and administration of analgesics, oral antihistamines, and topical calamine lotion may ease symptoms.
 - Anaphylaxis is treated with epinephrine hydrochloride (0.3 mL of a 1:1000 solution, given SC q20–30min as needed). For profound shock, the pt should be transferred to a hospital emergency room. Pts should be observed for 24 h for recurrent anaphylaxis, renal failure, or coagulopathy.
 - Pts with a history of allergy to insect stings should carry a sting kit and seek medical attention immediately after the kit is used.
-

30 Fever, Hyperthermia, and Rash



DEFINITIONS

- **Temperature:** The hypothalamic thermoregulatory center balances excess heat production from metabolic activity in muscle and liver with heat dissipation from the skin and lungs to maintain a normal body temperature of $36.8^{\circ} \pm 0.4^{\circ}\text{C}$ ($98.2^{\circ} \pm 0.7^{\circ}\text{F}$), with diurnal variation (lower in A.M., higher in P.M.)
- **Fever:** An elevation of body temperature ($>37.2^{\circ}\text{C}/98.9^{\circ}\text{F}$ in the morning and $>37.7^{\circ}\text{C}/99.9^{\circ}\text{F}$ in the evening) in conjunction with an increase in the hypothalamic set point
- **Fever of unknown origin (FUO):** Temperatures $>38.3^{\circ}\text{C}$ ($>101^{\circ}\text{F}$) on two or more occasions and an illness duration of ≥ 3 weeks, with no known immunocompromised state and unrevealing laboratory and radiologic investigations into the cause
- **Hyperpyrexia:** Temperatures $>41.5^{\circ}\text{C}$ ($>106.7^{\circ}\text{F}$) that can occur with severe infections but more commonly occur with CNS hemorrhages
- **Hyperthermia:** An uncontrolled increase in body temperature that exceeds the body's ability to lose heat *without* a change in the hypothalamic set point. Hyperthermia does not involve pyrogenic molecules.
- **Pyrogen:** Any fever-causing substance, including exogenous pyrogens (e.g., microbial toxins, lipopolysaccharide, superantigens) and pyrogenic cytokines (e.g., IL-1, IL-6, TNF)

FEVER

- **Pathogenesis:** The hypothalamic set point increases, causing peripheral vasoconstriction (i.e., heat conservation). The pt feels cold as a result of blood shunting to the internal organs. Mechanisms of heat production (e.g., shivering, increased hepatic thermogenesis) help to raise the body temperature to the new set point. Increases in peripheral prostaglandin E_2 account for the nonspecific myalgias and arthralgias that often accompany fever. When the set point is lowered again by resolution or treatment of fever, processes of heat loss (e.g., peripheral vasodilation and sweating) commence.
- **Etiology:** Most fevers are associated with self-limited infections (usually viral) and have causes that are easily identified.

APPROACH TO THE PATIENT

Fever

- **History:** A meticulous history is essential, with particular attention to the chronology of events (e.g., in the case of rash: the site of onset and the direction and rate of spread; see below) and the relation of symptoms to medications, pet exposure, sick contacts, sexual contacts, travel, trauma, and the presence of prosthetic materials.
- **Physical examination:** A thorough physical examination should be performed. A consistent site for taking temperatures should be used. Temperature-pulse dissociations (*relative bradycardia*) should be noted if present (sometimes present, for example, with typhoid fever, brucellosis, leptospirosis, factitious

fever). Close attention should be paid to any rash, with precise definition of its salient features.

1. Lesion type (e.g., macule, papule, nodule, vesicle, pustule, purpura, ulcer; see **Chap. 60** for details), configuration (e.g., annular or target), arrangement, and distribution (e.g., central or peripheral)

2. Classification of rash

- a. Centrally distributed maculopapular eruptions (e.g., viral exanthems, exanthematous drug-induced eruptions)
- b. Peripheral eruptions (e.g., Rocky Mountain spotted fever, secondary syphilis, bacterial endocarditis)
- c. Confluent desquamative erythemas (e.g., toxic shock syndrome)
- d. Vesicubullous eruptions (e.g., varicella, primary HSV infection, ecthyma gangrenosum)
- e. Urticaria-like eruptions: In the presence of fever, usually due to urticarial vasculitis caused by serum sickness, connective-tissue disease, infection (hepatitis B virus, enteroviral, or parasitic infection), or malignancy (particularly lymphoma)
- f. Nodular eruptions (e.g., disseminated fungal infection, erythema nodosum, Sweet's syndrome)
- g. Purpuric eruptions (e.g., meningococemia, viral hemorrhagic fever, disseminated gonococemia)
- h. Eruptions with ulcers or eschars (e.g., rickettsial diseases, tularemia, anthrax)

- *Laboratory tests:* CBC with differential, ESR, and C-reactive protein; other tests as indicated by history and physical examination

TREATMENT

Fever

- The use of antipyretics is not contraindicated in common viral or bacterial infections and can relieve symptoms without slowing resolution of infection. Withholding of antipyretics may be useful, however, in evaluating the effectiveness of a particular antibiotic or in diagnosing conditions with temperature-pulse dissociations or relapsing fevers (e.g., infection with *Plasmodium* or *Borrelia* species).
- Treatment of fever in pts with preexisting impairment of cardiac, pulmonary, or CNS function is recommended to reduce oxygen demand.
- Aspirin, NSAIDs, and glucocorticoids are effective antipyretics. Acetaminophen is preferred because it does not mask signs of inflammation, does not impair platelet function, and is not associated with Reye's syndrome.
- Hyperpyretic pts should be treated with cooling blankets in addition to oral antipyretics.

FEVER OF UNKNOWN ORIGIN

- **Etiology:** FUO is more commonly caused by an atypical presentation of a common disease than by a very rare disease. The most common causes of FUO can be categorized as infections, neoplasms, or noninfectious inflammatory

diseases (NIIDs; e.g., “collagen or rheumatic diseases,” vasculitis syndromes, and granulomatous disorders). The frequency of each category differs between Western countries and countries in other parts of the world: infections, neoplasms, and NIIDs account for 19%, 12%, and 24% of Western cases, respectively, and for 43%, 20%, and 14% of cases in other geographic regions.

- Atypical presentations of endocarditis, diverticulitis, vertebral osteomyelitis, and extrapulmonary tuberculosis represent the more common infectious-disease diagnoses.
- The most common NIIDs that result in FUO are large-vessel vasculitis, polymyalgia rheumatica, sarcoidosis, familial Mediterranean fever, and adult-onset Still’s disease.
- Among the neoplasms, malignant lymphoma is by far the most common cause of FUO. Fever occasionally precedes lymphadenopathy detectable by physical examination.

APPROACH TO THE PATIENT

FUO

A structured approach to the pt with FUO is shown in [Fig. 30-1](#). The most important step in the diagnostic workup is the search for potentially diagnostic clues (PDCs) through complete and repeated history taking and physical examination. ^{18}F -fluorodeoxyglucose positron emission tomography combined with low-dose CT (FDG-PET/CT) can be used to guide additional diagnostic tests (e.g., targeted biopsies and culture) and aids in final diagnosis of FUO in ~50% of cases.

TREATMENT

FUO

Empirical therapeutic trials with antibiotics, glucocorticoids, or antituberculous agents should be avoided in FUO except when a pt’s condition is rapidly deteriorating after diagnostic tests have failed to provide a definitive result.

- Hemodynamic instability and neutropenia may prompt earlier empirical anti-infective therapies.
- Use of glucocorticoids and NSAIDs should be avoided unless infection and malignant lymphoma have been largely ruled out and unless inflammatory disease is both probable and debilitating or life-threatening.
- Anakinra, a recombinant form of the naturally occurring IL-1 receptor antagonist, blocks the activity of both IL-1 α and IL-1 β and is extremely effective in the treatment of many autoinflammatory syndromes. A therapeutic trial with anakinra can be considered in pts whose FUO has not been diagnosed after later-stage diagnostic tests.

- **Prognosis:** When no underlying source of FUO is identified after prolonged observation (>6 months), the prognosis is generally good.

HYPERTHERMIA

- **Etiology:** Exogenous heat exposure (e.g., heat stroke) and endogenous heat production (e.g., drug-induced hyperthermia, malignant hyperthermia) are two mechanisms by which hyperthermia can result in dangerously high internal temperatures.

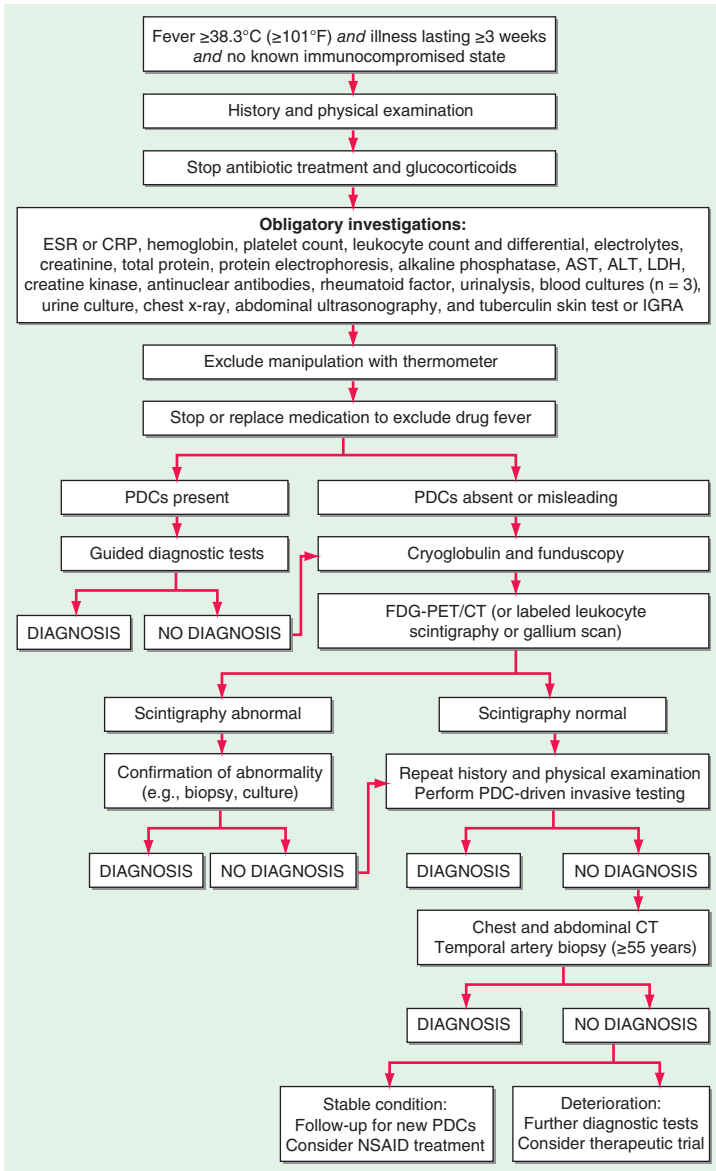


FIGURE 30-1 Structured approach to pts with fever of unknown origin (FUO). ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FDG-PET/CT, ^{18}F -fluorodeoxyglucose positron emission tomography combined with low-dose computed tomography; IGRA, interferon γ release assay; LDH, lactate dehydrogenase; NSAID, nonsteroidal anti-inflammatory drug; PDCs, potentially diagnostic clues (all localizing signs, symptoms, and abnormalities potentially pointing toward a diagnosis).

- *Heat stroke*: Thermoregulatory failure in association with a warm environment; can be categorized as *exertional* (e.g., due to exercise in high heat or humidity) or *classic* (typically occurring in pts with chronic diseases that predispose to heat-related illnesses)
- **Clinical features**: High core temperature in association with an appropriate history (heat exposure, certain drug treatments) and dry skin, hallucinations, delirium, pupil dilation, muscle rigidity, and/or elevated levels of CPK
- **Diagnosis**: It can be difficult to distinguish fever from hyperthermia. The clinical history is often most useful (e.g., a history of heat exposure or of treatment with drugs that interfere with thermoregulation).
 - *Hyperthermic* pts have hot, dry skin; antipyretic agents do not lower the body temperature.
 - *Febrile* pts can have cold skin (as a result of vasoconstriction) or hot, moist skin; antipyretics usually result in some lowering of the body temperature.

TREATMENT

Hyperthermia

- Before cooling is initiated, endotracheal intubation, central venous pressure (CVP) determination, and continuous core-temperature monitoring should be considered.
- Evaporative cooling (spraying cool water on exposed skin while fans direct continuous airflow over the moistened skin) is the most practical and effective technique for reducing body temperature. Invasive methods (e.g., IV infusion of cold fluids, cold thoracic and peritoneal lavage, cardiopulmonary bypass) are effective but rarely necessary.
- Given the risk of dehydration, IV fluids are necessary or at least appropriate. The central venous pressure (CVP), particularly in classic heat stroke, may be deceptively high; rarely, measurement of wedge pressures via a pulmonary artery catheter may be necessary to guide resuscitation.

31

Generalized Fatigue



Fatigue is one of the most common complaints related by pts. It usually refers to nonspecific sense of a low energy level, or the feeling that near exhaustion is reached after relatively little exertion. Fatigue should be distinguished from true neurologic *weakness*, which describes a reduction in the normal power of one or more muscles (**Chap. 55**). It is not uncommon for pts, especially the elderly, to present with generalized failure to thrive, which may include components of fatigue and weakness, depending on the cause.

■ CLINICAL MANIFESTATIONS

Because the causes of generalized fatigue are numerous, a thorough history, review of systems (ROS), and physical examination are paramount to narrow the focus to likely causes. The history and ROS should focus on the temporal onset of fatigue and its progression. Has it lasted days, weeks, or months? Activities of daily living, exercise, eating habits/appetite, sexual practices, and sleep habits should be reviewed. Features of depression or dementia should be sought.

Travel history and possible exposures to infectious agents should be reviewed, along with the medication list. The ROS may elicit important clues as to organ system involvement. The past medical history may elucidate potential precursors to the current presentation, such as previous malignancy or cardiac problems. The physical examination should specifically assess weight and nutritional status, lymphadenopathy, hepatosplenomegaly, abdominal masses, pallor, rash, heart failure, new murmurs, painful joints or trigger points, and evidence of weakness or neurologic abnormalities. A finding of true weakness or paralysis should prompt consideration of neurologic disorders ([Chap. 55](#)).

■ DIFFERENTIAL DIAGNOSIS

Determining the cause of fatigue can be one of the most challenging diagnostic problems in medicine because the differential diagnosis is very broad, including infection, malignancy, cardiac disease, endocrine disorders, neurologic disease, depression, or serious abnormalities of virtually any organ system, as well as side effects of many medications ([Table 31-1](#)). Symptoms of fever and weight loss will focus attention on infectious causes, whereas symptoms of progressive dyspnea might point toward cardiac, pulmonary, or renal causes. A presentation that includes arthralgia suggests the possibility of a rheumatologic disorder. Fatigue is a common presenting symptom of cancer. A previous malignancy, thought to be cured or in remission, may have recurred or metastasized widely. A previous history of valvular heart disease or cardiomyopathy may identify

TABLE 31-1 Potential Causes of Generalized Fatigue

DISEASE CATEGORY	EXAMPLES
Infection	HIV, TB, Lyme disease, endocarditis, hepatitis, sinusitis, fungal, EBV, malaria (chronic phase)
Inflammatory disease	RA, polymyalgia rheumatica, chronic fatigue syndrome, fibromyalgia, sarcoidosis
Cancer	Lung, GI, breast, prostate, leukemia, lymphoma, metastases
Psychiatric	Depression, alcoholism, chronic anxiety
Metabolic	Hypothyroidism, hyperthyroidism, diabetes mellitus, Addison's disease, hyperparathyroidism, hypogonadism, hypopituitarism (TSH, ACTH, growth hormone deficiency), McArdle's disease
Electrolyte imbalance	Hypercalcemia, hypokalemia, hyponatremia, hypomagnesemia
Nutrition, vitamin deficiency	Starvation, obesity, iron deficiency, vitamin B ₁₂ , folic acid deficiency, vitamin C deficiency (scurvy), thiamine deficiency (beriberi)
Neurologic	Multiple sclerosis, myasthenia gravis, dementia
Cardiac	Heart failure, CAD, valvular disease, cardiomyopathy
Pulmonary	COPD, pulmonary hypertension, chronic pulmonary emboli, sarcoidosis
Sleep disturbances	Sleep apnea, insomnia, restless leg syndrome
Gastrointestinal	Celiac disease, Crohn's, ulcerative colitis, chronic hepatitis, cirrhosis
Hematologic	Anemia
Renal	Renal failure
Medication	Sedatives, antihistamines, narcotics, β blockers, and many other medications

Abbreviations: ACTH, adrenocorticotropic hormone; CAD, coronary artery disease; COPD; chronic obstructive pulmonary disorder; EBV, Epstein-Barr virus; RA, rheumatoid arthritis; TSH, thyroid-stimulating hormone.

a condition that has decompensated. Treatment for Graves' disease may have resulted in hypothyroidism. Sleep apnea is under-recognized and is a common cause of unexplained fatigue. Changes in medication should always be pursued, whether discontinued or recently started. Almost any new medication has the potential to cause fatigue. However, a temporal association with a new medication should not eliminate other causes, because many pts may have received new medications in an effort to address their complaints. Medications and their dosages should be carefully assessed, especially in elderly pts, in whom polypharmacy and inappropriate or misunderstood dosing is a frequent cause of fatigue. The time course for presentation is also valuable. Indolent presentations over months to years are more likely to be associated with slowly progressive organ failure or endocrinopathies, whereas a more rapid course over weeks to months suggests infection or malignancy.

■ LABORATORY TESTING

Laboratory testing and imaging should be guided by the history and physical examination. However, a CBC with differential, electrolytes, BUN, creatinine, glucose, calcium, TFTs, and LFTs are useful in most pts with undifferentiated fatigue, because these tests will rule out many causes and may provide clues to unsuspected disorders. Similarly, a CXR is useful to evaluate many possible disorders rapidly, including heart failure, pulmonary disease, or occult malignancy that may be detected in the lungs or bony structures. Subsequent testing should be based on the initial results and clinical assessment of the likely differential diagnoses. For example, a finding of anemia would dictate the need to assess whether it has features of iron deficiency or hemolysis, thereby narrowing potential causes. Hyponatremia might be caused by syndrome of inappropriate antidiuretic hormone (SIADH), hypothyroidism, adrenal insufficiency, or medications or by underlying cardiac, pulmonary, liver, or renal dysfunction. An elevated WBC count would raise the possibility of infection or malignancy. Thus, the approach is generally one of gathering information in a serial but cost-effective manner to narrow the differential diagnosis progressively.

TREATMENT

Generalized Fatigue

Treatment should be based on the diagnosis, if known. Many conditions, such as metabolic, nutritional, or endocrine disorders, can be corrected quickly by appropriate treatment of the underlying causes. Specific treatment can also be initiated for many infections, such as TB, sinusitis, or endocarditis. Pts with chronic conditions such as chronic obstructive pulmonary disorder (COPD), heart failure, renal failure, or liver disease may benefit from interventions that enhance organ function or correct associated metabolic problems, and it may be possible to gradually improve physical conditioning. In pts with cancer, fatigue may be caused by chemotherapy or radiation and may resolve with time; treatment of associated anemia, nutritional deficiency, hyponatremia, or hypercalcemia may increase energy levels. Replacement therapy in endocrine deficiencies typically results in improvement. Treatment of depression or sleep disorders, whether a primary cause of fatigue or secondary to a medical disorder, may be beneficial. A variety of treatments are now available for sleep apnea, including continuous positive airway pressure (CPAP). Withdrawal of medications that potentially contribute to fatigue should be considered, recognizing that other medications may need to be substituted for the underlying condition. In elderly pts, appropriate medication dose adjustments (typically lowering the dose) and restricting the regimen to only essential drugs may improve fatigue.

TABLE 31-2 CDC Criteria for Diagnosis of ME/CFS

Consider a diagnosis of ME/CFS if these three criteria are met:

1. The individual has severe chronic fatigue for ≥ 6 consecutive months that is not due to ongoing exertion or other medical conditions associated with fatigue (these other conditions need to be ruled out by a doctor after diagnostic tests have been conducted).
2. The fatigue significantly interferes with daily activities and work.
3. The individual concurrently has four or more of the following eight symptoms:
 - postexertion malaise lasting >24 hours
 - unrefreshing sleep
 - significant impairment of short-term memory or concentration
 - muscle pain
 - multijoint pain without swelling or redness
 - headaches of a new type, pattern, or severity
 - tender cervical or axillary lymph nodes
 - sore throat that is frequent or recurring

Abbreviations: CDC, Centers for Disease Control and Prevention; CFS, chronic fatigue syndrome; ME, myalgic encephalitis.

Source: <https://www.cdc.gov/me-cfs/>.

CHRONIC FATIGUE SYNDROME

Myalgic encephalitis (ME)/chronic fatigue syndrome (CFS) is characterized by debilitating fatigue and several associated physical, constitutional, and neuropsychological complaints. The majority of pts (~75%) are women, generally 30–45 years old. The CDC has developed diagnostic criteria for CFS based upon symptoms and the exclusion of other illnesses (**Table 31-2**). The cause is uncertain, although clinical manifestations often follow an infectious illness (Q fever, Lyme disease, mononucleosis, or another viral illness). Many studies have attempted, without success, to link CFS to specific infectious agents such as EBV, a retrovirus (including a murine leukemia virus–related retrovirus), or an enterovirus, and many others. CFS might be caused by more than one infectious agent or by postinfectious immune responses. Physical or psychological stress is also often identified as a precipitating factor. Depression is present in half to two-thirds of pts.

CFS remains a diagnosis of exclusion, and no laboratory test can establish the diagnosis or measure its severity. CFS does not appear to progress but typically has a protracted course. The median annual recovery rate is 5% (range, 0–31%) with an improvement rate of 39% (range, 8–63%).

The management of CFS commences with acknowledgment by the physician that the pt's daily functioning is impaired. The pt should be informed of the current understanding of CFS (or lack thereof) and be offered general advice about disease management. NSAIDs alleviate headache, diffuse pain, and feverishness. Regular and adequate sleep is important. Antihistamines or decongestants may be helpful for symptoms of rhinitis and sinusitis. Although the pt may be averse to psychiatric diagnoses, features of depression and anxiety may justify treatment. Nonsedating antidepressants may improve mood and disordered sleep and may attenuate the fatigue. Cognitive behavioral therapy (CBT) and graded exercise therapy (GET) have been found to be effective treatment strategies in some pts.

32

Unintentional Weight Loss



Significant unintentional weight loss in a previously healthy individual is often a harbinger of underlying systemic disease. The routine medical history should always include inquiry about changes in weight. Rapid fluctuations of weight over days suggest loss or gain of fluid, whereas long-term changes usually involve loss of tissue mass. Loss of 5% of body weight over 6–12 months should prompt further evaluation. Gradual weight loss is physiologic in persons aged >80, but this demographic group also has a high risk for malignancy or other serious illness.

■ ETIOLOGY

The principal causes of involuntary weight loss can be assigned to four categories: (1) malignant neoplasms, (2) chronic inflammatory or infectious diseases, (3) metabolic disorders, or (4) psychiatric disorders ([Table 32-1](#)). In older persons, the most common causes of weight loss are depression, cancer, and benign GI disease. Social isolation and/or poverty can contribute to undernutrition and weight loss. Lung and GI cancers are the most common malignancies in pts presenting with weight loss. In younger individuals, diabetes mellitus, hyperthyroidism, anorexia nervosa, and infection, especially with HIV, should be considered.

■ CLINICAL FEATURES

Before extensive evaluation is undertaken, it is important to confirm that weight loss has occurred (up to 50% of claims of weight loss cannot be substantiated). In the absence of documentation, changes in belt notch size or the fit of clothing may help to determine loss of weight.

The *history* should include questions about fever, pain, shortness of breath or cough, palpitations, and evidence of neurologic disease. A history of GI symptoms should be obtained, including difficulty eating, dysgeusia, dysphagia, anorexia, nausea, and change in bowel habits. Travel history, use of cigarettes, alcohol, and all medications should be reviewed, and pts should be questioned about previous illness or surgery as well as diseases in family members. Risk factors for HIV should be assessed. Signs of depression, evidence of dementia, and social factors, including isolation, loneliness, and financial issues that might affect food intake, should be considered.

Physical examination should begin with weight determination and documentation of vital signs. The skin should be examined for pallor, jaundice, turgor, surgical scars, and stigmata of systemic disease. Evaluation for oral thrush, dental disease, thyroid gland enlargement, and adenopathy and for respiratory, cardiac, or abdominal abnormalities should be performed. All men should have a rectal examination, including the prostate; all women should have a pelvic examination; and both should have testing of the stool for occult blood. Neurologic examination should include mental status assessment and screening for depression.

Initial *laboratory evaluation* is shown in [Table 32-2](#), with appropriate treatment based on the underlying cause of the weight loss. If an etiology of weight loss is not found, careful clinical follow-up, rather than persistent undirected testing, is reasonable. The absence of abnormal laboratory tests is a favorable prognostic sign.

TABLE 32-1 Causes of Weight Loss

Cancer	Medications
Endocrine and metabolic causes	Sedatives
Hyperthyroidism	Antibiotics
Diabetes mellitus	Nonsteroidal anti-inflammatory drugs
Pheochromocytoma	Serotonin reuptake inhibitors
Adrenal insufficiency	Metformin
Gastrointestinal disorders	Levodopa
Malabsorption	ACE inhibitors
Obstruction	Other drugs
Peptic ulcer	Disorders of the mouth and teeth
Celiac disease	Caries
Inflammatory bowel disease	Dysgeusia
Pancreatitis	Age-related factors
Pernicious anemia	Physiologic changes
Cardiac disorders	Decreased taste and smell
Chronic ischemia	Functional disabilities
Chronic congestive heart failure	Neurologic causes
Respiratory disorders	Stroke
Emphysema	Parkinson's disease
Chronic obstructive pulmonary disease	Neuromuscular disorders
Renal insufficiency	Dementia
Rheumatologic disease	Social causes
Infections	Isolation
HIV	Economic hardship
Tuberculosis	Psychiatric and behavioral causes
Parasitic infection	Depression
Subacute bacterial endocarditis	Anxiety
	Bereavement
	Alcoholism
	Eating disorders
	Increased activity or exercise
	Idiopathic

Abbreviation: ACE, angiotensin-converting enzyme.

TABLE 32-2 Screening Tests for Evaluation of Involuntary Weight Loss

Initial testing	Additional testing
CBC	HIV test
Electrolytes, calcium, glucose	Upper and/or lower gastrointestinal endoscopy
Renal and liver function tests	Abdominal ultrasound
Urinalysis	
Thyroid-stimulating hormone	
Chest x-ray	
Recommended cancer screening	

Abbreviation: CBC, complete blood count.

TREATMENT

Weight Loss

Treatment of weight loss should be directed at correcting the underlying physical cause or social circumstance. In specific situations, nutritional supplements and medications (megestrol acetate, dronabinol, or growth hormone) may be effective for stimulating appetite or increasing weight.

33

Chest Pain



There is little correlation between the severity of chest pain and the seriousness of its cause. The range of disorders that cause chest discomfort is shown in [Table 33-1](#).

POTENTIALLY SERIOUS CAUSES

The differential diagnosis of chest pain is shown in [Figs. 33-1](#) and [33-2](#). It is useful to characterize the chest pain as (1) new, acute, and ongoing; (2) recurrent, episodic; and (3) persistent, e.g., for hours or days at a time.

Myocardial Ischemia: Angina Pectoris

Substernal pressure, squeezing, constriction, with radiation often to left arm; usually on exertion, especially after meals or with emotional arousal. Characteristically relieved by rest and nitroglycerin.

Acute Myocardial Infarction or Unstable Angina ([Chaps. 121 and 122](#))

Similar to angina but more severe, of longer duration (≥ 30 min), and not immediately relieved by rest or nitroglycerin. S3 and/or S4 may be present.

TABLE 33-1 Diagnoses of Pts Admitted to Hospital with Acute Chest Pain Ruled Not Myocardial Infarction

DIAGNOSIS	PERCENTAGE
Gastroesophageal disease ^a	42
Gastroesophageal reflux	
Esophageal motility disorders	
Peptic ulcer	
Gallstones	
Ischemic heart disease	31
Chest wall syndromes	28
Pericarditis	4
Pleuritis/pneumonia	2
Pulmonary embolism	2
Lung cancer	1.5
Aortic aneurysm	1
Aortic stenosis	1
Herpes zoster	1

^aIn order of frequency.

Source: Fruergaard P et al: The diagnoses of patients admitted with acute chest pain but without myocardial infarction. *Eur Heart J* 17:1028, 1996.

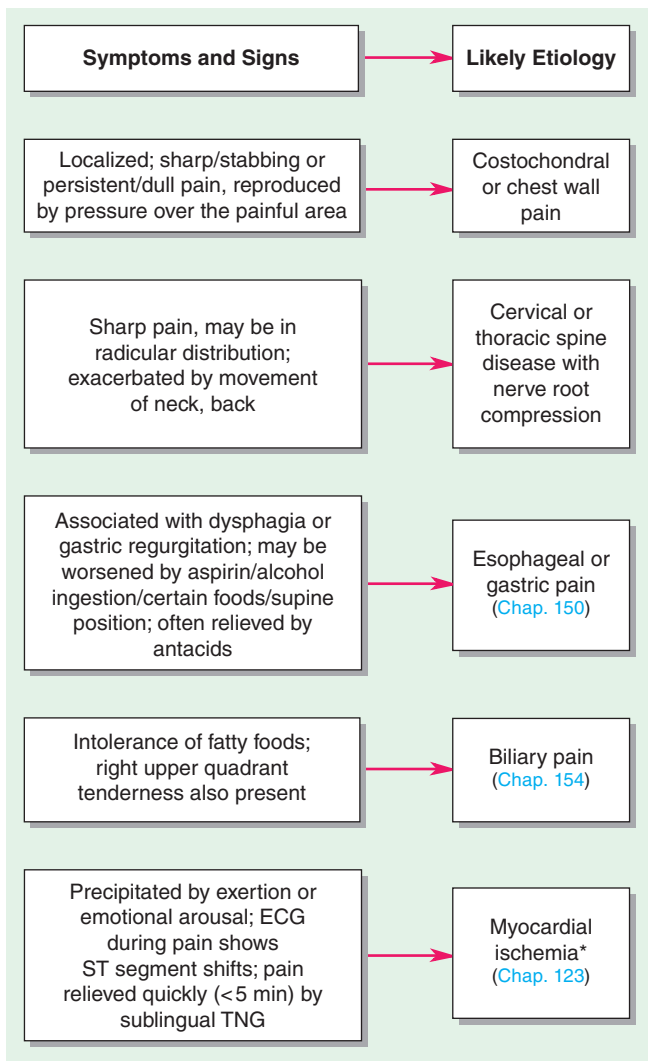


FIGURE 33-1 Differential diagnosis of recurrent chest pain. *If myocardial ischemia suspected, also consider aortic valve disease (Chap. 116) and hypertrophic obstructive cardiomyopathy (Chap. 117) if systolic murmur present. TNG, trinitroglycerin.

Pulmonary Embolism (Chap. 135)

May be substernal or lateral, pleuritic in nature, and associated with hemoptysis, tachycardia, and hypoxemia.

Thoracic Aortic Aneurysm (Chap. 127)

May impinge on neighboring structures and cause deep, persistent chest pain, dysphagia, hoarseness, or cough.

Description of pain	Oppressive, constrictive, or squeezing; may radiate to arm(s), neck, back	"Tearing" or "ripping"; may travel from anterior chest to mid-back	Crushing, sharp, pleuritic; relieved by sitting forward	Pleuritic, sharp; possibly accompanied by cough/hemoptysis	Very sharp, pleuritic	Intense substernal and epigastric; accompanied by vomiting ± hematemesis
Background history	Less severe, similar pain on exertion; + coronary risk factors	Hypertension or Marfan syndrome (Chap. 119, 127)	Recent upper respiratory tract infection, or other conditions which predispose to pericarditis (Chap. 118)	Recent surgery or other immobilization	Recent chest trauma, or history of chronic obstructive lung disease	Recent recurrent vomiting/retching
Key physical findings	Diaphoresis, pallor; S4 common; S3 less common	Weak, asymmetric peripheral pulses; possible diastolic murmur of aortic insufficiency (Chap. 116)	Pericardial friction rub (usually three components, best heard by sitting pt forward)	Tachypnea; possible pleural friction rub	Tachypnea; decreased breath sounds and hyperresonance over affected lung field	Subcutaneous emphysema; audible crepitus adjacent to the sternum
Consider	Acute coronary syndromes (Chaps. 121 and 122)	Aortic dissection (Chap. 127)	Acute pericarditis (Chap. 118)	Pulmonary embolism (Chap. 135)	Acute pneumothorax (Chap. 137)	Rupture of esophagus
Confirmatory tests	<ul style="list-style-type: none"> Serial ECGs Serial cardiac markers (esp. cardiac troponin) 	<ul style="list-style-type: none"> CXR – widened mediastinal silhouette CT or transesophageal echogram: intimal flap visualized 	<ul style="list-style-type: none"> ECG: diffuse ST elevation and PR segment depression Echogram: pericardial effusion often visualized 	<ul style="list-style-type: none"> Normal D-dimer makes diagnosis unlikely CT angiography or lung scan: \dot{V}/\dot{Q} mismatch Pulmonary angiogram: arterial luminal filling defects 	<ul style="list-style-type: none"> CXR: radiolucency within pleural space; poss. collapse of adjacent lung segment; if tension pneumothorax, mediastinum is shifted to opp. side 	<ul style="list-style-type: none"> CXR: pneumo-mediastinum Esophageal endoscopy is diagnostic

FIGURE 33-2 Differential diagnosis of serious conditions that cause acute chest pain. CK, creatine phosphokinase.

Aortic Dissection (Chap. 127)

Very severe, in center of chest, a sharp “ripping” quality, radiates to back, not affected by changes in position. May be associated with weak or absent peripheral pulses.

Mediastinal Emphysema

Sharp, intense, localized to substernal region; often associated with audible crepitus.

Acute Pericarditis (Chap. 118)

Usually steady, crushing, substernal; often has pleuritic component aggravated by cough, deep inspiration, supine position, and relieved by sitting upright; pericardial friction rub often audible.

Pleurisy

Due to inflammation; less commonly tumor and pneumothorax. Usually unilateral, knifelike, superficial, aggravated by cough and respiration.

■ LESS SERIOUS CAUSES**Costochondral Pain**

In anterior chest, usually sharply localized, may be brief and darting or a persistent dull ache. Can be reproduced by pressure on costochondral and/or chondrosternal junctions. In Tietze’s syndrome (costochondritis), joints are swollen, red, and tender.

Chest Wall Pain

Due to strain of muscles or ligaments from excessive exercise or rib fracture from trauma; accompanied by local tenderness.

Esophageal Pain

Deep thoracic discomfort; may be accompanied by dysphagia and regurgitation.

Emotional Disorders

Prolonged ache or dartlike, fleeting pain; associated with fatigue, emotional strain.

■ OTHER CAUSES

(1) Cervical disk disease; (2) osteoarthritis of cervical or thoracic spine; (3) abdominal disorders: peptic ulcer, hiatus hernia, pancreatitis, biliary colic; (4) tracheobronchitis, pneumonia; (5) diseases of the breast (inflammation, tumor); (6) intercostal neuritis (herpes zoster).

APPROACH TO THE PATIENT**Chest Pain**

A meticulous history of the behavior of pain, what precipitates it and what relieves it, aids diagnosis of recurrent chest pain. Figure 33-2 presents clues to diagnosis and workup of acute, life-threatening chest pain. Critical pathway algorithms help differentiate pts with acute high-risk cardiopulmonary conditions from those with more benign causes. In particular, the history, ECG, and measurement of cardiac troponin (especially high sensitivity assay) are key to the initial evaluation to distinguish pts with acute ST-elevation MI, who warrant immediate reperfusion approaches (Chap. 121). CT angiography may be appropriate for pts with low-intermediate probability of an acute coronary syndrome, to exclude important CAD and to assess for aortic dissection, pulmonary embolism, and pericardial effusion.

34 Palpitations



Palpitations represent an intermittent or sustained awareness of the heartbeat, often described by the pt as a thumping, pounding, or fluttering sensation in the chest. The symptom may reflect a cardiac etiology, an extracardiac cause (e.g., hyperthyroidism, use of stimulants [e.g., caffeine, cocaine]), or a high catecholamine state (e.g., exercise, anxiety, pheochromocytoma). Contributory cardiac dysrhythmias include atrial or ventricular premature beats or, when sustained and regular, supraventricular or ventricular tachyarrhythmias ([Chap. 125](#)). *Irregular* sustained palpitations are often due to atrial fibrillation. Asking the pt to “tap out” the sense of palpitation can help distinguish regular from irregular rhythms.

APPROACH TO THE PATIENT

Palpitations

Palpitations are often benign but may represent an important dysrhythmia if associated with hemodynamic compromise (light-headedness, syncope, angina, dyspnea) or if found in pts with preexisting coronary artery disease (CAD), ventricular dysfunction, hypertrophic cardiomyopathy, aortic stenosis, or other valvular disease.

Helpful diagnostic studies include *electrocardiography* (if symptoms present at time of recording), *exercise testing* (if exertion typically precipitates the sense of palpitation or if underlying CAD is suspected), and *echocardiography* (if structural heart disease is suspected). If symptoms are episodic, ambulatory electrocardiographic monitoring can be diagnostic, including use of a Holter monitor (24–48 h of monitoring), event/loop monitor (for 2–4 weeks), or implantable loop monitor (for 1–2 years). Helpful laboratory studies may include testing for hypokalemia, hypomagnesemia, and/or hyperthyroidism.

For pts with benign atrial or ventricular premature beats in the absence of structural heart disease, therapeutic strategies include reduction of ethanol and caffeine intake, reassurance, and consideration of beta-blocker therapy for symptomatic suppression. Treatment of more serious dysrhythmias is presented in [Chaps. 124 and 125](#).

35 Dyspnea



DEFINITION

Dyspnea, a subjective experience of uncomfortable breathing, is a symptom that typically results from cardiac, pulmonary, and neurologic etiologies that cause an increased drive to breathe, increased work of breathing, and/or stimulation of specific receptors in the heart, lungs, or vasculature. Assessment begins by determining the quality and intensity of the discomfort. Chronic dyspnea is typically defined as symptoms lasting >1 month.

CAUSES**Respiratory System Dyspnea**

- *Airway disease:* Asthma and chronic obstructive pulmonary disorder (COPD) are common causes of dyspnea associated with increased work of breathing. Bronchospasm can cause chest tightness and hyperventilation. Hypoxemia and hypercapnia can result from ventilation-perfusion mismatch.
- *Chest wall disorders:* Chest wall stiffness (e.g., kyphoscoliosis) and neuromuscular weakness (e.g., myasthenia gravis) cause increased work of breathing.
- *Lung parenchymal disorders:* Interstitial lung diseases ([Chap. 136](#)) cause reduced lung compliance and increased work of breathing. Ventilation-perfusion mismatch and pulmonary fibrosis may lead to hypoxemia. Stimulation of lung receptors can cause hyperventilation.

Cardiovascular System Dyspnea

- *Left heart disorders:* Elevations of left-ventricular end-diastolic and pulmonary capillary wedge pressures lead to dyspnea related to stimulation of pulmonary receptors and hypoxemia from ventilation-perfusion mismatch. Coronary artery disease and cardiomyopathy are examples of diseases affecting left heart function.
- *Pulmonary vascular disorders:* Pulmonary emboli, primary pulmonary arterial hypertension, and pulmonary vasculitis stimulate pulmonary receptors via increased pulmonary artery pressures. Hyperventilation and hypoxemia also may contribute to dyspnea.
- *Pericardial diseases:* Constrictive pericarditis and pericardial tamponade cause increased intracardiac and pulmonary arterial pressures, leading to dyspnea.

Dyspnea with Normal Respiratory and Cardiovascular Systems

Anemia can cause dyspnea, especially with exertion. Obesity is associated with dyspnea due to high cardiac output and impaired ventilatory function. Deconditioning and anxiety may also cause dyspnea in pts with normal respiratory and cardiovascular systems.

APPROACH TO THE PATIENT**Dyspnea (Fig. 35-1)**

History: Obtain description of discomfort, including the impact of position, infections, and environmental exposures. Orthopnea is commonly observed in CHF. Nocturnal dyspnea is seen in CHF and asthma. Acute intermittent dyspnea suggests myocardial ischemia, asthma, or pulmonary embolism.

Physical examination: Assess increased work of breathing indicated by accessory ventilatory muscle use or supraclavicular retractions. Determine if chest movement is symmetric. Use percussion (dullness or hyperresonance) and auscultation (decreased or adventitious breath sounds) to assess the lungs. Cardiac examination should note jugular venous distention, heart murmurs, and S3 or S4 gallops. Clubbing can relate to interstitial lung disease or lung cancer. To evaluate exertional dyspnea, reproduce the dyspnea with observation while assessing pulse oximetry.

Radiographic studies: Chest radiograph should be obtained as initial evaluation. Chest CT can be used subsequently to assess lung parenchyma (e.g., emphysema or interstitial lung disease) and pulmonary embolism.

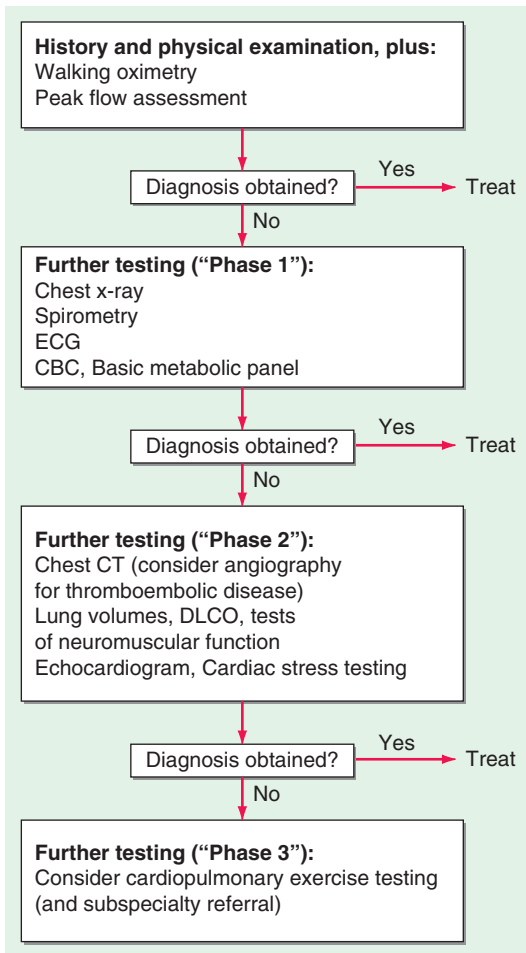


FIGURE 35-1 Algorithm for the evaluation of the pt with dyspnea. EKG, electrocardiogram; DLCO, diffusing capacity for carbon monoxide; CBC, complete blood count. (From Baron RM: *Dyspnea*, in Jameson J et al (eds). *Harrison's Principles of Internal Medicine*, 20th ed. New York, NY: McGraw-Hill; 2019.)

Laboratory studies: Hematocrit should be assessed for anemia, and a basic metabolic panel (for metabolic acidosis) and brain natriuretic peptide should be considered. ECG should be obtained; echocardiography can assess left ventricular dysfunction, pulmonary hypertension, and valvular disease. Pulmonary function tests to consider include spirometry, lung volumes, diffusing capacity, and tests of neuromuscular function. Methacholine challenge testing can assess for asthma in subjects with normal spirometry. Cardiac stress testing can be performed to assess for coronary artery ischemia, while cardiopulmonary exercise testing can determine whether pulmonary or cardiac disease limits exercise capacity.

TREATMENT**Dyspnea**

Ideally, treatment involves correcting the underlying problem that caused dyspnea. Supplemental oxygen is required for significant oxygen desaturation at rest, during sleep, or with exertion. Pulmonary rehabilitation is helpful to improve exercise tolerance in COPD.

Pulmonary Edema

Cardiogenic pulmonary edema results from cardiac abnormalities that cause increased pulmonary venous pressure leading to interstitial edema; with greater pressures, alveolar edema and pleural effusions develop. Symptoms include exertional dyspnea and orthopnea. Physical examination can reveal S3 gallop, elevated jugular venous pressure, and peripheral edema. Chest radiographs show prominent vascular markings in the upper lung zones. CXRs demonstrate perihilar alveolar opacities progressing to diffuse parenchymal abnormalities as pulmonary edema worsens.

Noncardiogenic pulmonary edema results from damage to the pulmonary capillary lining. Hypoxemia relates to intrapulmonary shunt; decreased pulmonary compliance is observed. Clinical impact can range from mild dyspnea to severe respiratory failure. Normal intracardiac pressures are typically observed. Etiologies may be direct injury (e.g., aspiration, smoke inhalation, pneumonia, oxygen toxicity, or chest trauma), indirect injury (e.g., sepsis, pancreatitis, and transfusion-related acute lung injury), or pulmonary vascular (e.g., high altitude and neurogenic pulmonary edema). Chest radiograph typically shows normal heart size and diffuse alveolar infiltrates; pleural effusions are atypical. Hypoxemia in noncardiogenic pulmonary edema often requires treatment with high concentrations of oxygen.

36**Cyanosis**

Bluish discoloration of the skin and/or mucous membranes are usually due to elevated quantity of reduced hemoglobin (>4 g/dL) in the capillary blood vessels. Findings are most apparent in the lips, nail beds, ears, and malar eminences. Cyanosis depends on absolute, not relative, quantity of desaturated hemoglobin, so may be less evident in pts with severe anemia, and more notable in pts with polycythemia.

■ CENTRAL CYANOSIS

Results from arterial desaturation or presence of an abnormal hemoglobin. Usually evident when arterial saturation is $\leq 85\%$, or $\leq 75\%$ in dark-skinned individuals. Etiologies include:

1. *Impaired pulmonary function:* Poorly ventilated alveoli or impaired oxygen diffusion; most frequent in pneumonia, pulmonary edema, and chronic obstructive pulmonary disease (COPD); in COPD with cyanosis, secondary polycythemia is often present.

TABLE 36-1 Causes of Cyanosis**Central Cyanosis**

Decreased arterial oxygen saturation
Decreased atmospheric pressure—high altitude
Impaired pulmonary function
Alveolar hypoventilation
Inhomogeneity in pulmonary ventilation and perfusion (perfusion of hypoventilated alveoli)
Impaired oxygen diffusion
Anatomic shunts
Certain types of congenital heart disease
Pulmonary arteriovenous fistulas
Multiple small intrapulmonary shunts
Hemoglobin with low affinity for oxygen
Hemoglobin abnormalities
Methemoglobinemia—hereditary, acquired
Sulfhemoglobinemia—acquired
Carboxyhemoglobinemia (not true cyanosis)

Peripheral Cyanosis

Reduced cardiac output
Cold exposure
Redistribution of blood flow from extremities
Arterial obstruction
Venous obstruction

2. *Anatomic vascular shunting*: Shunting of desaturated venous blood into the arterial circulation may result from congenital heart disease or pulmonary atrioventricular (AV) fistula.
3. *Decreased inspired O₂*: Cyanosis may develop in ascents to altitudes >4000 m (>13,000 ft).
4. *Abnormal hemoglobins*: Methemoglobinemia, sulfhemoglobinemia (see [Chap. 94](#), HPIM-20).

■ PERIPHERAL CYANOSIS

Occurs with normal arterial O₂ saturation with increased extraction of O₂ from capillary blood caused by decreased localized blood flow. Contributors include vasoconstriction due to cold exposure, decreased cardiac output (e.g., in shock, [Chap. 12](#)), heart failure ([Chap. 126](#)), and peripheral vascular disease ([Chap. 128](#)) with arterial obstruction or vasospasm ([Table 36-1](#)). Local (e.g., thrombophlebitis) or central (e.g., constrictive pericarditis) venous hypertension intensifies cyanosis.

APPROACH TO THE PATIENT**Cyanosis**

- Inquire about duration (cyanosis since birth suggests congenital heart disease) and exposures (drugs or chemicals that result in abnormal hemoglobins).
- Differentiate central from peripheral cyanosis by examining nailbeds, lips, and mucous membranes. Peripheral cyanosis is most intense in nailbeds and may resolve with gentle warming of extremities.

- Check for clubbing, i.e., selective enlargement of the distal segments of fingers and toes, due to proliferation of connective tissue. Clubbing may be hereditary, idiopathic, or acquired in association with lung cancer, infective endocarditis, bronchiectasis, or hepatic cirrhosis. Combination of clubbing and cyanosis is frequent in congenital heart disease and occasionally in pulmonary disease (lung abscess, pulmonary AV shunts, but not with uncomplicated obstructive lung disease).
- Examine chest for evidence of pulmonary disease, pulmonary edema, or murmurs associated with congenital heart disease.
- If cyanosis is localized to an extremity, evaluate for peripheral vascular obstruction.
- Obtain arterial blood gas to measure systemic O₂ saturation. Repeat while pt inhales 100% O₂; if saturation fails to increase to >95%, intravascular shunting of blood bypassing the lungs is likely (e.g., right-to-left intracardiac shunts).
- Evaluate for abnormal hemoglobins (e.g., spectroscopy, measurement of methemoglobin level).

37

Cough and Hemoptysis



COUGH

■ ETIOLOGY

Acute cough, which is defined as duration <21 days, is usually related to respiratory infection, aspiration, or inhalation of respiratory irritants. Subacute cough (present for 3–8 weeks) is often related to persistent inflammation from a tracheobronchitis episode. Chronic cough (>8 weeks in duration) can be caused by many pulmonary and cardiac diseases. Chronic bronchitis related to cigarette smoking is a common cause. If the chest radiograph and physical examination are unremarkable, other common causes of chronic cough include cough-variant asthma, gastroesophageal reflux disease (GERD), postnasal drip related to sinus disease, and medications including ACE inhibitors. Irritation of tympanic membranes and chronic eosinophilic bronchitis also can cause chronic cough with a normal chest radiograph. Ineffective cough can predispose to serious respiratory infections due to difficulty clearing lower respiratory secretions; abnormal airway secretions (e.g., due to bronchiectasis) or tracheomalacia can contribute. Weakness or pain limiting abdominal and intercostal muscle use also can lead to ineffective cough.

■ CLINICAL ASSESSMENT

Key issues in the history include triggers for onset of cough, determinants of increased or decreased cough, and sputum production. Symptoms of nasopharyngeal disease should be assessed, including postnasal drip, sneezing, and rhinorrhea. GERD may be suggested by heartburn, hoarseness, sore throat, and frequent eructation, but GERD also may be asymptomatic. Cough-variant asthma (without other asthmatic symptoms) is suggested by noting the relationship of cough onset to asthmatic triggers. Usage of ACE inhibitors, but not angiotensin receptor blockers, can cause cough long after treatment is initiated.

On physical examination, signs of cardiopulmonary diseases should be assessed, including adventitious lung sounds and digital clubbing. Examination of the nasal passages, posterior pharyngeal wall, auditory canals, and tympanic membranes should be performed.

Laboratory evaluation should include chest radiography. Spirometry with bronchodilator testing can assess for reversible airflow obstruction. With normal spirometry, methacholine challenge testing can be used to assess for asthma. Purulent sputum should be sent for routine bacterial and possibly mycobacterial cultures. Sputum cytology can reveal malignant cells in lung cancer and eosinophils in eosinophilic bronchitis. Esophageal pH probes or radiotracer capsules can be used to assess for GERD. Chest CT should be considered in pts with normal chest radiographs who fail to improve with treatment. Evaluation of hemoptysis is discussed next.

TREATMENT

Chronic Cough

In pts with chronic cough and a normal chest x-ray, empiric treatment is directed at the most likely cause based on the history and physical examination. If treatment directed at one empiric cause fails, empiric treatment of an alternative etiology can be considered. Postnasal drainage treatment may include systemic antihistamines, nasal corticosteroids, decongestants, anticholinergics, nasal saline irrigation, and/or antibiotics. GERD can be treated with antacids, type 2 histamine blockers, or proton pump inhibitors. Cough-variant asthma is treated with inhaled glucocorticoids and as-needed inhaled β agonists. Pts on ACE inhibitors should be given a 1-month trial of discontinuing this medication. Chronic eosinophilic bronchitis often improves with inhaled glucocorticoid treatment. Symptomatic treatment of cough can include narcotics such as codeine; however, somnolence, constipation, and addiction can result. Dextromethorphan and benzonatate have fewer side effects but reduced efficacy.

HEMOPTYSIS

■ ETIOLOGY

Hemoptysis, expectoration of blood from the respiratory tract, must be differentiated from expectorated blood originating from the nasopharynx or GI tract. Hemoptysis can result from infections, malignancies, or vascular disease. Acute bronchitis is the most common cause of hemoptysis in the United States; tuberculosis is the leading cause worldwide.

Hemoptysis originating from the alveoli is known as diffuse alveolar hemorrhage (DAH). DAH can be caused by inflammatory diseases including granulomatosis with polyangiitis, systemic lupus erythematosus, and anti-glomerular basement membrane disease. Within the first 100 days after bone marrow transplant, inflammatory DAH can cause severe hypoxemia. Noninflammatory DAH usually results from inhalational injuries from toxic exposures, such as smoke inhalation or cocaine.

Hemoptysis most commonly originates from small- to medium-sized bronchi. Because the bleeding source is usually bronchial arteries, there is potential for rapid blood loss. Airway hemoptysis is often caused by viral or bacterial bronchitis. Pts with bronchiectasis have increased risk of hemoptysis. Cavitory lung disease with hemoptysis can result from infections with endemic fungi, *Nocardia*, *Aspergillus*, and atypical mycobacteria. Pneumonia can cause hemoptysis, especially if cavitation (e.g., tuberculosis) and/or necrotizing pneumonia

(e.g., *Klebsiella pneumoniae* and *Staphylococcus aureus*) develop. Paragonimiasis, a helminthic infection common in pts from Southeast Asia and China, can cause hemoptysis and must be differentiated from tuberculosis. Cancers developing in central airways (e.g., squamous cell carcinoma, small-cell carcinoma, and carcinoid tumors) often cause hemoptysis. Cancers that metastasize to the lungs cause hemoptysis less commonly.

Pulmonary vascular sources of hemoptysis include congestive heart failure with pulmonary edema, which usually causes pink, frothy sputum. Pulmonary embolism with infarction and pulmonary arteriovenous malformations are additional pulmonary vascular etiologies to consider.

■ CLINICAL ASSESSMENT

The approaches to assess and treat hemoptysis are shown in Fig. 37-1. History should determine whether the bleeding source is likely the respiratory tract or an alternative source (e.g., nasopharynx, upper GI tract). The quantity of expectorated blood should be estimated, because it influences the urgency of evaluation and treatment. Massive hemoptysis, variably defined as 400 mL within 24 h or 100–150 mL at one time, requires emergent care. The presence of purulent or frothy secretions should be assessed. History of previous hemoptysis episodes and cigarette smoking should be ascertained. Fever and chills should be assessed as potential indicators of acute infection. Recent inhalation of illicit drugs and other toxins should be determined.

Physical examination should include assessment of the nares for epistaxis, and evaluation of the heart and lungs. Pedal edema could indicate congestive heart failure if symmetric, and deep-vein thrombosis with pulmonary embolism if asymmetric. Clubbing could indicate lung cancer or bronchiectasis. Assessment of vital signs and oxygen saturation can provide information about hemodynamic stability and respiratory compromise.

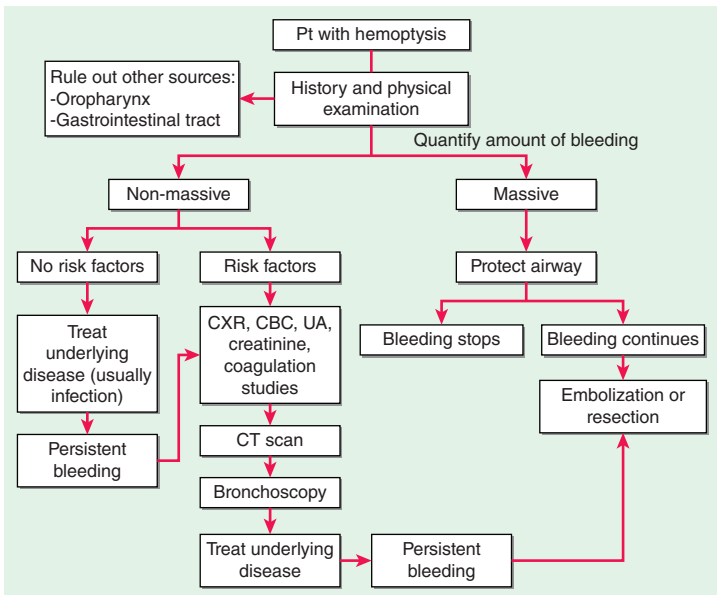


FIGURE 37-1 Approach to the management of hemoptysis. CBC, complete blood count; CT, computed tomography; CXR, chest x-ray; UA, urinalysis.

Radiographic evaluation with a chest x-ray should be performed. Chest CT may be helpful to assess for bronchiectasis, pneumonia, and lung cancer; with CT angiography, pulmonary embolism and location of bleeding may be determined. Laboratory studies include a complete blood count and coagulation studies; electrolytes, renal function, and urinalysis should be assessed, with additional blood tests including antineutrophil cytoplasmic antibody (ANCA), anti-GBM (glomerular basement membrane), and ANA if DAH is suspected. Sputum should be sent for Gram's stain and routine culture as well as acid-fast bacillus (AFB) smear and culture.

Bronchoscopy is often required to complete the evaluation. In massive hemoptysis, rigid bronchoscopy may be necessary.

TREATMENT

Hemoptysis

As shown in Fig. 37-1, massive hemoptysis may require endotracheal intubation and mechanical ventilation to provide airway stabilization. If the source of bleeding can be identified, isolating the bleeding lung with an endobronchial blocker or double-lumen endotracheal tube is optimal. Pts should be positioned with the bleeding side down. If bleeding persists, bronchial arterial embolization by angiography may be beneficial; however, risk of spinal artery embolization is an important potential adverse event. As a last resort, surgical resection can be considered to stop the bleeding.

38

Edema



DEFINITION

Soft tissue swelling due to abnormal expansion of interstitial fluid volume. Edema fluid is a plasma transudate that accumulates when movement of fluid from vascular to interstitial space is favored. Because detectable generalized edema in the adult reflects a gain of ≥ 3 L, renal retention of salt and water is necessary. Distribution of edema can be an important guide to cause.

Localized Edema

Limited to a particular organ or vascular bed; easily distinguished from generalized edema. Unilateral extremity edema is usually due to venous or lymphatic obstruction (e.g., deep venous thrombosis, tumor obstruction, primary lymphedema). Stasis edema of a paralyzed lower extremity also may occur. Allergic reactions ("angioedema") and superior vena caval obstruction are causes of localized facial edema. Bilateral lower-extremity edema may have localized causes, e.g., inferior vena caval obstruction, compression due to ascites, and abdominal mass. Ascites (fluid in peritoneal cavity) and hydrothorax (in pleural space) also may present as isolated localized edema, due to inflammation or neoplasm.

Generalized Edema

Soft tissue swelling of most or all regions of the body. Bilateral lower-extremity swelling, more pronounced after standing for several hours, and pulmonary edema are usually cardiac in origin. Periorbital edema noted on awakening often results from renal disease and impaired Na excretion. Ascites and edema

of lower extremities and scrotum are frequent in cirrhosis, nephrotic syndrome, or CHF.

In *CHF*, diminished cardiac output and arterial underfilling result in both decreased renal perfusion and increased venous pressure with resultant renal Na retention due to renal vasoconstriction, intrarenal blood flow redistribution, direct Na-retentive effects of norepinephrine and angiotensin II, and secondary hyperaldosteronism leading to distal tubular Na retention.

In *cirrhosis*, arteriovenous shunts and peripheral vasodilation are the proximate causes of Na retention. Ascites accumulates when increased intrahepatic vascular resistance produces portal hypertension. As in heart failure, the effects of excess intrarenal and circulating norepinephrine, angiotensin II, and aldosterone lead to renal Na retention and worsening edema. Reduced serum albumin and increased abdominal pressure also promote lower-extremity edema.

In acute or chronic *renal failure*, edema occurs if Na intake exceeds kidneys' ability to excrete Na secondary to marked reductions in glomerular filtration. Severe hypoalbuminemia (<25 g/L [2.5 g/dL]) of any cause (e.g., nephrotic syndrome, nutritional deficiency, chronic liver disease) may lower plasma oncotic pressure, promoting fluid transudation into interstitium; lowering of effective blood volume stimulates renal Na retention and causes edema. In nephrotic syndrome, loss of protein into the urine also leads to primary Na retention, through effects on tubular Na transport.

Less common causes of generalized edema: idiopathic edema, a syndrome of recurrent rapid weight gain and edema in women of reproductive age; *hypothyroidism*, in which myxedema is typically located in the pretibial region; *drugs* (Table 38-1).

TABLE 38-1 Drugs Associated with Edema Formation

Nonsteroidal anti-inflammatory drugs
Antihypertensive agents
Direct arterial/arteriolar vasodilators
Hydralazine
Clonidine
Methyldopa
Guanethidine
Minoxidil
Calcium channel antagonists
α -Adrenergic antagonists
Thiazolidinediones
Steroid hormones
Glucocorticoids
Anabolic steroids
Estrogens
Progestins
Cyclosporine
Growth hormone
Immunotherapies
Interleukin 2
OKT3 monoclonal antibody

Source: From Chertow GM, in Braunwald E, Goldman L (eds): *Primary Cardiology*, 2nd ed. Philadelphia, Saunders, 2003.

TREATMENT

Edema

Primary management is to identify and treat the underlying cause of edema (Fig. 38-1).

Dietary Na restriction (<500 mg/d) may prevent further edema formation. Bed rest enhances response to salt restriction in CHF and cirrhosis. Supportive stockings and elevation of edematous lower extremities help to mobilize interstitial fluid. If severe hyponatremia (<132 mmol/L) is present, water intake also should be reduced (<1500 mL/d). Diuretics (Table 38-2) are indicated for marked

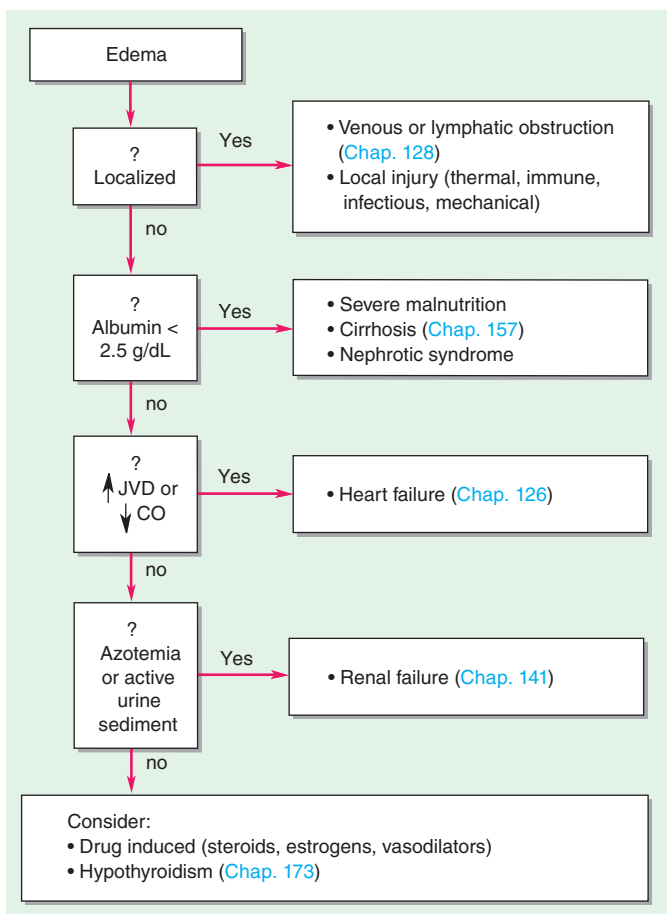


FIGURE 38-1 Diagnostic approach to edema. CO, cardiac output; JVD, jugular venous distention. (From Chap. 36, *HMOM-19*.)

TABLE 38-2 Diuretics for Edema		
DRUG	USUAL DOSE	COMMENTS
Loop (may be administered PO or IV)		
Furosemide	20–200 mg qd or bid	Short acting; potent; effective with low GFR
Bumetanide	0.5–5 mg qd or bid	Better oral absorption than furosemide, but shorter duration of action; enhanced metabolism in CKD
Torsemide	20–100 mg qd	Better oral absorption than furosemide, longer duration of action
Distal, K-losing		
Hydrochlorothiazide	12.5–25 mg qd	Causes hypokalemia; need GFR >25 mL/min
Chlorthalidone	12.5–25 mg qd	Long acting (up to 72 h); hypokalemia
Metolazone	1–5 mg qd	Long acting; hypokalemia
Distal, K-sparing		
Spironolactone	12.5–100 mg qd	Hyperkalemia; acidosis; blocks aldosterone; gynecomastia, impotence, amenorrhea; onset takes 2–3 days; avoid use in renal failure, use with caution in combination with ACE inhibitors or angiotensin receptor blockers
Eplerenone	25–50 mg qd	Similar side effects to spironolactone, but more specific for mineralocorticoid receptor; lower incidence of gynecomastia and amenorrhea
Amiloride	5–10 mg qd or bid	Hyperkalemia; once daily; less potent than spironolactone

Abbreviations: ACE, angiotensin-converting enzyme; GFR, glomerular filtration rate.

Source: From Chap. 36, *HMOM-19*.

peripheral edema, pulmonary edema, CHF, and inadequate dietary salt restriction. Complications are listed in [Table 38-3](#). Weight loss by diuretics should be limited to 1–1.5 kg/d. Should diuretic resistance occur, distal (“potassium sparing”) diuretics or metolazone may be added to loop diuretics for enhanced effect. Note that intestinal edema may impair absorption of oral diuretics and reduce effectiveness, requiring the use of intravenous diuretics. When desired weight is achieved, diuretic doses should be reduced.

In *CHF* ([Chap. 126](#)), avoid overdiuresis because it may bring a fall in cardiac output and prerenal azotemia. Avoid diuretic-induced hypokalemia, which predisposes to arrhythmia and metabolic alkalosis.

In *cirrhosis* and other hepatic causes of edema, spironolactone is the initial diuretic of choice but may produce acidosis and hyperkalemia. Loop diuretics may also be necessary. However, renal failure may result from volume depletion. Overdiuresis may result in hyponatremia, hypokalemia, and alkalosis, which may worsen hepatic encephalopathy ([Chap. 157](#)).

TABLE 38-3 Complications of Diuretics

COMMON	UNCOMMON
Volume depletion	Interstitial nephritis (thiazides, furosemide)
Prerenal azotemia	Pancreatitis (thiazides)
Potassium depletion	Loss of hearing (loop diuretics)
Hyponatremia (thiazides)	Anemia, leukopenia, thrombocytopenia (thiazides)
Metabolic alkalosis	
Hypercholesterolemia	
Hyperglycemia (thiazides)	
Hyperkalemia (K-sparing)	
Hypomagnesemia	
Hyperuricemia	
Hypercalcemia (thiazides)	
GI complaints	
Rash (thiazides)	

Abbreviation: GI, gastrointestinal.

Source: From Chap. 36, *HMOM-19*.

39

Abdominal Pain



Numerous causes, ranging from acute, life-threatening emergencies to chronic functional disease and disorders of several organ systems, can generate abdominal pain. Evaluation of acute pain requires rapid assessment of likely causes and early initiation of appropriate therapy. A more detailed and time-consuming approach to diagnosis may be followed in less acute situations. **Table 39-1** lists the common causes of abdominal pain.

APPROACH TO THE PATIENT**Abdominal Pain**

History: History is of critical diagnostic importance. Physical examination may be unrevealing or misleading, and laboratory and radiologic examinations delayed or unhelpful.

Characteristic Features of Abdominal Pain *Duration and pattern:* These provide clues to nature and severity, although acute abdominal crisis may occasionally present insidiously or on a background of chronic pain.

Type and location provide a rough guide to nature of disease. *Visceral pain* (due to distention of a hollow viscus) localizes poorly and is often perceived in the midline. Intestinal pain tends to be crampy; when originating proximal to the ileocecal valve, it usually localizes above and around the umbilicus. Pain of colonic origin is perceived in the hypogastrium and lower quadrants. Pain from biliary or ureteral obstruction often causes pts to writhe in discomfort. *Somatic pain* (due to peritoneal inflammation) is usually sharper and more precisely localized to the diseased region (e.g., acute appendicitis; capsular distention of liver, kidney, or spleen), exacerbated by movement,

TABLE 39-1 Some Important Causes of Abdominal Pain

Pain Originating in the Abdomen	
Parietal peritoneal inflammation	Vascular disturbances
Bacterial contamination	Embolism or thrombosis
Perforated appendix or other perforated viscus	Vascular rupture
Pelvic inflammatory disease	Pressure or torsional occlusion
Chemical irritation	Sickle cell anemia
Perforated ulcer	Abdominal wall
Pancreatitis	Distortion or traction of mesentery
Mittelschmerz	Trauma or infection of muscles
Blood	Distension of visceral surfaces, e.g., by hemorrhage
Mechanical obstruction of hollow viscera	Hepatic or renal capsules
Obstruction of the small or large intestine	Inflammation
Obstruction of the biliary tree	Appendicitis
Obstruction of the ureter	Typhoid fever
	Neutropenic enterocolitis or “typhlitis”
Pain Referred from Extraabdominal Source	
Cardiothoracic	Pleurodynia
Acute myocardial infarction	Pneumothorax
Myocarditis, endocarditis, pericarditis	Empyema
Congestive heart failure	Esophageal disease, including spasm, rupture, or inflammation
Pneumonia (especially lower lobes)	Genitalia
Pulmonary embolus	Torsion of the testis
Metabolic Causes	
Diabetes	Acute adrenal insufficiency
Uremia	Familial Mediterranean fever
Hyperlipidemia	Porphyria
Hyperparathyroidism	C1-esterase-inhibitor deficiency (angioneurotic edema)
Neurologic/Psychiatric Causes	
Herpes zoster	Spinal cord or nerve root compression
Tabes dorsalis	Functional disorders
Causalgia	Psychiatric disorders
Radiculitis from infection or arthritis	
Toxic Causes	
Lead poisoning	
Insect or animal envenomation	
Black widow spider bites	
Snakebites	
Uncertain Mechanisms	
Narcotic withdrawal	
Heat stroke	

causing pts to remain still. Pattern of radiation may be helpful: right shoulder (hepatobiliary origin), left shoulder (splenic), midback (pancreatic), flank (proximal urinary tract), and groin (genital or distal urinary tract).

Factors that precipitate or relieve pain: Ask about its relationship to eating (e.g., upper GI, biliary, pancreatic, ischemic bowel disease), defecation (colorectal), urination (genitourinary or colorectal), respiratory (pleuropulmonary, hepatobiliary), position (pancreatic, gastroesophageal reflux, musculoskeletal), menstrual cycle/menarche (tuboovarian, endometrial, including endometriosis), exertion (coronary/intestinal ischemia, musculoskeletal), medication or specific foods (motility disorders, food intolerance, gastroesophageal reflux, porphyria, adrenal insufficiency, ketoacidosis, toxins), and stress (motility disorders, nonulcer dyspepsia, irritable bowel syndrome).

Associated symptoms: Look for fevers/chills (infection, inflammatory disease, infarction), weight loss (tumor, inflammatory disease, malabsorption, ischemia), nausea/vomiting (obstruction, infection, inflammatory disease, metabolic disease), dysphagia/odynophagia (esophageal), early satiety (gastric), hematemesis (esophageal, gastric, duodenal), constipation (colorectal, perianal, genitourinary), jaundice (hepatobiliary, hemolytic), diarrhea (inflammatory disease, infection, malabsorption, secretory tumors, ischemia, genitourinary), dysuria/hematuria/vaginal or penile discharge (genitourinary), hematochezia (colorectal or, rarely, urinary), and skin/joint/eye disorders (inflammatory disease, bacterial or viral infection).

Predisposing factors: Inquire about family history (inflammatory disease, tumors, pancreatitis), hypertension and atherosclerotic disease (ischemia), diabetes mellitus (motility disorders, ketoacidosis), connective tissue disease (motility disorders, serositis), depression (motility disorders, tumors), smoking (ischemia), recent smoking cessation (inflammatory disease), and ethanol use (motility disorders, hepatobiliary, pancreatic, gastritis, peptic ulcer disease).

Physical examination: Evaluate abdomen for prior trauma or surgery, current trauma; abdominal distention, fluid, or air; direct, rebound, and referred tenderness; liver and spleen size; masses, bruits, altered bowel sounds, hernias, arterial masses. Rectal examination assesses presence and location of tenderness, masses, blood (gross or occult). Pelvic examination in women is essential.

General examination: Evaluate for evidence of hemodynamic instability, acid-base disturbances, nutritional deficiency, coagulopathy, arterial occlusive disease, stigmata of liver disease, cardiac dysfunction, lymphadenopathy, and skin lesions.

Routine laboratory and radiologic studies: Choices depend on clinical setting (esp. severity of pain, rapidity of onset) and may include complete blood count, serum electrolytes, coagulation parameters, serum glucose, and biochemical tests of liver, kidney, and pancreatic function; chest x-ray to determine the presence of diseases involving heart, lung, mediastinum, and pleura; electrocardiogram is helpful to exclude referred pain from cardiac disease; plain abdominal radiographs to evaluate bowel displacement, intestinal distention, fluid and gas pattern, free peritoneal air, liver size, and abdominal calcifications (e.g., gallstones, renal stones, chronic pancreatitis).

Special studies: These include abdominal ultrasonography (to visualize biliary ducts, gallbladder, liver, pancreas, and kidneys); CT to identify masses, abscesses, evidence of inflammation (bowel wall thickening, mesenteric "stranding," lymphadenopathy, appendicitis), aortic aneurysm; barium contrast radiographs (barium swallow, upper GI series, small-bowel

follow-through, barium enema); upper GI endoscopy, sigmoidoscopy, or colonoscopy; cholangiography (endoscopic, percutaneous, or via MRI), angiography (direct or via CT or MRI), and radionuclide scanning. In selected cases, percutaneous biopsy, laparoscopy, and exploratory laparotomy may be required.

ACUTE, CATASTROPHIC ABDOMINAL PAIN

Intense abdominal pain of acute onset or pain associated with syncope, hypotension, or toxic appearance necessitates rapid yet orderly evaluation. Consider obstruction, perforation, or rupture of hollow viscus; dissection or rupture of major blood vessels (esp. aortic aneurysm); ulceration; abdominal sepsis; ketoacidosis; and adrenal crisis.

■ BRIEF HISTORY AND PHYSICAL EXAMINATION

Historic features of importance include age; time of onset of the pain; activity of the pt when the pain began; location and character of the pain; radiation to other sites; presence of nausea, vomiting, or anorexia; temporal changes; changes in bowel habits; and menstrual history. Physical examination should focus on the pt's overall appearance (writhing in pain [ureteral lithiasis] vs. still [peritonitis, perforation]), position (a pt leaning forward may have pancreatitis or gastric perforation into the lesser sac), presence of fever or hypothermia, hyperventilation, cyanosis, bowel sounds, direct or rebound abdominal tenderness, pulsating abdominal mass, abdominal bruits, ascites, rectal blood, rectal or pelvic tenderness, and evidence of coagulopathy. Useful laboratory studies include hematocrit (may be normal with acute hemorrhage or misleadingly high with dehydration), WBC with differential count, arterial blood gases, serum electrolytes, BUN, creatinine, glucose, lipase or amylase, and UA. Females of reproductive age should have a pregnancy test. Radiologic studies should include supine and upright abdominal films (left lateral decubitus view if upright unobtainable) to evaluate bowel caliber and presence of free peritoneal air, cross-table lateral film to assess aortic diameter; CT (when available) to detect evidence of bowel perforation, inflammation, solid organ infarction, retroperitoneal bleeding, abscess, or tumor. Abdominal paracentesis (or peritoneal lavage in cases of trauma) can detect evidence of bleeding or peritonitis. Abdominal ultrasound (when available) reveals evidence of abscess, cholecystitis, biliary or ureteral obstruction, or hematoma and is used to determine aortic diameter.

■ DIAGNOSTIC STRATEGIES

The initial decision point is based on whether the pt is hemodynamically stable. If not, one must suspect a vascular catastrophe such as a leaking abdominal aortic aneurysm. Such pts receive limited resuscitation and move immediately to surgical exploration. If the pt is hemodynamically stable, the next decision point is whether the abdomen is rigid. Rigid abdomens are most often due to perforation or obstruction. The diagnosis can generally be made by a chest and plain abdominal radiograph.

If the abdomen is not rigid, the causes may be grouped based on whether the pain is poorly localized or well localized. In the presence of poorly localized pain, one should assess whether an aortic aneurysm is possible. If so, a CT scan can make the diagnosis; if not, early appendicitis, early obstruction, mesenteric ischemia, inflammatory bowel disease, pancreatitis, and metabolic problems are all in the differential diagnosis.

Pain localized to the epigastrium may be of cardiac origin or due to esophageal inflammation or perforation, gastritis, peptic ulcer disease, biliary colic or cholecystitis, or pancreatitis. Pain localized to the right upper quadrant includes those same entities plus pyelonephritis or nephrolithiasis, hepatic abscess, subdiaphragmatic abscess, pulmonary embolus, or pneumonia, or it may be of musculoskeletal origin. Additional considerations with left upper quadrant localization are infarcted or ruptured spleen, splenomegaly, and gastric or peptic ulcer. Right lower quadrant pain may be from appendicitis, Meckel's diverticulum, Crohn's disease, diverticulitis, mesenteric adenitis, rectus sheath hematoma, psoas abscess, ovarian abscess or torsion, ectopic pregnancy, salpingitis, familial fever syndromes, urolithiasis, or herpes zoster. Left lower quadrant pain may be due to diverticulitis, perforated neoplasm, or other entities previously mentioned.

TREATMENT

Acute, Catastrophic Abdominal Pain

IV fluids, correction of life-threatening acid-base disturbances, and assessment of need for emergent surgery are the first priority; careful follow-up with frequent reexamination (when possible, by the same examiner) is essential. Relieve the pain. The use of narcotic analgesia is controversial. Traditionally, narcotic analgesics were withheld pending establishment of diagnosis and therapeutic plan, because masking of diagnostic signs may delay needed intervention. However, evidence that narcotics actually mask a diagnosis is sparse.

40

Nausea, Vomiting, and Indigestion



NAUSEA AND VOMITING

Nausea refers to the imminent desire to vomit and often precedes or accompanies vomiting. *Vomiting* refers to the forceful expulsion of gastric contents through the mouth. *Retching* refers to labored rhythmic respiratory activity that precedes emesis. *Regurgitation* refers to the gentle expulsion of gastric contents in the absence of nausea and abdominal diaphragmatic muscular contraction. *Rumination* refers to the regurgitation, rechewing, and reswallowing of food from the stomach.

■ PATHOPHYSIOLOGY

Gastric contents are propelled into the esophagus when there is relaxation of the gastric fundus and gastroesophageal sphincter followed by a rapid increase in intraabdominal pressure produced by contraction of the abdominal and diaphragmatic musculature. Increased intrathoracic pressure results in further movement of the material to the mouth. Reflex elevation of the soft palate and closure of the glottis protect the nasopharynx and trachea and complete the act of vomiting. Vomiting is controlled by two brainstem areas, the vomiting center and chemoreceptor trigger zone. Activation of the chemoreceptor trigger zone

results in impulses to the vomiting center, which controls the physical act of vomiting.

■ ETIOLOGY

Nausea and vomiting are manifestations of a large number of disorders (Table 40-1).

■ EVALUATION

The history, including a careful drug history, and the timing and character of the vomitus can be helpful. For example, vomiting that occurs predominantly in the morning is often seen in pregnancy, uremia, and alcoholic gastritis; feculent

TABLE 40-1 Causes of Nausea and Vomiting

INTRAPERITONEAL	EXTRAPERITONEAL	MEDICATIONS/ METABOLIC DISORDERS
Obstructing disorders	Cardiopulmonary disease	Drugs
Pyloric obstruction	Cardiomyopathy	Cancer chemotherapy
Small-bowel obstruction	Myocardial infarction	Antibiotics
Colonic obstruction	Labyrinthine disease	Cardiac antiarrhythmics
Superior mesenteric artery syndrome	Motion sickness	Digoxin
Enteric infections	Labyrinthitis	Oral hypoglycemics
Viral	Malignancy	Oral contraceptives
Bacterial	Intracerebral disorders	Antidepressants
Inflammatory diseases	Malignancy	Smoking cessation agents
Cholecystitis	Hemorrhage	Parkinson's disease treatments
Pancreatitis	Abscess	Endocrine/metabolic disease
Appendicitis	Hydrocephalus	Pregnancy
Hepatitis	Psychiatric illness	Uremia
Altered sensorimotor function	Anorexia and bulimia nervosa	Ketoacidosis
Gastroparesis	Depression	Thyroid and parathyroid disease
Intestinal pseudoobstruction	Postoperative vomiting	Adrenal insufficiency
Gastroesophageal reflux		Systemic effects of cancer
Chronic idiopathic nausea		Toxins
Functional vomiting		Liver failure
Cyclic vomiting syndrome		Ethanol
Cannabinoid hyperemesis syndrome		
Rumination syndrome		
Biliary colic		
Abdominal irradiation		

emesis implies distal intestinal obstruction or gastrocolic fistula; projectile vomiting suggests increased intracranial pressure; vomiting during or shortly after a meal may be due to psychogenic causes or peptic ulcer disease. Associated symptoms may also be helpful: vertigo and tinnitus in Ménière's disease, relief of abdominal pain with vomiting in peptic ulcer, and early satiety in gastroparesis. Plain radiographs can suggest diagnoses such as intestinal obstruction. The upper GI series assesses motility of the proximal GI tract as well as the mucosa. Other studies may be indicated, such as gastric emptying scans (diabetic gastroparesis) and CT scan of the brain.

■ COMPLICATIONS

Rupture of the esophagus (Boerhaave's syndrome), hematemesis from a mucosal tear (Mallory-Weiss syndrome), dehydration, malnutrition, dental caries and erosions, metabolic alkalosis, hypokalemia, and aspiration pneumonitis.

TREATMENT

Nausea and Vomiting

Treatment is aimed at correcting the specific cause. The effectiveness of antiemetic medications depends on etiology of symptoms, pt responsiveness, and side effects. Antihistamines such as meclizine and dimenhydrinate are effective for nausea due to inner ear dysfunction. Anticholinergics such as scopolamine are effective for nausea associated with motion sickness. Haloperidol and phenothiazine derivatives such as prochlorperazine are often effective in controlling mild nausea and vomiting, but sedation, hypotension, and parkinsonian symptoms are common side effects. Selective dopamine antagonists such as metoclopramide may be superior to the phenothiazines in treating severe nausea and vomiting and are particularly useful in treatment of gastroparesis. IV metoclopramide may be effective as prophylaxis against nausea when given before chemotherapy. Ondansetron and granisetron, serotonin receptor blockers, and glucocorticoids are used for treating nausea and vomiting associated with cancer chemotherapy. Aprepitant, a neurokinin receptor blocker, is effective at controlling nausea from highly emetic drugs like cisplatin. The atypical antipsychotic agent, olanzapine, can help control and prevent emesis caused by highly emetogenic chemotherapy. Erythromycin is effective in some pts with gastroparesis.

INDIGESTION

Indigestion is a nonspecific term that encompasses a variety of upper abdominal complaints including heartburn, regurgitation, and dyspepsia (upper abdominal discomfort or pain). These symptoms are overwhelmingly due to gastroesophageal reflux disease (GERD).

■ PATHOPHYSIOLOGY

GERD occurs as a consequence of acid reflux into the esophagus from the stomach, gastric motor dysfunction, or visceral afferent hypersensitivity. A wide variety of situations promote GERD: increased gastric contents (from a large meal, gastric stasis, or acid hypersecretion), physical factors (lying down, bending over), increased pressure on the stomach (tight clothes, obesity, ascites, pregnancy), and loss (usually intermittent) of lower esophageal sphincter tone (diseases such as scleroderma, smoking, anticholinergics, calcium antagonists). Hiatal hernia also promotes acid flow into the esophagus.

■ NATURAL HISTORY

Heartburn is reported once monthly by 40% of Americans and daily by 7%. Functional dyspepsia is defined as >3 months of dyspepsia without an organic cause. Functional dyspepsia is the cause of symptoms in 60% of pts with dyspeptic symptoms. However, peptic ulcer disease from either *Helicobacter pylori* infection or ingestion of NSAIDs is present in 15% of cases.

In most cases, the esophagus is not damaged, but 5% of pts develop esophageal ulcers and some form strictures; 8–20% develop glandular epithelial cell metaplasia, termed *Barrett's esophagus*, which can progress to adenocarcinoma.

Extraesophageal manifestations include asthma, laryngitis, chronic cough, aspiration pneumonitis, chronic bronchitis, sleep apnea, dental caries, halitosis, and hiccups.

■ EVALUATION

The presence of “alarm” signals, shown in [Table 40-2](#), demands directed radiographic, endoscopic, and surgical evaluation. Pts without alarm features are generally treated empirically. Individuals >45 years can be tested for the presence of *H. pylori*. Pts positive for the infection are treated to eradicate the organism. Pts who fail to respond to *H. pylori* treatment, those >45 years old, and those with alarm factors generally undergo upper GI endoscopy.

TREATMENT

Indigestion

Weight reduction; elevation of the head of the bed; and avoidance of large meals, smoking, caffeine, alcohol, chocolate, fatty food, citrus juices, and NSAIDs may prevent GERD. Antacids are widely used. Clinical trials suggest that proton pump inhibitors (omeprazole) are more effective than histamine receptor blockers (ranitidine) in pts with or without esophageal erosions. *H. pylori* eradication regimens are discussed in [Chap. 150](#). Motor stimulants like metoclopramide and erythromycin may be useful in a subset of pts with postprandial distress.

Surgical techniques (Nissen fundoplication, Belsey procedure) work best in young individuals whose symptoms have improved on proton pump inhibitors and who otherwise may require lifelong therapy. They can be used in the rare pts who are refractory to medical management. Clinical trials have not documented the superiority of one over another.

Dietary exclusion of gas-producing foods (i.e., low FODMAP [fermentable oligosaccharide, disaccharide, monosaccharide, and polyol] diets), and therapies to modify gut flora can reduce symptoms.

TABLE 40-2 Alarm Symptoms in Gastroesophageal Reflux Disease

Odynophagia or dysphagia
Unexplained weight loss
Recurrent vomiting
Occult or gross gastrointestinal bleeding
Jaundice
Palpable mass or adenopathy
Family history of gastroesophageal malignancy

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Dysphagia

**DYSPHAGIA**

Dysphagia is difficulty moving food or liquid through the mouth, pharynx, and esophagus. The pt senses swallowed material sticking along the path. *Odynophagia* is pain on swallowing. *Globus pharyngeus* is the sensation of a lump lodged in the throat, with swallowing unaffected.

■ PATHOPHYSIOLOGY

Dysphagia is caused by two main mechanisms: mechanical obstruction or motor dysfunction. Mechanical causes of dysphagia can be luminal (e.g., large food bolus, foreign body), intrinsic to the esophagus (e.g., inflammation, webs and rings, strictures, tumors), or extrinsic to the esophagus (e.g., cervical spondylitis, enlarged thyroid or mediastinal mass, vascular compression). The motor function abnormalities that cause dysphagia may be related to defects in initiating the swallowing reflex (e.g., tongue paralysis, lack of saliva, lesions affecting sensory components of cranial nerves X and XI), disorders of the pharyngeal and esophageal striated muscle (e.g., muscle disorders such as polymyositis and dermatomyositis, neurologic lesions such as myasthenia gravis, polio, or amyotrophic lateral sclerosis), and disorders of the esophageal smooth muscle (e.g., achalasia, scleroderma, myotonic dystrophy).

APPROACH TO THE PATIENT**Dysphagia**

History can provide a presumptive diagnosis in about 80% of pts. Difficulty only with solids implies mechanical dysphagia. Difficulty with both solids and liquids may occur late in the course of mechanical dysphagia but is an early sign of motor dysphagia. Pts can sometimes pinpoint the site of food sticking. Weight loss out of proportion to the degree of dysphagia may be a sign of underlying malignancy. Hoarseness may be related to involvement of the larynx in the primary disease process (e.g., neuromuscular disorders), neoplastic disruption of the recurrent laryngeal nerve, or laryngitis from gastroesophageal reflux.

Physical examination may reveal signs of skeletal muscle, neurologic, or oropharyngeal diseases. Neck examination can reveal masses impinging on the esophagus. Skin changes might suggest the systemic nature of the underlying disease (e.g., scleroderma).

Dysphagia is nearly always a symptom of organic disease rather than a functional complaint. If oropharyngeal dysphagia is suspected, videofluoroscopy of swallowing may be diagnostic. Mechanical dysphagia can be evaluated by barium swallow and esophagogastrosocopy with endoscopic biopsy. Barium swallow and esophageal motility studies can show the presence of motor dysphagia. An algorithm outlining an approach to the pt with dysphagia is shown in [Fig. 41-1](#).

■ OROPHARYNGEAL DYSPHAGIA

Pt has difficulty initiating the swallow; food sticks at the level of the suprasternal notch; nasopharyngeal regurgitation and aspiration may be present.

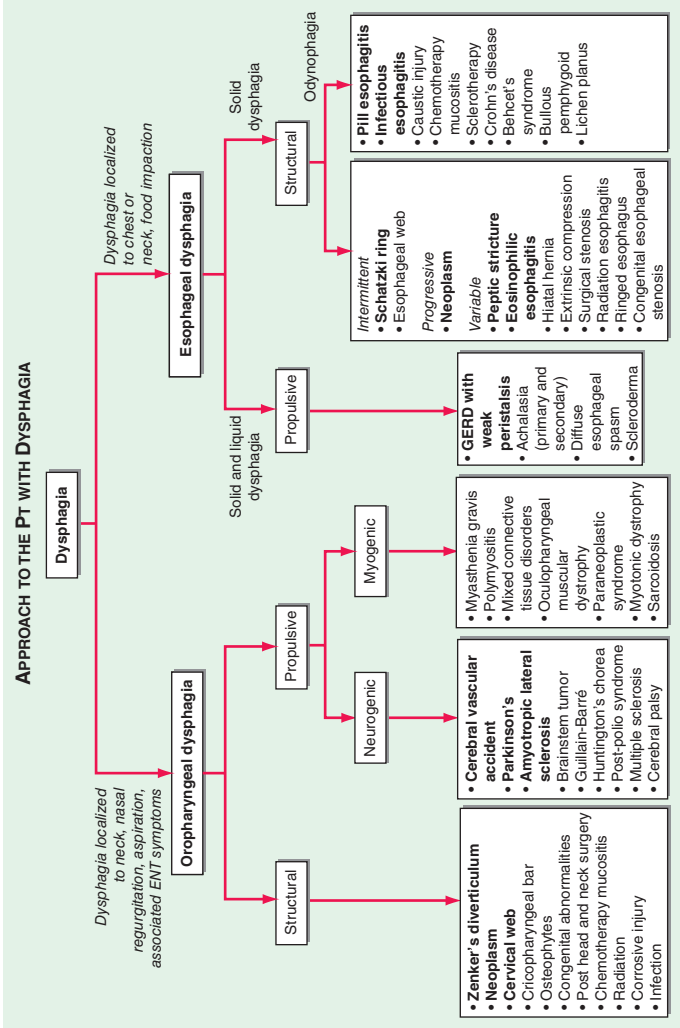


FIGURE 41-1 Approach to the pt with dysphagia. Etiologies in bold print are the most common. ENT, ear, nose, and throat; GERD, gastroesophageal reflux disease.

Causes include the following: for solids only, carcinoma, aberrant vessel, congenital or acquired web (Plummer-Vinson syndrome in iron deficiency), cervical osteophyte; for solids and liquids, cricopharyngeal bar (e.g., hypertensive or hypotensive upper esophageal sphincter), Zenker's diverticulum (outpouching in the posterior midline at the intersection of the pharynx and the cricopharyngeus muscle), myasthenia gravis, glucocorticoid myopathy, hyperthyroidism, hypothyroidism, myotonic dystrophy, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, stroke, bulbar palsy, and pseudobulbar palsy.

■ ESOPHAGEAL DYSPHAGIA

Food sticks in the mid or lower sternal area; can be associated with regurgitation, aspiration, odynophagia. Causes include the following: for solids only, lower esophageal ring (Schatzki's ring—symptoms are usually intermittent), peptic stricture (heartburn accompanies this), carcinoma, lye stricture; for solids and liquids, diffuse esophageal spasm (occurs with chest pain and is intermittent), scleroderma (progressive and occurs with heartburn), achalasia (progressive and occurs without heartburn).

NONCARDIAC CHEST PAIN

Of pts presenting with chest pain, 30% have an esophageal source rather than angina. History and physical examination often cannot distinguish cardiac from noncardiac pain. Exclude cardiac disease first. Causes include the following: gastroesophageal reflux disease, esophageal motility disorders, peptic ulcer disease, gallstones, psychiatric disease (anxiety, panic attacks, depression).

■ EVALUATION

Consider a trial of antireflux therapy (omeprazole); if no response, 24-h ambulatory luminal pH monitoring; if negative, esophageal manometry may show motor disorder. Trial of imipramine, 50 mg PO qhs, may be worthwhile. Consider psychiatric evaluation in selected cases.

ESOPHAGEAL MOTILITY DISORDERS

Pts may have a spectrum of manometric findings ranging from nonspecific abnormalities to defined clinical entities.

■ ACHALASIA

Motor obstruction caused by hypertensive lower esophageal sphincter (LES), incomplete relaxation of LES, or loss of peristalsis in smooth-muscle portion of esophagus. Causes include the following: primary (idiopathic) or secondary due to Chagas' disease, lymphoma, carcinoma, chronic idiopathic intestinal pseudoobstruction, ischemia, neurotropic viruses, drugs, toxins, radiation therapy, postvagotomy.

■ EVALUATION

Chest x-ray shows absence of gastric air bubble. Barium swallow shows dilated esophagus with distal beaklike narrowing and air-fluid level. Endoscopy is done to rule out cancer, particularly in persons >50 years. Manometry shows normal or elevated LES pressure, decreased LES relaxation, absent peristalsis.

TREATMENT

Achalasia

Pneumatic balloon dilatation is effective in 85%, with 3–5% risk of perforation or bleeding. Injection of botulinum toxin at endoscopy to relax LES is safe and effective in two-thirds of pts, but effects last 6–12 months. Myotomy of LES

(Heller procedure) is effective, but 10–30% of pts develop gastroesophageal reflux. Nifedipine, 10–20 mg, or isosorbide dinitrate, 5–10 mg SL ac, may avert need for dilation or surgery. Sildenafil may also augment swallow-induced relaxation of the LES.

■ SPASTIC DISORDERS

Diffuse esophageal spasm involves multiple spontaneous and swallow-induced contractions of the esophageal body that are of simultaneous onset and long duration and are recurrent. Causes include the following: primary (idiopathic) or secondary due to gastroesophageal reflux disease, emotional stress, diabetes, alcoholism, neuropathy, radiation therapy, ischemia, or collagen vascular disease.

An important variant is nutcracker esophagus: high-amplitude (>180 mmHg) peristaltic contractions; particularly associated with chest pain or dysphagia, but correlation between symptoms and manometry is inconsistent. Condition may resolve over time or evolve into diffuse spasm; associated with increased frequency of depression, anxiety, and somatization.

■ EVALUATION

Barium swallow shows corkscrew esophagus, pseudodiverticula, and diffuse spasm. Manometry shows spasm with multiple simultaneous esophageal contractions of high amplitude and long duration. In nutcracker esophagus, the contractions are peristaltic and of high amplitude. If heart disease has been ruled out, edrophonium, ergonovine, or bethanechol can be used to provoke spasm.

TREATMENT

Spastic Disorders

Anticholinergics are usually of limited value; nitrates (isosorbide dinitrate, 5–10 mg PO ac) and calcium antagonists (nifedipine, 10–20 mg PO ac) are more effective. Those refractory to medical management may benefit from balloon dilation. Rare pts require surgical intervention: longitudinal myotomy of esophageal circular muscle. Treatment of concomitant depression or other psychological disturbance may help.

■ SCLERODERMA

Atrophy of the esophageal smooth muscle and fibrosis can make the esophagus aperistaltic and lead to an incompetent LES with attendant reflux esophagitis and stricture. Treatment of gastroesophageal reflux disease is discussed in [Chap. 40](#).

ESOPHAGEAL INFLAMMATION

■ VIRAL ESOPHAGITIS

Herpesviruses I and II, varicella-zoster virus, and CMV can all cause esophagitis; particularly common in immunocompromised pts (e.g., AIDS). Odynophagia, dysphagia, fever, and bleeding are symptoms and signs. Diagnosis is made by endoscopy with biopsy, brush cytology, and culture.

TREATMENT

Viral Esophagitis

Disease is usually self-limited in the immunocompetent person; viscous lidocaine can relieve pain; in immunocompetent pts, herpes and varicella esophagitis are treated with acyclovir, 200 mg PO five times a day for 7–10 days;

in prolonged cases and in immunocompromised hosts, treatment is with acyclovir, 400 mg PO five times a day for 14–21 days, famciclovir, 500 mg PO tid, or valacyclovir 1 g PO tid for 7 days. CMV is treated with ganciclovir, 5 mg/kg IV q12h, until healing occurs, which may take weeks. Oral valganciclovir (900 mg bid) is an effective alternative to parenteral treatment. In nonresponders, foscarnet, 90 mg/kg IV q12h for 21 days, may be effective.

■ CANDIDA ESOPHAGITIS

In immunocompromised hosts, or those with malignancy, diabetes, hypoparathyroidism, hemoglobinopathy, systemic lupus erythematosus, corrosive esophageal injury, candidal esophageal infection may present with odynophagia, dysphagia, and oral thrush (50%). Diagnosis is made on endoscopy by identifying yellow-white plaques or nodules on friable red mucosa. Characteristic hyphae are seen on KOH stain. In pts with AIDS, the development of symptoms may prompt an empirical therapeutic trial.

TREATMENT

Candida Esophagitis

In immunocompromised hosts, fluconazole, 200 mg PO on day 1 followed by 100 mg daily for 2–3 weeks, is treatment of choice; alternatives include itraconazole, 200 mg PO bid, or ketoconazole, 200–400 mg PO daily; long-term maintenance therapy is often required. Poorly responsive pts or those who cannot swallow may respond to caspofungin 50 mg IV qd for 7–21 days.

■ PILL-RELATED ESOPHAGITIS

Doxycycline, tetracycline, aspirin, nonsteroidal anti-inflammatory drugs, KCl, quinidine, ferrous sulfate, clindamycin, alprenolol, and alendronate can induce local inflammation in the esophagus. Predisposing factors include recumbency after swallowing pills with small sips of water and anatomic factors impinging on the esophagus and slowing transit.

TREATMENT

Pill-Related Esophagitis

Withdraw offending drug, use antacids, and dilate any resulting stricture.

■ EOSINOPHILIC ESOPHAGITIS

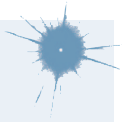
Mucosal inflammation with eosinophils with submucosal fibrosis can be seen especially in pts with food allergies. This diagnosis relies on the presence of symptoms of esophagitis with the appropriate findings on esophageal biopsy. Eotaxin 3, an eosinophil chemokine, has been implicated in its etiology. IL-5 and TARC (thymus and activation-related chemokine) levels may be elevated. Treatment involves a 12-week course of swallowed fluticasone (440 µg bid) using a metered-dose inhaler. In 30–50% of pts, proton pump inhibitors can reduce eosinophil infiltrates.

■ OTHER CAUSES OF ESOPHAGITIS IN AIDS

Mycobacteria, *Cryptosporidium*, *Pneumocystis*, idiopathic esophageal ulcers, and giant ulcers (possible cytopathic effect of HIV) can occur. Ulcers may respond to systemic glucocorticoids.

42

Diarrhea, Malabsorption, and Constipation



NORMAL GASTROINTESTINAL FUNCTION

■ ABSORPTION OF FLUID AND ELECTROLYTES

Fluid delivery to the GI tract is 8–10 L/d, including 2 L/d ingested; most is absorbed in small bowel. About 2 L/d is delivered to the colon; about 0.2 L/d is excreted in the stool. Colonic absorption is normally 0.05–2 L/d, with capacity for 6 L/d if required. Intestinal water absorption passively follows active transport of Na^+ , Cl^- , glucose, and bile salts. Additional transport mechanisms include $\text{Cl}^-/\text{HCO}_3^-$ exchange, Na^+/H^+ exchange, H^+ , K^+ , Cl^- , and HCO_3^- secretion, Na^+ -glucose cotransport, and active Na^+ transport across the basolateral membrane by Na^+/K^+ -ATPase.

■ NUTRIENT ABSORPTION

1. *Proximal small intestine:* iron, calcium, folate, fats (after hydrolysis of triglycerides to fatty acids by pancreatic lipase and colipase), proteins (after hydrolysis by pancreatic and intestinal peptidases), carbohydrates (after hydrolysis by amylases and disaccharidases); triglycerides absorbed as micelles after solubilization by bile salts; amino acids and dipeptides absorbed via specific carriers; sugars absorbed by active transport
2. *Distal small intestine:* vitamin B_{12} , bile salts, water
3. *Colon:* water, electrolytes

■ INTESTINAL MOTILITY

Allows propulsion of intestinal contents from stomach to anus and separation of components to facilitate nutrient absorption. Propulsion is controlled by neural, myogenic, and hormonal mechanisms; mediated by migrating motor complex, an organized wave of neuromuscular activity that originates in the distal stomach during fasting and migrates slowly down the small intestine. Colonic motility is mediated by local peristalsis to propel feces. Defecation is effected by relaxation of internal anal sphincter in response to rectal distention, with voluntary control by contraction of external anal sphincter.

DIARRHEA

■ PHYSIOLOGY

Formally defined as fecal output >200 g/d on low-fiber (western) diet; also frequently used to connote loose or watery stools. Considered acute if <2 weeks duration, persistent if 2–4 weeks, and chronic if >4 weeks. Mediated by one or more of the following mechanisms:

■ OSMOTIC DIARRHEA

Nonabsorbed solutes increase intraluminal oncotic pressure, causing outpouring of water; usually ceases with fasting; stool osmolal gap >40 (see below). Causes include disaccharidase (e.g., lactase) deficiencies, pancreatic insufficiency, bacterial overgrowth, lactulose or sorbitol ingestion, polyvalent laxative abuse, celiac or tropical sprue, and short bowel syndrome. Lactase deficiency can be either primary (more prevalent in blacks and Asians, usually presenting in early adulthood) or secondary (from viral, bacterial, or protozoal gastroenteritis, celiac or tropical sprue, or kwashiorkor).

■ SECRETORY DIARRHEA

Active ion secretion causes obligatory water loss; diarrhea is usually watery, often profuse, unaffected by fasting; stool Na^+ and K^+ are elevated with osmolal gap <40 . Causes include viral infections (e.g., rotavirus, Norwalk virus), bacterial infections (e.g., cholera, enterotoxigenic *Escherichia coli*, *Staphylococcus aureus*), protozoa (e.g., *Giardia*, *Isoospora*, *Cryptosporidium*), AIDS-associated disorders (including mycobacterial and HIV-induced), medications (e.g., theophylline, colchicine, prostaglandins, diuretics), Zollinger-Ellison syndrome (excess gastrin production), vasoactive intestinal peptide (VIP)-producing tumors, carcinoid tumors (histamine and serotonin), medullary thyroid carcinoma (prostaglandins and calcitonin), systemic mastocytosis, basophilic leukemia, distal colonic villous adenomas (direct secretion of potassium-rich fluid), collagenous and microscopic colitis, and choleraic diarrhea (from ileal malabsorption of bile salts).

■ EXUDATIVE DIARRHEA

Inflammation, necrosis, and sloughing of colonic mucosa; may include component of secretory diarrhea due to prostaglandin release by inflammatory cells; stools usually contain polymorphonuclear leukocytes as well as occult or gross blood. Causes include bacterial infections (e.g., *Campylobacter*, *Salmonella*, *Shigella*, *Yersinia*, invasive or enterotoxigenic *E. coli*, *Vibrio parahaemolyticus*, *Clostridium difficile* colitis [frequently antibiotic-induced]), colonic parasites (e.g., *Entamoeba histolytica*), Crohn's disease, ulcerative proctocolitis, idiopathic inflammatory bowel disease, radiation enterocolitis, cancer chemotherapeutic agents, and intestinal ischemia.

■ ALTERED INTESTINAL MOTILITY

Alteration of coordinated control of intestinal propulsion; diarrhea often intermittent or alternating with constipation. Causes include diabetes mellitus, adrenal insufficiency, hyperthyroidism, collagen-vascular diseases, parasitic infestations, gastrin and VIP hypersecretory states, amyloidosis, laxatives (esp. magnesium-containing agents), antibiotics (esp. erythromycin), cholinergic agents, primary neurologic dysfunction (e.g., Parkinson's disease, traumatic neuropathy), fecal impaction, diverticular disease, and irritable bowel syndrome. Blood in intestinal lumen is cathartic, and major upper GI bleeding leads to diarrhea from increased motility.

■ DECREASED ABSORPTIVE SURFACE

Usually arises from surgical manipulation (e.g., extensive bowel resection or rearrangement) that leaves inadequate absorptive surface for fat and carbohydrate digestion and fluid and electrolyte absorption; occurs spontaneously from enteroenteric fistulas (esp. gastrocolic).

■ EVALUATION HISTORY

Diarrhea must be distinguished from fecal incontinence, change in stool caliber, rectal bleeding, and small, frequent, but otherwise normal stools. Careful medication history is essential. Alternating diarrhea and constipation suggests fixed colonic obstruction (e.g., from carcinoma) or irritable bowel syndrome. A sudden, acute course, often with nausea, vomiting, and fever, is typical of viral and bacterial infections, diverticulitis, ischemia, radiation enterocolitis, or drug-induced diarrhea and may be the initial presentation of inflammatory bowel disease. More than 90% of acute diarrheal illnesses are infectious in etiology. A longer (>4 weeks), more insidious course suggests malabsorption, inflammatory bowel disease, metabolic or endocrine disturbance, pancreatic insufficiency, laxative abuse, ischemia, neoplasm (hypersecretory state or partial obstruction), or irritable bowel syndrome. Parasitic and certain forms of bacterial enteritis can

also produce chronic symptoms. Particularly foul-smelling or oily stool suggests fat malabsorption. Fecal impaction may cause apparent diarrhea because only liquids pass partial obstruction. Several infectious causes of diarrhea are associated with an immunocompromised state. A pathophysiologic mechanism-based list of causes is shown in [Table 42-1](#).

TABLE 42-1 Major Causes of Chronic Diarrhea According to Predominant Pathophysiologic Mechanism

Secretory Causes

Exogenous stimulant laxatives
 Chronic ethanol ingestion
 Other drugs and toxins
 Endogenous laxatives (dihydroxy bile acids)
 Idiopathic secretory diarrhea or bile acid diarrhea
 Certain bacterial infections
 Bowel resection, disease, or fistula (\downarrow absorption)
 Partial bowel obstruction or fecal impaction
 Hormone-producing tumors (carcinoid, VIPoma, medullary cancer of thyroid, mastocytosis, gastrinoma, colorectal villous adenoma)
 Addison's disease
 Congenital electrolyte absorption defects

Osmotic Causes

Osmotic laxatives (Mg^{2+} , PO_4^{-3} , SO_4^{-2})
 Lactase and other disaccharide deficiencies
 Nonabsorbable carbohydrates (sorbitol, lactulose, polyethylene glycol)
 Gluten and FODMAP intolerance

Steatorrheal Causes

Intraluminal maldigestion (pancreatic exocrine insufficiency, bacterial overgrowth, bariatric surgery, liver disease)
 Mucosal malabsorption (celiac sprue, Whipple's disease, infections, abetalipoproteinemia, ischemia, drug-induced enteropathy)
 Postmucosal obstruction (1° or 2° lymphatic obstruction)

Inflammatory Causes

Idiopathic inflammatory bowel disease (Crohn's, chronic ulcerative colitis)
 Lymphocytic and collagenous colitis
 Immune-related mucosal disease (1° or 2° immunodeficiencies, food allergy, eosinophilic gastroenteritis, graft-versus-host disease)
 Infections (invasive bacteria, viruses, and parasites, Brainerd diarrhea)
 Radiation injury
 Gastrointestinal malignancies

Dysmotile Causes

Irritable bowel syndrome (including postinfectious IBS)
 Visceral neuromyopathies
 Hyperthyroidism
 Drugs (prokinetic agents)
 Postvagotomy

(Continued)

TABLE 42-1 Major Causes of Chronic Diarrhea According to Predominant Pathophysiologic Mechanism (Continued)**Factitial Causes**

Munchausen
Eating disorders

Iatrogenic Causes

Cholecystectomy
Ileal resection
Bariatric surgery
Vagotomy, fundoplication

Abbreviation: FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

PHYSICAL EXAMINATION

Signs of dehydration are often prominent in severe, acute diarrhea. Fever and abdominal tenderness suggest infection or inflammatory disease but are often absent in viral enteritis. Evidence of malnutrition suggests chronic course. Certain signs are frequently associated with specific deficiency states secondary to malabsorption (e.g., cheilosis with riboflavin or iron deficiency, glossitis with B₁₂, folate deficiency). Questions to address in pts with chronic diarrhea are shown in [Table 42-2](#).

STOOL EXAMINATION

Culture for bacterial pathogens, examination for leukocytes, measurement of *C. difficile* toxin, and examination for ova and parasites are important components of evaluation of pts with severe, protracted, or bloody diarrhea. Presence of blood (fecal occult blood test) or leukocytes (Wright's stain) suggests inflammation (e.g., ulcerative colitis, Crohn's disease, infection, or ischemia). Gram's stain of stool can be diagnostic of *Staphylococcus*, *Campylobacter*, or *Candida* infection. Steatorrhea (determined with Sudan III stain of stool sample or 72-h quantitative fecal fat analysis) suggests malabsorption or pancreatic insufficiency. Measurement of Na⁺ and K⁺ levels in fecal water helps to distinguish osmotic from other types of diarrhea; osmotic diarrhea is implied by stool osmolal gap > 40, where stool osmolal gap = $\text{osmol}_{\text{serum}} [2 \times (\text{Na}^+ + \text{K}^+)_{\text{stool}}]$.

LABORATORY STUDIES

Complete blood count may indicate anemia (acute or chronic blood loss or malabsorption of iron, folate, or B₁₂), leukocytosis (inflammation), eosinophilia

TABLE 42-2 Physical Examination in Pts with Chronic Diarrhea

1. Are there general features to suggest malabsorption or inflammatory bowel disease (IBD) such as anemia, dermatitis herpetiformis, edema, or clubbing?
2. Are there features to suggest underlying autonomic neuropathy or collagen-vascular disease in the pupils, orthostasis, skin, hands, or joints?
3. Is there an abdominal mass or tenderness?
4. Are there any abnormalities of rectal mucosa, rectal defects, or altered anal sphincter functions?
5. Are there any mucocutaneous manifestations of systemic disease such as dermatitis herpetiformis (celiac disease), erythema nodosum (ulcerative colitis), flushing (carcinoid), or oral ulcers for IBD or celiac disease?

(parasitic, neoplastic, and inflammatory bowel diseases). Serum levels of calcium, albumin, iron, cholesterol, folate, B₁₂, vitamin D, and carotene; serum iron-binding capacity; and prothrombin time can provide evidence of intestinal malabsorption or maldigestion.

■ OTHER STUDIES

D-Xylose absorption test is a convenient screen for small-bowel absorptive function. Small-bowel biopsy is especially useful for evaluating intestinal malabsorption. Specialized studies include Schilling test (B₁₂ malabsorption), lactose H₂ breath test (carbohydrate malabsorption), [¹⁴C]xylose and lactulose H₂ breath tests (bacterial overgrowth), glycocholic breath test (ileal malabsorption), triolein breath test (fat malabsorption), and bentiromide and secretin tests (pancreatic insufficiency). Sigmoidoscopy or colonoscopy with biopsy is useful in the diagnosis of colitis (esp. pseudomembranous, ischemic, microscopic); it may not allow distinction between infectious and noninfectious (esp. idiopathic ulcerative) colitis. Barium contrast x-ray studies may suggest malabsorption (thickened bowel folds), inflammatory bowel disease (ileitis or colitis), tuberculosis (ileocecal inflammation), neoplasm, intestinal fistula, or motility disorders.

TREATMENT

Diarrhea

An approach to the management of acute diarrheal illnesses is shown in [Fig. 42-1](#). Symptomatic therapy includes vigorous rehydration (IV or with oral glucose-electrolyte solutions), electrolyte replacement, binders of osmotically active substances (e.g., kaolin-pectin), and opiates to decrease bowel motility (e.g., loperamide, diphenoxylate); opiates may be contraindicated in infectious or inflammatory causes of diarrhea. An approach to the management of chronic diarrhea is shown in [Fig. 42-2](#).

MALABSORPTION SYNDROMES

Intestinal malabsorption of ingested nutrients may produce osmotic diarrhea, steatorrhea, or specific deficiencies (e.g., iron; folate; B₁₂; vitamins A, D, E, and K). [Table 42-3](#) lists common causes of intestinal malabsorption. Protein-losing enteropathy may result from several causes of malabsorption; it is associated with hypoalbuminemia and can be detected by measuring stool α_1 -antitrypsin or radiolabeled albumin levels. Therapy is directed at the underlying disease.

CONSTIPATION

Defined as decrease in frequency of stools to <1 per week or difficulty in defecation; may result in abdominal pain, distention, and fecal impaction, with consequent obstruction or, rarely, perforation. Constipation is a frequent and often subjective complaint. Contributory factors may include inactivity, low-fiber diet, and inadequate allotment of time for defecation.

■ SPECIFIC CAUSES

Altered colonic motility due to neurologic dysfunction (diabetes mellitus, spinal cord injury, multiple sclerosis, Chagas' disease, Hirschsprung's disease, chronic idiopathic intestinal pseudoobstruction, idiopathic megacolon), scleroderma, drugs (esp. anticholinergic agents, opiates, aluminum- or calcium-based

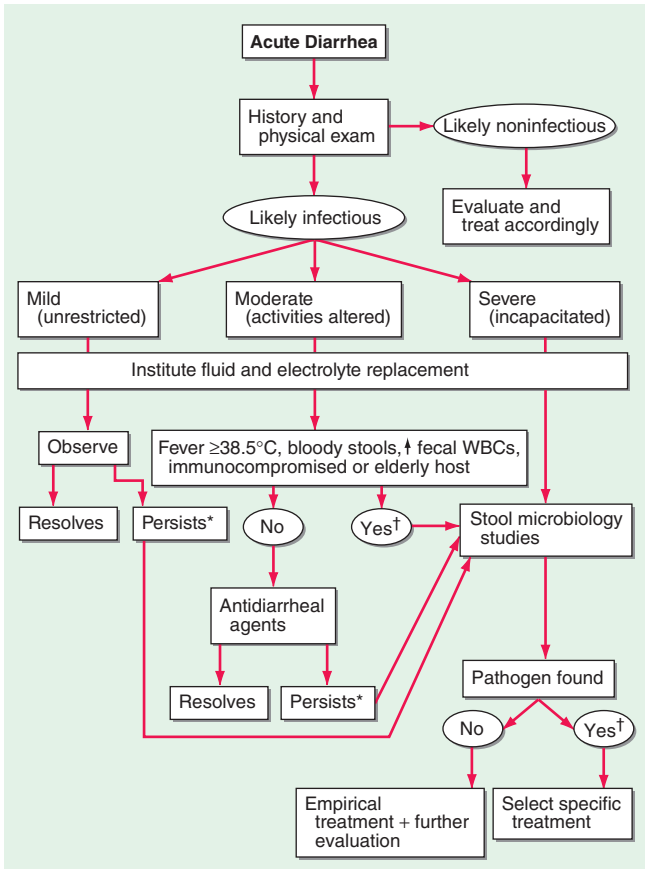


FIGURE 42-1 Algorithm for the management of acute diarrhea. Consider empirical treatment before evaluation with (*) metronidazole and with (†) quinolone. WBCs, white blood cells.

antacids, calcium channel blockers, iron supplements, sucralfate), hypothyroidism, Cushing's syndrome, hypokalemia, hypercalcemia, dehydration, mechanical causes (colorectal tumors, diverticulitis, volvulus, hernias, intussusception), and anorectal pain (from fissures, hemorrhoids, abscesses, or proctitis) leading to retention, constipation, and fecal impaction.

TREATMENT

Constipation

A management approach is shown in [Fig. 42-3](#). In the absence of identifiable cause, constipation may improve with reassurance, exercise, increased dietary fiber, bulking agents (e.g., psyllium), and increased fluid intake. Specific

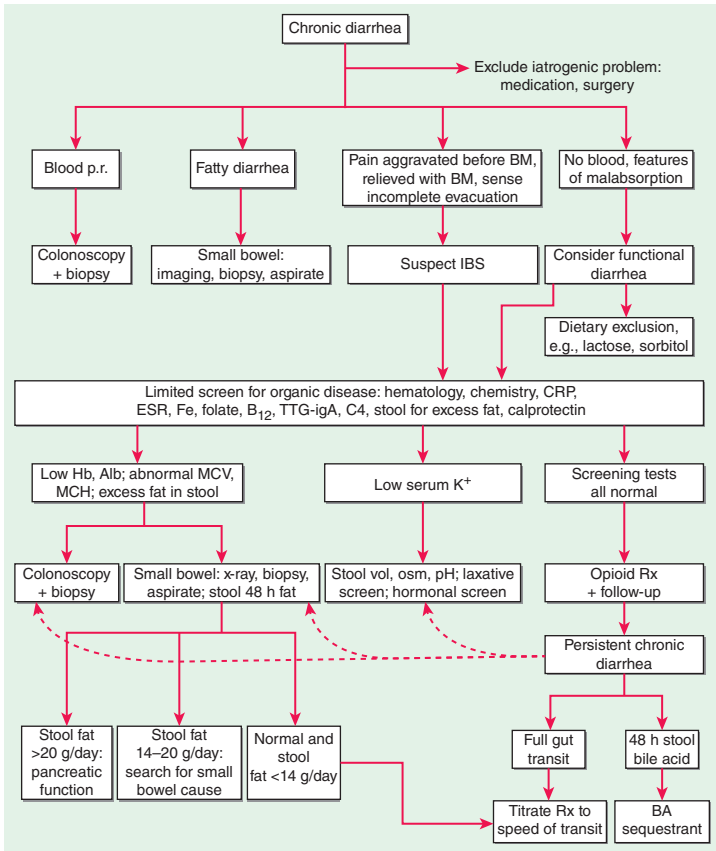


FIGURE 42-2 Chronic diarrhea. **A.** Initial management based on accompanying symptoms or features. **B.** Evaluation based on findings from a limited age-appropriate screen for organic disease. Alb, albumin; BM, bowel movement; Hb, hemoglobin; IBS, irritable bowel syndrome; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; OSM, osmolality; pr, per rectum. (Reprinted from Camilleri M et al: *Pathophysiology, evaluation, and management of chronic watery diarrhea*. *Gastroenterology* 152:515, 2017.)

therapies include removal of bowel obstruction (fecalith, tumor), discontinuance of nonessential hypomotility agents (esp. aluminum or calcium-containing antacids, opiates), or substitution of magnesium-based antacids for aluminum-based antacids. For symptomatic relief, magnesium-containing agents or other cathartics are occasionally needed. With severe hypo- or dysmotility or in the presence of opiates, osmotically active agents (e.g., oral lactulose, intestinal polyethylene glycol-containing lavage solutions) and oral or rectal emollient laxatives (e.g., docusate salts) and mineral oil are most effective.

TABLE 42-3 Common Causes of Malabsorption

Maldigestion: Chronic pancreatitis, cystic fibrosis, pancreatic carcinoma

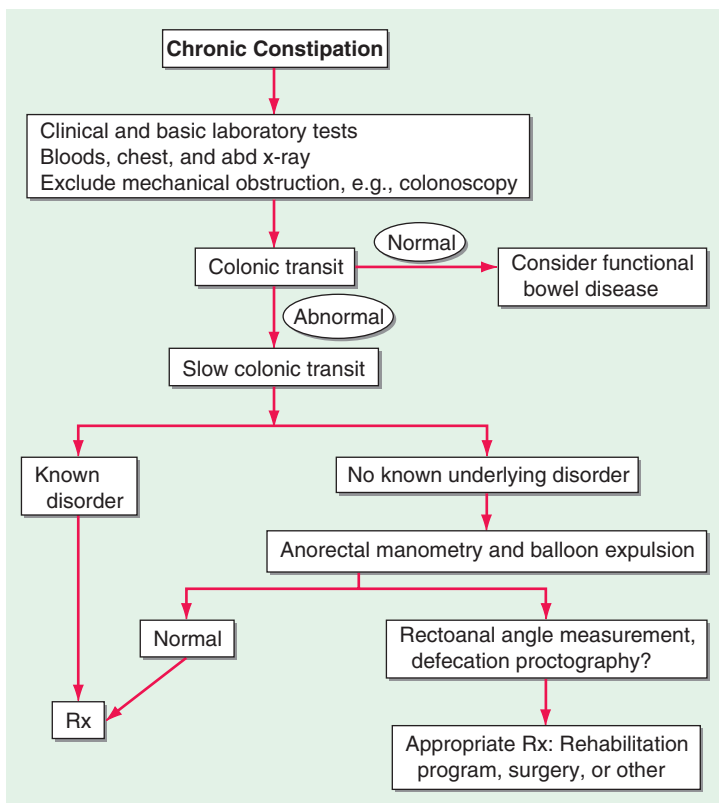
Bile salt deficiency: Cirrhosis, cholestasis, bacterial overgrowth (blind loop syndromes, intestinal diverticula, hypomotility disorders), impaired ileal reabsorption (resection, Crohn's disease), bile salt binders (cholestyramine, calcium carbonate, neomycin)

Inadequate absorptive surface: Massive intestinal resection, gastrocolic fistula, jejunoleal bypass

Lymphatic obstruction: Lymphoma, Whipple's disease, intestinal lymphangiectasia

Vascular disease: Constrictive pericarditis, right-sided heart failure, mesenteric arterial or venous insufficiency

Mucosal disease: Infection (esp. *Giardia*, Whipple's disease, tropical sprue), inflammatory diseases (esp. Crohn's disease), radiation enteritis, eosinophilic enteritis, ulcerative jejunitis, mastocytosis, tropical sprue, infiltrative disorders (amyloidosis, scleroderma, lymphoma, collagenous sprue, microscopic colitis), biochemical abnormalities (gluten-sensitive enteropathy, disaccharidase deficiency, hypogammaglobulinemia, abetalipoproteinemia, amino acid transport deficiencies), endocrine disorders (diabetes mellitus, hypoparathyroidism, adrenal insufficiency, hyperthyroidism, Zollinger-Ellison syndrome, carcinoid syndrome)

**FIGURE 42-3** Algorithm for the management of constipation. abd, abdominal.

43

Gastrointestinal Bleeding

**PRESENTATION**

1. *Hematemesis*: Vomiting of blood or altered blood (“coffee grounds”) indicates bleeding proximal to ligament of Treitz.
2. *Melena*: Altered (black) blood per rectum (>100-mL blood required for one melanic stool) usually indicates bleeding proximal to ligament of Treitz but may be as distal as ascending colon; pseudomelena may be caused by ingestion of iron, bismuth, licorice, beets, blueberries, and charcoal.
3. *Hematochezia*: Bright red or maroon rectal bleeding usually implies bleeding beyond ligament of Treitz but may be due to rapid upper GI bleeding (>1000 mL).
4. *Positive fecal occult blood test with or without iron deficiency*.
5. *Symptoms of blood loss*: e.g., light-headedness or shortness of breath.

HEMODYNAMIC CHANGES

Orthostatic drop in bp >10 mmHg usually indicates >20% reduction in blood volume (\pm syncope, light-headedness, nausea, sweating, thirst).

SHOCK

BP <100 mmHg systolic usually indicates <30% reduction in blood volume (\pm pallor, cool skin).

LABORATORY CHANGES

Hematocrit may not reflect extent of blood loss because of delayed equilibration with extravascular fluid. Mild leukocytosis and thrombocytosis. Elevated blood urea nitrogen is common in upper GI bleeding.

ADVERSE PROGNOSTIC SIGNS

Age >60 years, associated illnesses, coagulopathy, immunosuppression, presentation with shock, rebleeding, onset of bleeding in hospital, variceal bleeding, endoscopic stigmata of recent bleeding (e.g., “visible vessel” in ulcer base [see next]).

UPPER GI BLEEDING**CAUSES****Common**

Peptic ulcer (accounts for ~50%), erosions (gastropathy from alcohol, aspirin, NSAIDs, stress), esophagitis, Mallory-Weiss tear (mucosal tear at gastroesophageal junction due to retching), gastroesophageal varices.

Less Common

Swallowed blood (nosebleed); esophageal, gastric, or intestinal neoplasm; anti-coagulant and fibrinolytic therapy; hypertrophic gastropathy (Ménétrier’s disease); aortic aneurysm; aortoenteric fistula (from aortic graft); arteriovenous malformation; telangiectases (Osler-Weber-Rendu syndrome); Dieulafoy lesion (ectatic submucosal vessel); vasculitis; connective tissue disease (pseudoxanthoma elasticum, Ehlers-Danlos syndrome); blood dyscrasias; neurofibroma; amyloidosis; hemobilia (biliary origin).

EVALUATION

After hemodynamic resuscitation (see next and [Fig. 43-1](#)).

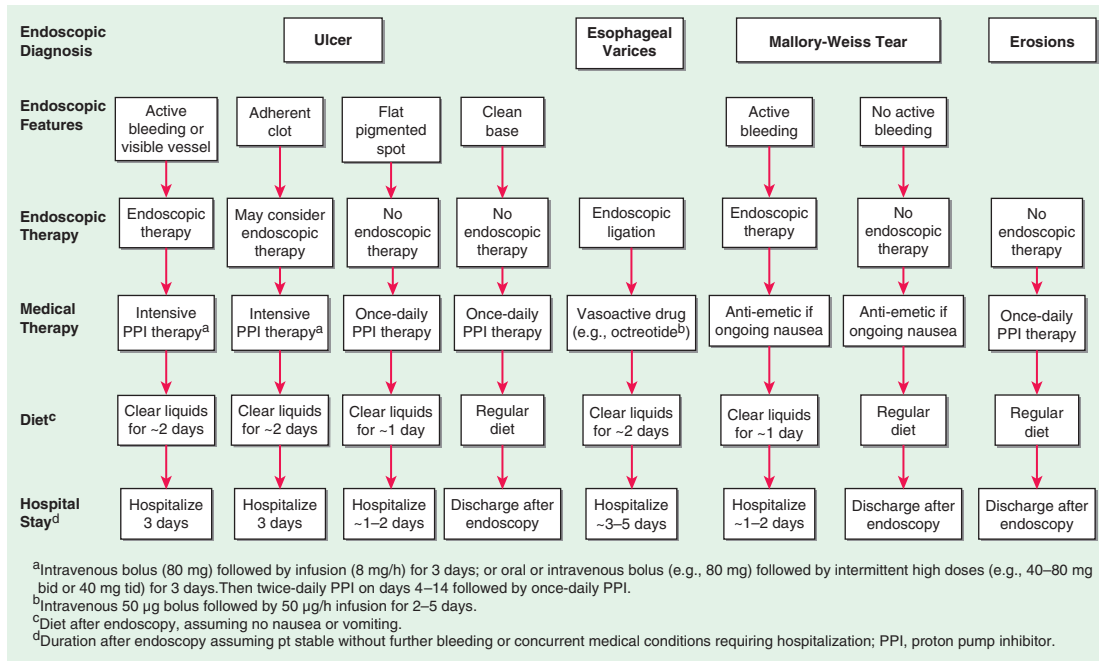


FIGURE 43-1 Suggested algorithm for pts with acute upper GI bleeding. Recommendations on level of care and time of discharge assume pt is stabilized without further bleeding or other concomitant medical problems.

- History and physical examination: Drugs (increased risk of upper and lower GI tract bleeding with aspirin and NSAIDs), prior ulcer, bleeding history, family history, features of cirrhosis or vasculitis, etc. Hyperactive bowel sounds favor upper GI source.
- Nasogastric aspirate for gross blood, if source (upper versus lower) not clear from history; may be falsely negative in up to 16% of pts if bleeding has ceased or duodenum is the source. Testing aspirate for occult blood is meaningless.
- Upper endoscopy: Accuracy >90%; allows visualization of bleeding site and possibility of therapeutic intervention; mandatory for suspected varices, aortoenteric fistulas; permits identification of “visible vessel” (protruding artery in ulcer crater), which connotes high (~50%) risk of rebleeding.
- Upper GI barium radiography: Accuracy ~80% in identifying a lesion, though does not confirm source of bleeding; acceptable alternative to endoscopy in resolved or chronic low-grade bleeding.
- Selective mesenteric arteriography: When brisk bleeding precludes identification of source at endoscopy.
- Radioisotope scanning (e.g., ⁹⁹Tc tagged to red blood cells or albumin); used primarily as screening test to confirm bleeding is rapid enough for arteriography to be of value or when bleeding is intermittent and of unclear origin.

LOWER GI BLEEDING

■ CAUSES

Anal lesions (hemorrhoids, fissures), rectal trauma, proctitis, colitis (ulcerative colitis, Crohn’s disease, infectious colitis, ischemic colitis, radiation), colonic polyps, colonic carcinoma, angiodysplasia (vascular ectasia), diverticulosis, intussusception, solitary ulcer, blood dyscrasias, vasculitis, connective tissue disease, neurofibroma, amyloidosis, anticoagulation.

■ EVALUATION (SEE BELOW AND FIG. 43-2)

- History and physical examination.
- In the presence of hemodynamic changes, perform upper endoscopy followed by colonoscopy. In the absence of hemodynamic changes, perform anoscopy and either flexible sigmoidoscopy or colonoscopy: Exclude hemorrhoids, fissure, ulcer, proctitis, neoplasm.
- Colonoscopy: Often test of choice, but may be impossible if bleeding is massive.
- Barium enema: No role in active bleeding.
- Arteriography: When bleeding is severe (requires bleeding rate >0.5 mL/min; may require prestudy radioisotope bleeding scan as above); defines site of bleeding or abnormal vasculature.
- Surgical exploration (last resort).

■ BLEEDING OF OBSCURE ORIGIN

Often small-bowel source. Consider small-bowel enteroclysis x-ray (careful barium radiography via peroral intubation of small bowel), Meckel’s scan, enteroscopy (small-bowel endoscopy), or exploratory laparotomy with intraoperative enteroscopy.

TREATMENT

Upper and Lower GI Bleeding

- Venous access with large-bore IV (14–18 gauge); central venous line for major bleed and pts with cardiac disease; monitor vital signs, urine output, Hct (fall may lag). Gastric lavage of unproven benefit but clears stomach before

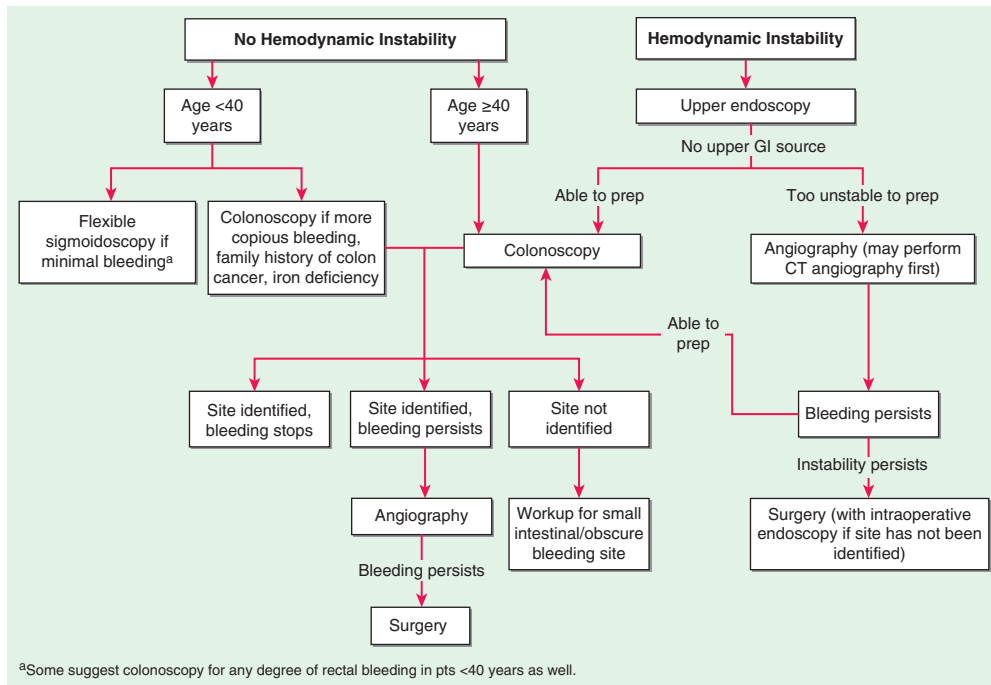


FIGURE 43-2 Suggested algorithm for pts with acute lower GI bleeding.

endoscopy. Iced saline may lyse clots; room-temperature tap water may be preferable. Intubation may be required to protect airway.

- Type and cross-match blood (six units for major bleed).
- Surgical standby when bleeding is massive.
- Support blood pressure with isotonic fluids (normal saline); albumin and fresh frozen plasma in cirrhotics. Packed red blood cells when available (whole blood if massive bleeding); maintain Hct >25–30. Fresh frozen plasma and vitamin K (10 mg SC or IV) in cirrhotics with coagulopathy.
- IV calcium (e.g., up to 10–20 mL 10% calcium gluconate IV over 10–15 min) if serum calcium falls (due to transfusion of citrated blood). Empirical drug therapy (antacids, H₂ receptor blockers, omeprazole) of unproven benefit.
- Specific measures: *Varices*: octreotide (50- μ g bolus, 50- μ g/h infusion for 2–5 days), Sengstaken-Blakemore tube tamponade, endoscopic sclerosis, or band ligation; propranolol or nadolol in doses sufficient to cause beta blockade reduces risk of recurrent or initial variceal bleeding (do not use in acute bleed) (**Chap. 158**); *ulcer with visible vessel or active bleeding*: endoscopic bipolar, heater-probe, or laser coagulation or injection of epinephrine; *gastritis*: embolization or vasopressin infusion of left gastric artery; *GI telangiectases*: ethinyl-estradiol/norethisterone (0.05/1.0 mg PO qd) may prevent recurrent bleeding, particularly in pts with chronic renal failure; *diverticulosis*: mesenteric arteriography with intraarterial vasopressin; *angiodysplasia*: colonoscopic bipolar or laser coagulation, may regress with replacement of stenotic aortic valve.
- Indications for emergency surgery: Uncontrolled or prolonged bleeding, severe rebleeding, aortoenteric fistula. For intractable variceal bleeding, consider transjugular intrahepatic portosystemic shunt (TIPS).

44

Jaundice and Evaluation of Liver Function



JAUNDICE

■ DEFINITION

Yellow skin pigmentation caused by elevation in serum bilirubin level (also termed *icterus*); often more easily discernible in sclerae. Scleral icterus becomes clinically evident at a serum bilirubin level of $\geq 51 \mu\text{mol/L}$ ($\geq 3 \text{ mg/dL}$); yellow skin discoloration also occurs with elevated serum carotene levels but without pigmentation of the sclerae.

■ BILIRUBIN METABOLISM

Bilirubin is the major breakdown product of hemoglobin released from senescent erythrocytes. Initially, it is bound to albumin, transported into the liver, conjugated to a water-soluble form (glucuronide) by glucuronosyltransferase, excreted into the bile, and converted to urobilinogen in the colon. Urobilinogen is mostly excreted in the stool; a small portion is reabsorbed and excreted by the kidney. Bilirubin can be filtered by the kidney only in its conjugated form (measured as the “direct” fraction); thus, increased *direct* serum bilirubin level is associated with bilirubinuria. Increased bilirubin production and excretion

(even without hyperbilirubinemia, as in hemolysis) produce elevated urinary urobilinogen levels.

■ ETIOLOGY

Hyperbilirubinemia occurs as a result of (1) overproduction; (2) impaired uptake, conjugation, or excretion of bilirubin; (3) regurgitation of unconjugated or conjugated bilirubin from damaged hepatocytes or bile ducts ([Table 44-1](#)).

■ EVALUATION

The initial steps in evaluating the pt with jaundice are to determine whether (1) hyperbilirubinemia is conjugated or unconjugated, and (2) other biochemical liver tests are abnormal ([Figs. 44-1](#) and [44-2](#), [Tables 44-2](#) and [44-3](#)). Essential clinical examination includes history (especially duration of jaundice, pruritus, associated pain, risk factors for parenterally transmitted diseases, medications, ethanol use, travel history, surgery, pregnancy, presence of any accompanying symptoms), physical examination (hepatomegaly, tenderness over liver, palpable gallbladder, splenomegaly, gynecomastia, testicular atrophy, other stigmata of chronic liver disease), blood liver tests (see below), and complete blood count.

■ GILBERT SYNDROME

Impaired conjugation of bilirubin due to reduced bilirubin UDP glucuronosyl-transferase activity. Results in mild unconjugated hyperbilirubinemia, almost always $<103 \mu\text{mol/L}$ ($<6 \text{ mg/dL}$). Affects 3–7% of the population; males/females 2–7:1.

BLOOD TESTS OF LIVER FUNCTION

Used to detect presence of liver disease ([Fig. 44-2](#)), discriminate among different types of liver disease ([Table 44-4](#)), gauge the extent of known liver damage, and follow response to treatment.

TABLE 44-1 Causes of Isolated Hyperbilirubinemia

- I. Indirect hyperbilirubinemia
 - A. Hemolytic disorders
 - B. Ineffective erythropoiesis
 - C. Increased bilirubin production
 1. Massive blood transfusion
 2. Resorption of hematoma
 - D. Drugs
 1. Rifampin
 2. Probenecid
 3. Ribavirin
 4. Protease inhibitors (Atazanavir, Indinavir)
 - E. Inherited conditions
 1. Crigler-Najjar types I and II
 2. Gilbert's syndrome
- II. Direct hyperbilirubinemia (inherited conditions)
 - A. Dubin-Johnson syndrome
 - B. Rotor syndrome

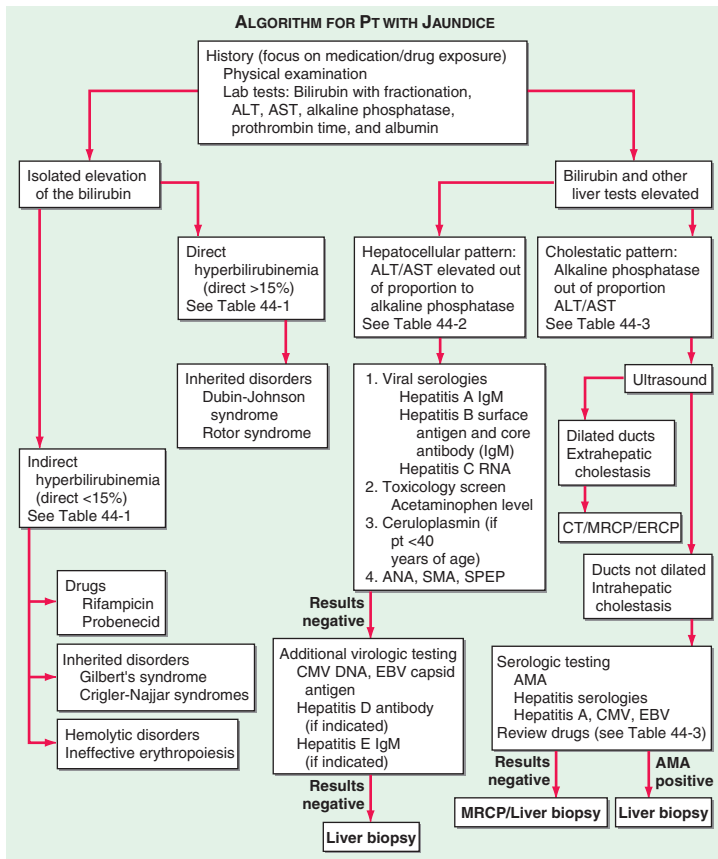


FIGURE 44-1 Evaluation of the pt with jaundice. ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; AST, aspartate aminotransferase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; ERCP, endoscopic retrograde cholangiopancreatogram; MRCP, magnetic resonance cholangiopancreatography; SMA, smooth-muscle antibody; SPEP, serum protein electrophoresis.

■ BILIRUBIN

Provides indication of hepatic uptake, metabolic (conjugation) and excretory functions; conjugated fraction (direct) distinguished from unconjugated by chemical assay (Table 44-1).

■ AMINOTRANSFERASES (TRANSAMINASES)

Aspartate aminotransferase (AST; SGOT) and alanine aminotransferase (ALT; SGPT); sensitive indicators of liver cell injury; greatest elevations seen in hepatocellular necrosis (e.g., viral hepatitis, toxic or ischemic liver injury, acute hepatic vein obstruction), occasionally with sudden, complete biliary obstruction (e.g., from gallstone); milder abnormalities in cholestatic, cirrhotic, and infiltrative disease; poor correlation between degree of liver cell damage and level of aminotransferases; ALT more specific measure of liver injury, because AST also found

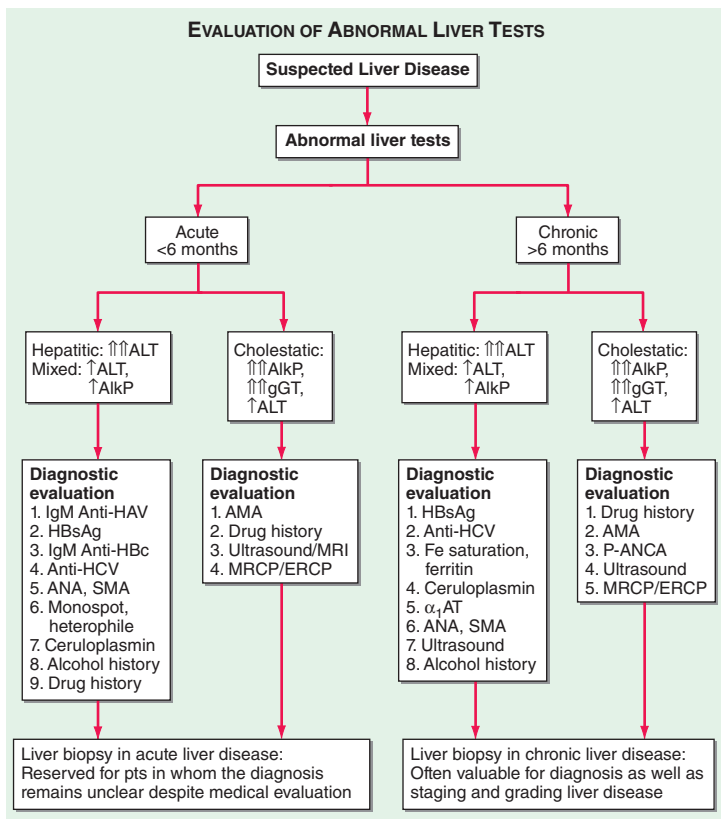


FIGURE 44-2 Algorithm for evaluation of abnormal liver tests. α_1 AT, α_1 antitrypsin; AlkP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ERCP, endoscopic retrograde cholangiopancreatogram; GGT, γ -glutamyl transpeptidase; HAV, hepatitis A virus; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; MRCP, magnetic resonance cholangiopancreatography; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; SMA, smooth-muscle antibody.

in striated muscle and other organs; ethanol-induced liver injury usually produces modest increases with more prominent elevation of AST than ALT.

■ ALKALINE PHOSPHATASE

Sensitive indicator of cholestasis, biliary obstruction (enzyme increases more quickly than serum bilirubin), and liver infiltration; mild elevations in other forms of liver disease; limited specificity because of wide tissue distribution; elevations also seen in normal childhood, pregnancy, and bone diseases; tissue-specific isoenzymes can be distinguished by fractionation or by differences in heat stability (liver enzyme activity stable under conditions that destroy bone enzyme activity).

■ 5'-NUCLEOTIDASE (5'-NT)

Pattern of elevation in hepatobiliary disease similar to alkaline phosphatase; has greater specificity for liver disorders; used to determine whether liver is source

TABLE 44-2 Hepatocellular Conditions That May Produce Jaundice

Viral hepatitis

Hepatitis A, B, C, D, and E

Epstein-Barr virus

Cytomegalovirus

Herpes simplex virus

Alcoholic hepatitis

Chronic liver disease and cirrhosis

Drug toxicity

Predictable, dose-dependent (e.g., acetaminophen)

Unpredictable, idiosyncratic (e.g., isoniazid)

Environmental toxins

Vinyl chloride

Jamaica bush tea—pyrrolizidine alkaloids

Kava Kava

Wild mushrooms—*Amanita phalloides*, *A. verna*

Wilson's disease

Autoimmune hepatitis

TABLE 44-3 Cholestatic Conditions That May Produce Jaundice

I. Intrahepatic

A. Viral hepatitis

1. Fibrosing cholestatic hepatitis—hepatitis B and C

2. Hepatitis A, Epstein-Barr virus infection, cytomegalovirus infection

B. Alcoholic hepatitis

C. Drug toxicity

1. Pure cholestasis—anabolic and contraceptive steroids

2. Cholestatic hepatitis—chlorpromazine, erythromycin estolate

3. Chronic cholestasis—chlorpromazine and prochlorperazine

D. Primary biliary cholangitis

E. Primary sclerosing cholangitis

F. Vanishing bile duct syndrome

1. Chronic rejection of liver transplants

2. Sarcoidosis

3. Drugs

G. Congestive hepatopathy and ischemic hepatitis

H. Inherited conditions

1. Progressive familial intrahepatic cholestasis

2. Benign recurrent intrahepatic cholestasis

I. Cholestasis of pregnancy

J. Total parenteral nutrition

(Continued)

TABLE 44-3 Cholestatic Conditions That May Produce Jaundice (Continued)

K. Nonhepatobiliary sepsis
L. Benign postoperative cholestasis
M. Paraneoplastic syndrome
N. Veno-occlusive disease
O. Graft-versus-host disease
P. Infiltrative disease
1. Tuberculosis
2. Lymphoma
3. Amyloidosis
Q. Infections
1. Malaria
2. Leptospirosis

II. Extrahepatic

A. Malignant

1. Cholangiocarcinoma
2. Pancreatic cancer
3. Gallbladder cancer
4. Ampullary cancer
5. Malignant involvement of the porta hepatis lymph nodes

B. Benign

1. Choledocholithiasis
2. Postoperative biliary strictures
3. Primary sclerosing cholangitis
4. Chronic pancreatitis
5. AIDS cholangiopathy
6. Mirizzi's syndrome
7. Parasitic disease (ascariasis)

of elevation in serum alkaline phosphatase, esp. in children, pregnant women, pts with possible concomitant bone disease.

■ γ -GLUTAMYL TRANSPEPTIDASE (GGT)

Correlates with serum alkaline phosphatase activity. Elevation is less specific for cholestasis than alkaline phosphatase or 5'-NT.

■ COAGULATION FACTORS (SEE ALSO CHAP. 65)

Measure of clotting factor activity; prolongation results from clotting factor deficiency or inactivity; all clotting factors except factor VIII are synthesized in the liver, and deficiency can occur rapidly from widespread liver disease as in hepatitis, toxic injury, or cirrhosis; single best acute measure of hepatic synthetic function; helpful in diagnosis and prognosis of acute liver disease. Clotting factors II, VII, IX, X function only in the presence of the fat-soluble vitamin K; PT prolongation from fat malabsorption distinguished from hepatic disease by rapid and complete response to vitamin K replacement.

TABLE 44-4 Liver Test Patterns in Hepatobiliary Disorders

TYPE OF DISORDER	BILIRUBIN	AMINOTRANSFERASES	ALKALINE PHOSPHATASE	ALBUMIN	PROTHROMBIN TIME
Hemolysis/Gilbert's syndrome	Normal to 86 $\mu\text{mol/L}$ (5 mg/dL) 85% due to indirect fractions No bilirubinuria	Normal	Normal	Normal	Normal
Acute hepatocellular necrosis (viral and drug hepatitis, hepatotoxins, acute heart failure)	Both fractions may be elevated Peak usually follows aminotransferases Bilirubinuria	Elevated, often >500 IU, ALT > AST	Normal to <3 \times normal elevation	Normal	Usually normal. If >5 \times above control and not corrected by parenteral vitamin K, suggests poor prognosis
Chronic hepatocellular disorders	Both fractions may be elevated Bilirubinuria	Elevated, but usually <300 IU	Normal to <3 \times normal elevation	Often decreased	Often prolonged Fails to correct with parenteral vitamin K
Alcoholic hepatitis, cirrhosis	Both fractions may be elevated Bilirubinuria	AST:ALT >2 suggests alcoholic hepatitis or cirrhosis	Normal to <3 \times normal elevation	Often decreased	Often prolonged Fails to correct with parenteral vitamin K
Intra- and extrahepatic cholestasis	Both fractions may be elevated	Normal to moderate elevation	Elevated, often >4 \times normal elevation	Normal, unless chronic	Normal If prolonged, will correct with parenteral vitamin K
(Obstructive jaundice) Infiltrative diseases (tumor, granulomata); partial bile duct obstruction	Bilirubinuria Usually normal	Rarely >500 IU Normal to slight elevation	Elevated, often >4 \times normal elevation Fractionate, or confirm liver origin with 5'-nucleotidase or γ glutamyl transpeptidase	Normal	Normal

■ ALBUMIN

Decreased serum levels result from decreased hepatic synthesis (chronic liver disease or prolonged malnutrition) or excessive losses in urine or stool; insensitive indicator of acute hepatic dysfunction, because serum half-life is 2–3 weeks; in pts with chronic liver disease, degree of hypoalbuminemia correlates with severity of liver dysfunction.

■ GLOBULIN

Mild polyclonal hyperglobulinemia often seen in chronic liver diseases; marked elevation frequently seen in *autoimmune* chronic active hepatitis.

■ AMMONIA

Elevated blood levels result from deficiency of hepatic detoxification pathways and portal-systemic shunting, as in fulminant hepatitis, hepatotoxin exposure, and severe portal hypertension (e.g., from cirrhosis); elevation of blood ammonia does not correlate well with hepatic function or the presence or degree of acute encephalopathy.

HEPATOBIILIARY IMAGING PROCEDURES**■ ULTRASONOGRAPHY (US)**

Rapid, noninvasive examination of abdominal structures; no radiation exposure; relatively low cost, equipment portable; images and interpretation strongly dependent on expertise of examiner; particularly valuable for detecting biliary duct dilation and gallbladder stones (>95%); much less sensitive for intraductal stones (~60%); most sensitive means of detecting ascites; moderately sensitive for detecting hepatic masses but excellent for discriminating solid from cystic structures; useful in directing percutaneous needle biopsies of suspicious lesions; Doppler US useful to determine patency and flow in portal, hepatic veins, and portal-systemic shunts; imaging improved by presence of ascites but severely hindered by bowel gas; endoscopic US less affected by bowel gas and is sensitive for determination of depth of tumor invasion through bowel wall.

■ CT

Particularly useful for detecting, differentiating, and directing percutaneous needle biopsy of abdominal masses, cysts, and lymphadenopathy; imaging enhanced by intestinal or intravenous contrast dye and unaffected by intestinal gas; somewhat less sensitive than US for detecting stones in gallbladder but more sensitive for choledocholithiasis; may be useful in distinguishing certain forms of diffuse hepatic disease (e.g., fatty infiltration, iron overload).

■ MRI

Most sensitive detection of hepatic masses and cysts; allows easy differentiation of hemangiomas from other hepatic tumors; most accurate noninvasive means of assessing hepatic and portal vein patency, vascular invasion by tumor; useful for monitoring iron, copper deposition in liver (e.g., in hemochromatosis, Wilson's disease). Magnetic resonance cholangiopancreatography (MRCP) can be useful for visualizing the head of the pancreas and the pancreatic and biliary ducts.

■ RADIONUCLIDE SCANNING

Using various radiolabeled compounds, different scanning methods allow sensitive assessment of biliary excretion (HIDA, PIPIDA, DISIDA scans), parenchymal changes (technetium sulfur colloid liver/spleen scan), and selected inflammatory and neoplastic processes (gallium scan); HIDA and related scans particularly useful for assessing biliary patency and excluding acute cholecystitis in situations where US is not diagnostic; CT, MRI, and colloid scans have

similar sensitivity for detecting liver tumors and metastases; CT and combination of colloidal liver and lung scans sensitive for detecting right subphrenic (suprahepatic) abscesses.

■ CHOLANGIOGRAPHY

Most sensitive means of detecting biliary ductal calculi, biliary tumors, sclerosing cholangitis, choledochal cysts, fistulas, and bile duct leaks; may be performed via endoscopic (transampullary) or percutaneous (transhepatic) route; allows sampling of bile and ductal epithelium for cytologic analysis and culture; allows placement of biliary drainage catheter and stricture dilation; endoscopic route (endoscopic retrograde cholangiopancreatogram [ERCP]) permits manometric evaluation of sphincter of Oddi, sphincterotomy, and stone extraction.

■ ANGIOGRAPHY

Most accurate means of determining portal pressures and assessing patency and direction of flow in portal and hepatic veins; highly sensitive for detecting small vascular lesions and hepatic tumors (esp. primary hepatocellular carcinoma); “gold standard” for differentiating hemangiomas from solid tumors; most accurate means of studying vascular anatomy in preparation for complicated hepatobiliary surgery (e.g., portal-systemic shunting, biliary reconstruction) and determining resectability of hepatobiliary and pancreatic tumors. Similar anatomic information (but not intravascular pressures) can often be obtained noninvasively by CT- and MR-based techniques.

■ PERCUTANEOUS LIVER BIOPSY

Most accurate in disorders causing diffuse changes throughout the liver; subject to sampling error in focal infiltrative disorders such as metastasis; should not be the initial procedure in the diagnosis of cholestasis. Contraindications to performing a percutaneous liver biopsy include significant ascites and prolonged international normalized ratio (INR). In such settings, the biopsy can be performed via the transjugular approach.

45

Ascites



■ DEFINITION

Accumulation of fluid within the peritoneal cavity. Small amounts may be asymptomatic; increasing amounts cause abdominal distention and discomfort, anorexia, nausea, early satiety, heartburn, flank pain, and respiratory distress.

■ DETECTION

Physical Examination

Bulging flanks, fluid wave, shifting dullness, “puddle sign” (dullness over dependent abdomen with pt on hands and knees). May be associated with penile or scrotal edema, umbilical or inguinal herniation, pleural effusion. Evaluation should include rectal and pelvic examination, assessment of liver and spleen. Palmar erythema and spider angiomas seen in cirrhosis. Periumbilical nodule (*Sister Mary Joseph’s nodule*) or supraclavicular node (*Virchow’s node*) suggests an abdominal malignancy.

Ultrasonography/CT

Very sensitive; able to distinguish fluid from cystic masses.

■ EVALUATION

Diagnostic paracentesis (50–100 mL) essential. Routine evaluation includes gross inspection, protein, albumin, glucose, cell count and differential, Gram's and acid-fast stains, culture, cytology; in selected cases check amylase, LDH, triglycerides, culture for tuberculosis (TB). Rarely, laparoscopy or even exploratory laparotomy may be required. Ascites due to CHF (e.g., pericardial constriction) may require evaluation by right-sided heart catheterization.

Differential Diagnosis

Cirrhosis counts for 84% of cases of ascites. Cardiac ascites, peritoneal carcinoma, and “mixed” ascites resulting from cirrhosis and a second disease account for 10–15%.

Diseases of peritoneum: Infections (bacterial, tuberculous, fungal, parasitic), neoplasms, connective tissue disease, miscellaneous (Whipple's disease, familial Mediterranean fever, endometriosis, starch peritonitis, etc.).

Diseases not involving peritoneum: Cirrhosis, CHF, Budd-Chiari syndrome, hepatic venoocclusive disease, hypoalbuminemia (nephrotic syndrome, protein-losing enteropathy, malnutrition), miscellaneous (myxedema, ovarian diseases, pancreatic disease, chylous ascites).

Pathophysiologic Classification Using Serum-Ascites Albumin Gradient (SAAG)

Difference in albumin concentrations between serum and ascites as a reflection of imbalances in hydrostatic pressures and can be used to differentiate between potential causes of ascites (Fig. 45-1).

■ CIRRHOTIC ASCITES

Pathogenesis

Contributing factors: (1) portal hypertension, (2) hypoalbuminemia, (3) hepatic lymph, (4) renal sodium retention—secondary to hyperaldosteronism, increased sympathetic nervous system activity (renin-angiotensin production). Initiating event may be peripheral arterial vasodilation triggered by endotoxin and cytokines and mediated by nitric oxide.

TREATMENT

Cirrhotic Ascites

1. Rigid salt restriction (<2 g Na/d).
2. For moderate ascites, diuretics usually necessary; spironolactone 100–200 mg/d PO (can be increased to 400 mg/d if low-sodium diet is confirmed and fluid not mobilized); furosemide 40–80 mg/d PO or IV may be added if necessary (greater risk of hepatorenal syndrome [HRS], encephalopathy), can increase to maximum of 120–160 mg/d until effect achieved or complication occurs.
3. Monitor weight, urinary Na and K, serum electrolytes, and creatinine. If ascites is still present with the above measures, this is defined as *refractory ascites*. Treatment modalities include:
 - a. Pharmacologic therapy: add midodrine or clonidine to diuretic therapy
 - b. Repeated large-volume paracentesis (5 L) with IV infusions of albumin (6–8 g/L ascites removed)
 - c. Consider transjugular intrahepatic portosystemic shunt (TIPS). While TIPS manages the ascites, it has not been found to improve survival and is often associated with encephalopathy.

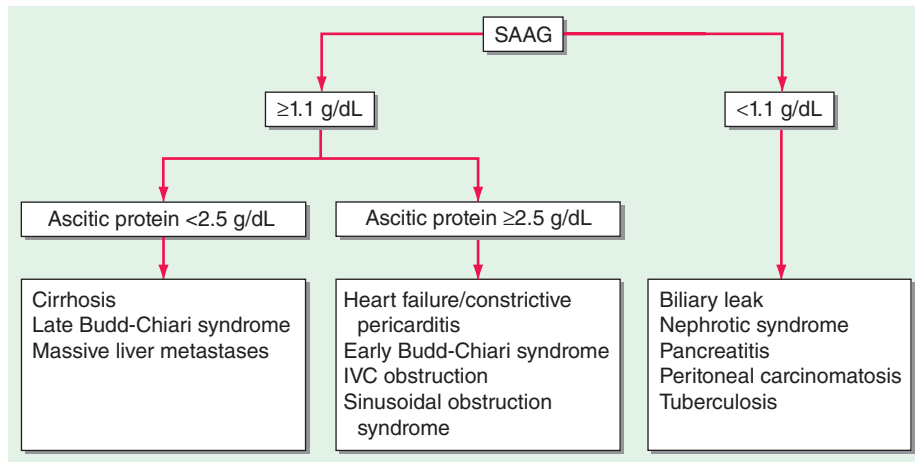


FIGURE 45-1 Algorithm for the diagnosis of ascites according to the serum-ascites albumin gradient (SAAG). IVC, inferior vena cava.

Prognosis for pts with cirrhotic ascites is poor with <50% survival 2 years after onset of ascites. Consider liver transplantation in appropriate candidates with the onset of ascites (Chap. 157).

■ COMPLICATIONS

Spontaneous Bacterial Peritonitis

Suspect in cirrhotic pt with ascites and fever, abdominal pain, worsening ascites, ileus, hypotension, worsening jaundice, or encephalopathy; low ascitic protein concentration (low opsonic activity) is predisposing factor. Diagnosis suggested by ascitic fluid PMN cell count >250/ μL ; confirmed by positive culture (usually *Escherichia coli* and other gut bacteria; however, gram-positive bacteria including *Streptococcus viridans*, *Staphylococcus aureus*, and *Enterococcus* spp. also can be found). Initial treatment: Cefotaxime 2 g IV q8h. Risk is increased in pts with variceal bleeding, and prophylaxis against spontaneous bacterial peritonitis is recommended when a pt presents with upper GI bleeding.

Hepatorenal Syndrome (HRS)

Functional renal failure without renal pathology; occurs in 10% of pts with advanced cirrhosis or acute liver failure. Thought to result from altered renal hemodynamics. Two types: type 1 HRS—decrease in renal function within 1–2 weeks of presentation; type 2 HRS—associated with a rise in serum creatinine but is associated with a better outcome. Often seen in pts with refractory ascites. Treatment: midodrine along with octreotide and IV albumin. For either type 1 or 2 HRS, prognosis is poor in the absence of liver transplantation.

46

Lymphadenopathy and Splenomegaly



LYMPHADENOPATHY

Exposure to antigen through a break in the skin or mucosa results in antigen being taken up by an antigen-presenting cell and carried via lymphatic channels to the nearest lymph node. Lymph channels course throughout the body except for the brain and the bones. Lymph enters the node through the afferent vessel and leaves through an efferent vessel. Because antigen-presenting cells pass through lymph nodes, they present antigen to lymphocytes residing there. Lymphocytes in a node are constantly being replaced by antigen-naïve lymphocytes from the blood. They are retained in the node via special homing receptors. B cells populate the lymphoid follicles in the cortex; T cells populate the paracortical regions. When a B cell encounters an antigen to which its surface immunoglobulin can bind, it stays in the follicle for a few days and forms a germinal center where the immunoglobulin gene is mutated in an effort to make an antibody with higher affinity for the antigen. The B cell then migrates to the medullary region, differentiates into a plasma cell, and secretes immunoglobulin into the efferent lymph.

When a T cell in the node encounters an antigen it recognizes, it proliferates and joins the efferent lymph. The efferent lymph laden with antibodies and T cells specific for the inciting antigen passes through several nodes on its way to the thoracic duct, which drains lymph from most of the body. From the thoracic

duct, lymph enters the bloodstream at the left subclavian vein. Lymph from the head and neck and the right arm drains into the right subclavian vein. From the bloodstream, the antibody and T cells localize to the site of infection.

Lymphadenopathy may be caused by infections, immunologic diseases, malignancies, lipid storage diseases, or other disorders of uncertain etiology (e.g., sarcoidosis, Castleman's disease; [Table 46-1](#)). The two major mechanisms of lymphadenopathy are *hyperplasia*, in response to immunologic or infectious stimuli, and *infiltration*, by cancer cells or lipid- or glycoprotein-laden macrophages.

APPROACH TO THE PATIENT

Lymphadenopathy

History Age, occupation, animal exposures, sexual orientation, substance abuse history, medication history, and concomitant symptoms influence diagnostic workup. Adenopathy is more commonly malignant in origin in those over age 40 years. Farmers have an increased incidence of brucellosis and lymphoma. Male homosexuals may have AIDS-associated adenopathy. Alcohol and tobacco abuse increase risk of malignancy. Phenytoin may induce adenopathy. The concomitant presence of cervical adenopathy with sore throat or with fever, night sweats, and weight loss suggests particular diagnoses (mononucleosis in the former instance, Hodgkin's disease in the latter).

Physical Examination Location of adenopathy, size, node texture, and the presence of tenderness are important in differential diagnosis. Generalized adenopathy (three or more anatomic regions) implies systemic infection or lymphoma. Subclavian or scalene adenopathy is always abnormal and should be biopsied. Nodes >4 cm should be biopsied immediately. Rock-hard nodes fixed to surrounding soft tissue are usually a sign of metastatic carcinoma. Tender nodes are most often benign.

Laboratory Tests Usually laboratory tests are not required in the setting of localized adenopathy. If generalized adenopathy is noted, an excisional node biopsy should be performed for diagnosis, rather than a panoply of laboratory tests.

TREATMENT

Lymphadenopathy

Pts over age 40 years, those with scalene or supraclavicular adenopathy, those with lymph nodes >4 cm in diameter, and those with hard nontender nodes should undergo immediate excisional biopsy. In younger pts with smaller nodes that are rubbery in consistency or tender, a period of observation for 7–14 days is reasonable. Empirical antibiotics are not indicated. If the nodes shrink, no further evaluation is necessary. If they enlarge, excisional biopsy is indicated.

SPLENOMEGALY

Just as the lymph nodes are specialized to fight pathogens in the tissues, the spleen is the lymphoid organ specialized to fight bloodborne pathogens. It has no afferent lymphatics. The spleen has specialized areas like the lymph node for making antibodies (follicles) and amplifying antigen-specific T cells

TABLE 46-1 Diseases Associated with Lymphadenopathy

1. Infectious diseases
 - a. Viral—*infectious mononucleosis syndromes (EBV, CMV), infectious hepatitis, herpes simplex, herpesvirus 6, varicella-zoster virus, rubella, measles, adenovirus, HIV, epidemic keratoconjunctivitis, vaccinia, herpesvirus 8*
 - b. Bacterial—*streptococci, staphylococci, cat-scratch disease, brucellosis, tularemia, plague, chancroid, melioidosis, glanders, tuberculosis, atypical mycobacterial infection, primary and secondary syphilis, diphtheria, leprosy*
 - c. Fungal—*histoplasmosis, coccidioidomycosis, paracoccidioidomycosis*
 - d. Chlamydial—*lymphogranuloma venereum, trachoma*
 - e. Parasitic—*toxoplasmosis, leishmaniasis, trypanosomiasis, filariasis*
 - f. Rickettsial—*scrub typhus, rickettsialpox, Q fever*
2. Immunologic diseases
 - a. Rheumatoid arthritis
 - b. Juvenile rheumatoid arthritis
 - c. Mixed connective tissue disease
 - d. Systemic lupus erythematosus
 - e. Dermatomyositis
 - f. Sjögren's syndrome
 - g. Serum sickness
 - h. Drug hypersensitivity—*diphenylhydantoin, hydralazine, allopurinol, primidone, gold, carbamazepine, etc.*
 - i. Angioimmunoblastic lymphadenopathy
 - j. Primary biliary cirrhosis
 - k. Graft-versus-host disease
 - l. Silicone-associated
 - m. Autoimmune lymphoproliferative syndrome
 - n. IgG4-related disease
 - o. Immune reconstitution inflammatory syndrome (IRIS)
3. Malignant diseases
 - a. Hematologic—*Hodgkin's lymphoma, non-Hodgkin's lymphomas, acute or chronic lymphocytic leukemia, hairy cell leukemia, histiocytic and dendritic cell neoplasms, amyloidosis*
 - b. Metastatic—*from numerous primary sites*
4. Lipid storage diseases—*Gaucher's, Niemann-Pick, Fabry, Tangier*
5. Endocrine diseases—*hyperthyroidism*
6. Other disorders
 - a. Castleman's disease (*giant lymph node hyperplasia*)
 - b. Sarcoidosis
 - c. Dermatopathic lymphadenitis
 - d. Lymphomatoid granulomatosis
 - e. Histiocytic necrotizing lymphadenitis (*Kikuchi's disease*)
 - f. Sinus histiocytosis with massive lymphadenopathy (*Rosai-Dorfman disease*)
 - g. Mucocutaneous lymph node syndrome (*Kawasaki's disease*)
 - h. Familial Mediterranean fever
 - i. Severe hypertriglyceridemia
 - j. Vascular transformation of sinuses
 - k. Inflammatory pseudotumor of lymph node
 - l. Congestive heart failure

(periarteriolar lymphatic sheath, or PALS). In addition, it has a well-developed reticuloendothelial system for removing particles and antibody-coated bacteria. The flow of blood through the spleen permits it to filter pathogens from the blood and to maintain quality control over erythrocytes (RBCs)—those that are old and nondeformable are destroyed, and intracellular inclusions (sometimes including pathogens such as *Babesia* and *Plasmodium*) are culled from the cells in a process called *pitting*. Under certain conditions, the spleen can generate hematopoietic cells in place of the marrow.

The normal spleen is about 12 cm in length and 7 cm in width and is not normally palpable. Dullness from the spleen can be percussed between the ninth and eleventh ribs with the pt lying on the right side. Palpation is best performed with the pt supine with knees flexed. The spleen may be felt because it descends when the pt inspires. Physical diagnosis is not sensitive. CT or ultrasound is a superior test.

Spleen enlargement occurs by three basic mechanisms: (1) hyperplasia or hypertrophy due to an increase in demand for splenic function (e.g., hereditary spherocytosis where demand for removal of defective RBCs is high or immune hyperplasia in response to systemic infection or immune diseases); (2) passive vascular congestion due to portal hypertension; and (3) infiltration with malignant cells, lipid- or glycoprotein-laden macrophages, or amyloid (Table 46-2).

TABLE 46-2 Diseases Associated with Splenomegaly Grouped by Pathogenic Mechanism

Enlargement due to increased demand for splenic function

Reticuloendothelial system hyperplasia (for removal of defective erythrocytes)	Leishmaniasis
Spherocytosis	Trypanosomiasis
Early sickle cell anemia	Ehrlichiosis
Ovalocytosis	Disordered immunoregulation
Thalassemia major	Rheumatoid arthritis (Felty's syndrome)
Hemoglobinopathies	Systemic lupus erythematosus
Paroxysmal nocturnal hemoglobinuria	Collagen vascular diseases
Pernicious anemia	Serum sickness
Immune hyperplasia	Immune hemolytic anemias
Response to infection (viral, bacterial, fungal, parasitic)	Immune thrombocytopenias
Infectious mononucleosis	Immune neutropenias
AIDS	Drug reactions
Viral hepatitis	Angioimmunoblastic lymphadenopathy
Cytomegalovirus	Sarcoidosis
Subacute bacterial endocarditis	Thyrotoxicosis (benign lymphoid hypertrophy)
Bacterial septicemia	Interleukin-2 therapy
Congenital syphilis	Extramedullary hematopoiesis
Splenic abscess	Myelofibrosis
Tuberculosis	Marrow damage by toxins, radiation, strontium
Histoplasmosis	Marrow infiltration by tumors, leukemias, Gaucher's disease
Malaria	

(Continued)

TABLE 46-2 Diseases Associated with Splenomegaly Grouped by Pathogenic Mechanism (Continued)

Enlargement due to abnormal splenic or portal blood flow	
Cirrhosis	Splenic artery aneurysm
Hepatic vein obstruction	Hepatic schistosomiasis
Portal vein obstruction, intrahepatic or extrahepatic	Congestive heart failure
Cavernous transformation of the portal vein	Hepatic echinococcosis
Splenic vein obstruction	Portal hypertension (any cause including the above): "Banti's disease"
Infiltration of the spleen	
Intracellular or extracellular depositions	Hodgkin's lymphoma
Amyloidosis	Myeloproliferative syndromes (e.g., polycythemia vera, essential thrombocytosis)
Gaucher's disease	Angiosarcomas
Niemann-Pick disease	Metastatic tumors (melanoma is most common)
Tangier disease	Eosinophilic granuloma
Hurler's syndrome and other mucopolysaccharidoses	Histiocytic and dendritic cell neoplasms (Histiocytosis X)
Hyperlipidemias	Hamartomas
Benign and malignant cellular infiltrations	Hemangiomas, fibromas, lymphangiomas
Leukemias (acute, chronic, lymphoid, myeloid, monocytic, hairy cell)	Splenic cysts
Lymphomas	
Unknown etiology	
Idiopathic splenomegaly	Iron-deficiency anemia
Berylliosis	

Massive enlargement, with spleen palpable >8 cm below the left costal margin, usually signifies a lymphoproliferative or myeloproliferative disorder.

Peripheral blood RBC count, white blood cell count, and platelet count may be normal, decreased, or increased depending on the underlying disorder. Decreases in one or more cell lineages could indicate hypersplenism, increased destruction. In cases with hypersplenism, the spleen is removed and the cytopenia is generally reversed. In the absence of hypersplenism, most causes of splenomegaly are diagnosed on the basis of signs and symptoms and laboratory abnormalities associated with the underlying disorder. Splenectomy is rarely performed for diagnostic purposes.

Individuals who have had splenectomy are at increased risk of sepsis from a variety of organisms including pneumococcus and *Haemophilus influenzae*. Vaccines for these agents should be given before splenectomy is performed. Splenectomy compromises the immune response to T-cell-independent polysaccharide antigens. Newer vaccine formulations are T-cell-dependent and are more effective in splenectomized persons.

47

Anemia and Polycythemia

**ANEMIA**

According to the World Health Organization criteria, anemia is defined as blood hemoglobin (Hb) concentration <130 g/L (<13 g/dL) or hematocrit (Hct) $<39\%$ in adult males; Hb <120 g/L (<12 g/dL) or Hct $<37\%$ in adult females.

Signs and symptoms of anemia are varied, depending on the level of anemia and the time course over which it developed. Acute anemia is nearly always due to blood loss or hemolysis. In acute blood loss, hypovolemia dominates the clinical picture; hypotension and decreased organ perfusion are the main issues. Symptoms associated with more chronic onset vary with the age of the pt and the adequacy of blood supply to critical organs. Moderate anemia is associated with fatigue, loss of stamina, breathlessness, and tachycardia. The pt's skin and mucous membranes may appear pale. If the palmar creases are lighter in color than the surrounding skin with the fingers extended, Hb level is often <80 g/L (8 g/dL). In pts with coronary artery disease, anginal episodes may appear or increase in frequency and severity. In pts with carotid artery disease, light-headedness or dizziness may develop.

A physiologic approach to anemia diagnosis is based on the understanding that a decrease in circulating RBCs can be related to either inadequate production of RBCs or increased RBC destruction or loss. Within the category of inadequate production, erythropoiesis can be either ineffective, due to an erythrocyte maturation defect (which usually results in RBCs that are too small or too large), or hypoproliferative (which usually results in RBCs of normal size, but too few of them).

Basic evaluations include (1) reticulocyte index (RI), and (2) review of blood smear and RBC indices (chiefly mean corpuscular volume [MCV]) (Fig. 47-1).

The RI is a measure of RBC production. The reticulocyte count is corrected for the Hct level and for early release of marrow reticulocytes into the circulation, which leads to an increase in the lifespan of the circulating reticulocyte beyond the usual 1 day. Thus, $RI = (\% \text{ reticulocytes} \times \text{pt Hct}/45\%) \times (1/\text{shift correction factor})$. The shift correction factor varies with the Hct: 1.5 for Hct = 35%, 2 for Hct = 25%, 2.5 for Hct = 15%. $RI < 2\text{--}2.5\%$ implies inadequate RBC production for the particular level of anemia; $RI > 2.5\%$ implies excessive RBC destruction or loss. About 75% of anemias are hypoproliferative.

If the anemia is associated with a low RI, RBC morphology helps distinguish a maturation disorder from hypoproliferative marrow states. Cytoplasmic maturation defects such as iron deficiency or Hb synthesis problems produce smaller RBCs, $MCV < 80$; nuclear maturation defects such as B_{12} and folate deficiency and drug effects produce larger RBCs, $MCV > 100$. In hypoproliferative marrow states, RBCs are generally normal in morphology but too few are produced. Bone marrow examination is often helpful in the evaluation of anemia but is done most frequently to diagnose hypoproliferative marrow states.

Other laboratory tests indicated to evaluate particular forms of anemia depend on the initial classification based on the pathophysiology of the defect. These are discussed in more detail in [Chap. 63](#).

POLYCYTHEMIA (ERYTHROCYTOSIS)

Polycythemia is an increase above the normal range of RBCs in the circulation. Concern that the Hb level may be abnormally high should be triggered at a level of 170 g/L (17 g/dL) in men and 150 g/L (15 g/dL) in women. Polycythemia is

ALGORITHM OF THE PHYSIOLOGIC CLASSIFICATION OF ANEMIA

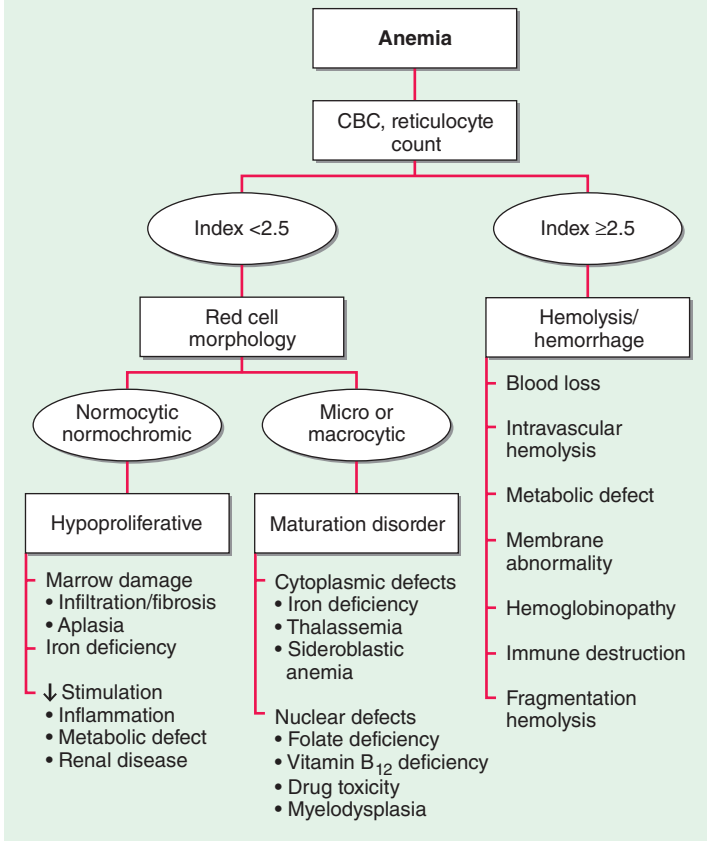


FIGURE 47-1 The physiologic classification of anemia. CBC, complete blood count.

usually found incidentally at routine blood count. Relative erythrocytosis, due to plasma volume loss (e.g., severe dehydration, burns), does not represent a true increase in total RBC mass. Absolute erythrocytosis is a true increase in total RBC mass.

■ CAUSES

Polycythemia vera (a clonal myeloproliferative disorder), erythropoietin-producing neoplasms (e.g., renal cancer, cerebellar hemangioma), chronic hypoxemia (e.g., high altitude, pulmonary disease), carboxyhemoglobin excess (e.g., smokers), high-affinity Hb variants, Cushing's syndrome, androgen excess. Polycythemia vera is distinguished from secondary polycythemia by the presence of splenomegaly, leukocytosis, thrombocytosis, and elevated vitamin B₁₂ levels, and by decreased erythropoietin levels and the presence of a mutation in the JAK2 kinase (V617F). An approach to evaluate polycythemic pts is shown in [Fig. 47-2](#).

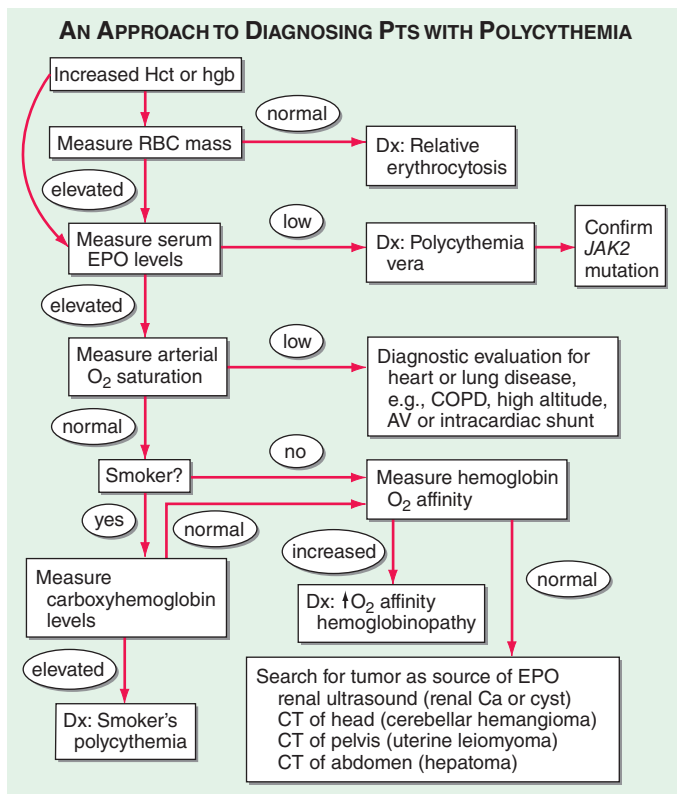


FIGURE 47-2 An approach to the differential diagnosis of pts with an elevated hemoglobin (possible polycythemia). AV, atrioventricular; COPD, chronic obstructive pulmonary disease; CT, computed tomography; EPO, erythropoietin; Hct, hematocrit; hgb, hemoglobin; IVP, intravenous pyelogram; RBC, red blood cell.

■ COMPLICATIONS

Hyperviscosity (with diminished O_2 delivery) with risk of ischemic organ injury and thrombosis (venous or arterial) are most common.

TREATMENT

Polycythemia

Phlebotomy recommended for Hct $\geq 55\%$ to low-normal range. Aspirin is routinely given to lower the thrombosis risk. For those in whom phlebotomy is inadequate, hydroxyurea may be used to control the hematocrit level.

48

Azotemia and Urinary Abnormalities



■ ABNORMALITIES OF RENAL FUNCTION, AZOTEMIA

Azotemia is the retention of nitrogenous waste products excreted by the kidney. Increased levels of blood urea nitrogen (BUN) (>10.7 mmol/L [>30 mg/dL]) and creatinine (>133 $\mu\text{mol/L}$ [>1.5 mg/dL]) are ordinarily indicative of impaired renal function. Renal function can be estimated by determining the clearance of creatinine (CL_{cr}) (normal >100 mL/min); this can be directly measured from a 24-h urine collection using the following equation:

$$\text{Creatinine clearance (mL/min)} = (\text{uCr} \times \text{uV}) / (\text{sCr} \times 1440)$$

1. Where uCr is urine creatinine in mg/dL
2. Where sCr is serum creatinine in mg/dL
3. Where uV is 24-h urine volume in mL
4. Where 1440 represents number of minutes in 24 h

The “adequacy” or “completeness” of the collection is estimated by the urinary volume and creatinine content; creatinine is produced from muscle and excreted at a relatively constant rate. For a 20- to 50-year-old man, creatinine excretion should be 18.5–25.0 mg/kg body weight; for a woman of the same age, it should be 16.5–22.4 mg/kg body weight. For example, an 80-kg man should excrete between ~1500 and 2000 mg of creatinine in an “adequate” collection. Creatinine excretion is also influenced by age and muscle mass. Notably, creatinine is an imperfect measure of glomerular filtration rate (GFR), because it is both filtered by glomeruli and secreted by proximal tubular cells; the relative contribution of tubular secretion increases with advancing renal dysfunction, such that creatinine clearance will provide an overestimate of the “true” GFR in pts with chronic kidney disease. Isotopic markers that are filtered and not secreted (e.g., iothalamate) provide more accurate estimates of GFR.

A formula that allows for an estimate of creatinine clearance in men that accounts for age-related decreases in GFR, body weight, and sex has been derived by Cockcroft-Gault:

$$\text{Creatinine clearance (mL/min)} = (140 - \text{age}) \times \text{lean body weight (kg)} / \text{plasma creatinine (mg/dL)} \times 72$$

This value should be multiplied by 0.85 for women.

GFR may also be estimated using serum creatinine-based equations derived from the Modification of Diet in Renal Disease Study. This “eGFR” (estimated glomerular filtration rate) is now reported with serum creatinine by most clinical laboratories in the United States and is the basis for the National Kidney Foundation classification of chronic kidney disease ([Table 48-1](#)).

More recently, estimation of GFR using measurement of an alternative circulating marker, cystatin C, has been incorporated into clinical practice. Cystatin C, a member of the cystatin superfamily of cysteine protease inhibitors, is produced at a relatively constant rate from all nucleated cells; as with creatinine, measurement of cystatin C generates an estimated GFR (eGFR). Serum cystatin C has been proposed to be a more sensitive marker of early GFR decline than is Cr, with lesser effects of muscle mass on circulating levels; however, like serum creatinine, cystatin C is influenced by the pt’s age, race, and sex.

Manifestations of impaired renal function include volume overload, hypertension, electrolyte abnormalities (e.g., hyperkalemia, hypocalcemia, hyperphosphatemia), metabolic acidosis, and hormonal disturbances (e.g., insulin resistance, functional vitamin D deficiency, secondary hyperparathyroidism).

TABLE 48-1 The Classification of Chronic Kidney Disease

KIDNEY DAMAGE STAGE	DESCRIPTION	EGFR (mL/min PER 1.73 m ²)
0	With risk factors for CKD ^a	>90
1	With evidence of kidney damage ^b	>90
2	Mild decrease in GFR	60–89
3a	Moderate decrease in GFR	45–59
3b		30–44
4	Severe decrease in GFR	15–29
5	Kidney failure	<15

^aDiabetes, high blood pressure, family history, older age, African ancestry.

^bAbnormal urinalysis, hematuria, proteinuria, albuminuria.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

When severe, the symptom complex of “uremia” may develop, encompassing one or more of the following symptoms and signs: anorexia, dysgeusia, nausea, vomiting, lethargy, confusion, asterixis, pleuritis, pericarditis, enteritis, pruritus, sleep and taste disturbance, hiccups, and nitrogenous fetor.

An approach to the pt with azotemia is shown in [Fig. 48-1](#).

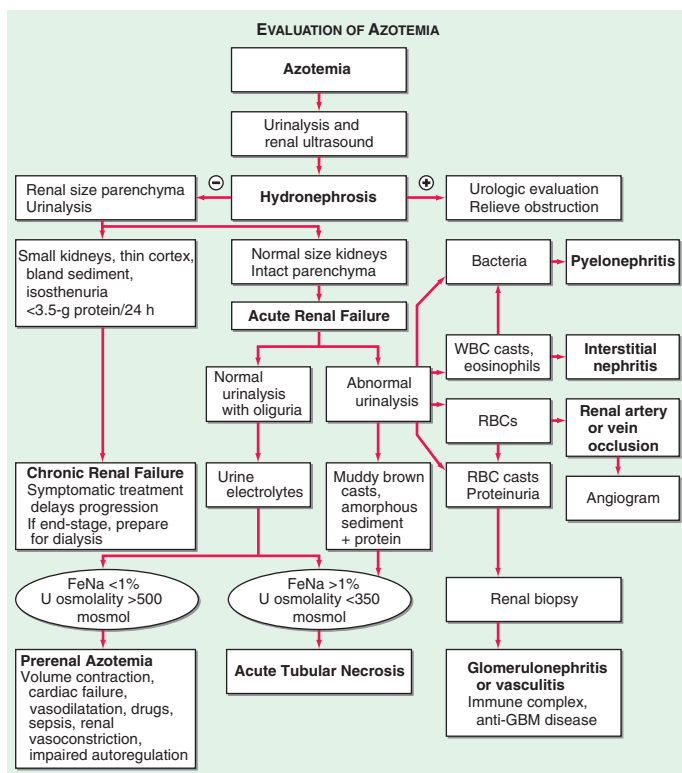


FIGURE 48-1 Approach to the pt with azotemia. FeNa, fractional excretion of sodium; GBM, glomerular basement membrane. (From Lin J, Denker BM: Azotemia and urinary abnormalities, in Kasper DL et al (eds). *Harrison's Principles of Internal Medicine*, 19th ed. New York, NY: McGraw-Hill; 2014.)

■ ABNORMALITIES OF URINE VOLUME

Oliguria

This refers to reduced urine output, usually defined as <400 mL/d. *Oligoanuria* refers to a more marked reduction in urine output, i.e., <100 mL/d. *Anuria* indicates the complete absence of urine output. Oliguria most often occurs in the setting of volume depletion and/or renal hypoperfusion, resulting in “prerenal azotemia” and acute renal failure (Chap. 141). Anuria can be caused by complete bilateral urinary tract obstruction; a vascular catastrophe (dissection or arterial occlusion); renal vein thrombosis; renal cortical necrosis; severe acute tubular necrosis; nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme (ACE) inhibitors, and/or angiotensin receptor blockers; and hypovolemic, cardiogenic, or septic shock. Oliguria is never normal, because at least 400 mL of maximally concentrated urine must be produced to excrete the obligate daily osmolar load.

Polyuria

Polyuria is defined as a urine output >3 L/d. It is often accompanied by nocturia and urinary frequency and must be differentiated from other more common conditions associated with lower urinary tract pathology and urinary urgency or frequency (e.g., cystitis, prostatism). It is often accompanied by hypernatremia (Chap. 1). Polyuria (Table 48-2) can occur as a response to a solute load (e.g., hyperglycemia) or to an abnormality in arginine vasopressin (AVP; also known as antidiuretic hormone [ADH]) action. Diabetes insipidus is termed *central* if due to the insufficient hypothalamic production of AVP and *nephrogenic* if the result of renal insensitivity to the action of AVP. Excess fluid intake can lead to polyuria, but primary polydipsia rarely results in changes in plasma osmolality unless urinary diluting capacity is impaired. Tubulointerstitial diseases, lithium therapy, and resolving acute tubular necrosis or urinary tract obstruction can be associated with nephrogenic diabetes insipidus, which is more rarely caused by mutations in the V2 AVP receptor, the aquaporin-1 water channel in the descending thin limb of the loop of Henle, and the AVP-regulated water channel in principal cells, aquaporin 2.

The approach to the pt with polyuria is shown in Fig. 48-2.

■ ABNORMALITIES OF URINE COMPOSITION

Proteinuria

This is the hallmark of glomerular disease. Levels up to 150 mg/d are considered within normal limits. Typical measurements are semiquantitative, using

TABLE 48-2 Major Causes of Polyuria

Excessive fluid intake	Nephrogenic diabetes insipidus
Primary polydipsia	Lithium exposure
Iatrogenic (IV fluids)	Urinary tract obstruction
Therapeutic	Papillary necrosis
Diuretic agents	Reflux nephropathy
Osmotic diuresis	Interstitial nephritis
Hyperglycemia	Hypercalcemia
Azotemia	Hereditary (V2R, AQP-1/2)
Mannitol	Central diabetes insipidus
Radiocontrast	Tumor
	Postoperative
	Head trauma
	Basilar meningitis
	Neurosarcoidosis

Abbreviations: AQP, aquaporin; V2R, vasopressin type 2 receptor.

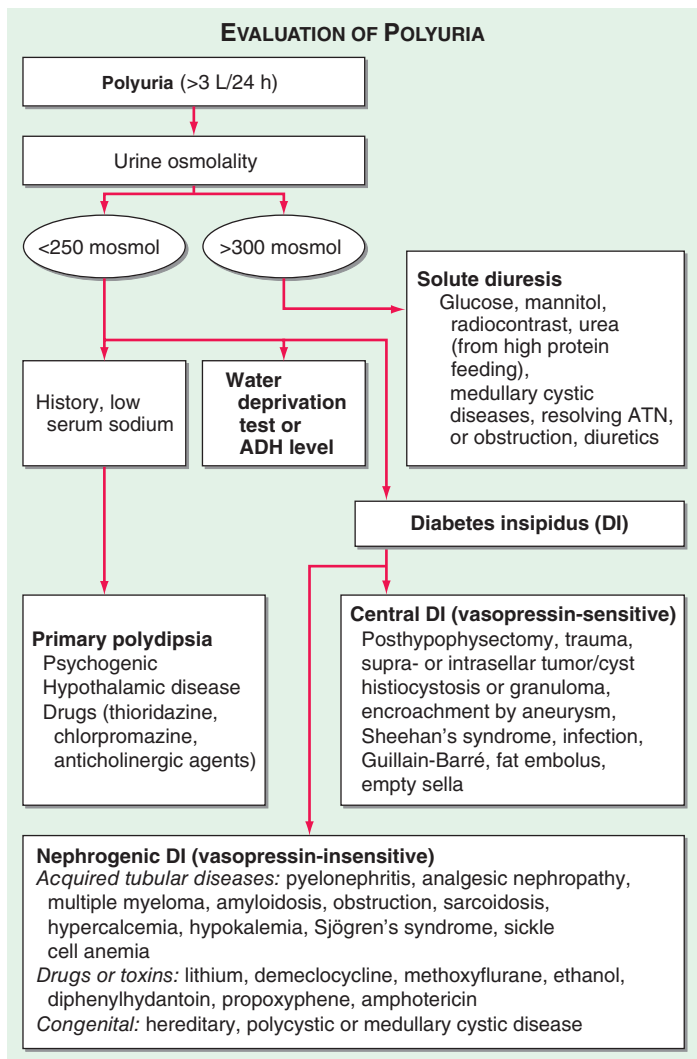


FIGURE 48-2 Approach to the pt with polyuria. ADH, antidiuretic hormone; ATN, acute tubular necrosis. (From Lin J, Denker BM: *Azotemia and urinary abnormalities*, in Kasper DL et al (eds). *Harrison's Principles of Internal Medicine*, 19th ed. New York, NY: McGraw-Hill; 2014.)

a moderately sensitive dipstick that estimates protein concentration; therefore, the degree of hydration may influence the dipstick protein determination. Most commercially available urine dipsticks detect albumin and do not detect smaller proteins, such as light chains, that require testing with sulfosalicylic acid. More sensitive assays can in turn be used to detect albuminuria, an important screening tool for diabetic nephropathy. Urinary albumin excretion between 30 and 300 mg/day (20–200 mcg/min) is called moderately increased albuminuria (formerly known as “microalbuminuria”); albumin excretion >300 mg/d (200 mcg/min) is considered to represent severely increased albuminuria (formerly known

as “macroalbuminuria”). The natural history of steadily increasing albuminuria over the years is a key diagnostic feature of diabetic nephropathy.

Formal assessment of urinary protein excretion requires a 24-h urine protein collection (see “Abnormalities of Renal Function, Azotemia,” above). The ratio of protein to creatinine in a random, “spot” urine can also provide a rough estimate of protein excretion; e.g., a protein/creatinine ratio of 3.0 correlates to ~3.0 g of proteinuria per day.

Urinary protein excretion rates between 500 mg/d and 3 g/d are nonspecific and can be seen in a variety of renal diseases (including hypertensive nephrosclerosis, interstitial nephritis, vascular disease, and other primary renal diseases with little or no glomerular involvement). Transient, lesser degrees of proteinuria (500 mg/d–1.5 g/d) may be seen after vigorous exercise, changes in body position, fever, or congestive heart failure. Protein excretion rates >3 g/d are termed *nephrotic range proteinuria* in that they may be accompanied by hypoalbuminemia, hypercholesterolemia, and edema (the nephrotic syndrome). Nephrotic syndrome can be associated with a variety of extrarenal complications ([Chap. 145](#)). Massive degrees of proteinuria (>10 g/d) can be seen with minimal change disease, primary focal segmental glomerulosclerosis (FSGS), membranous nephropathy, diabetic nephropathy, collapsing glomerulopathy (a subtype of primary FSGS), and HIV-associated nephropathy (a viral form of collapsing glomerulopathy).

Pharmacologic inhibition of ACE or blockade of angiotensin II should be employed to reduce proteinuria; successful reduction of proteinuria decreases the rate of progression to end-stage renal disease in diabetic nephropathy and other glomerulopathies. Specific therapy for a variety of causes of nephrotic syndrome is discussed in [Chap. 145](#).

Hematuria

Gross hematuria refers to the presence of frank blood in the urine and is more characteristic of lower urinary tract disease and/or bleeding diatheses than intrinsic renal disease ([Table 48-3](#)). Cyst rupture in polycystic kidney disease

TABLE 48-3 Major Causes of Hematuria

Lower Urinary Tract

Bacterial cystitis
 Interstitial cystitis
 Urethritis (infectious or inflammatory)
 Passed or passing kidney stone
 Transitional cell carcinoma of bladder or structures proximal to it
 Squamous cell carcinoma of bladder (e.g., following schistosomiasis)

Upper Urinary Tract

Renal cell carcinoma
 Age-related renal cysts
 Other neoplasms (e.g., oncocytoma, hamartoma)
 Acquired renal cystic disease
 Congenital cystic disease, including autosomal dominant form
 Glomerular diseases
 Interstitial renal diseases, including interstitial nephritis
 Nephrolithiasis
 Pyelonephritis
 Renal infarction
 Hypercalciuria
 Hyperuricosuria

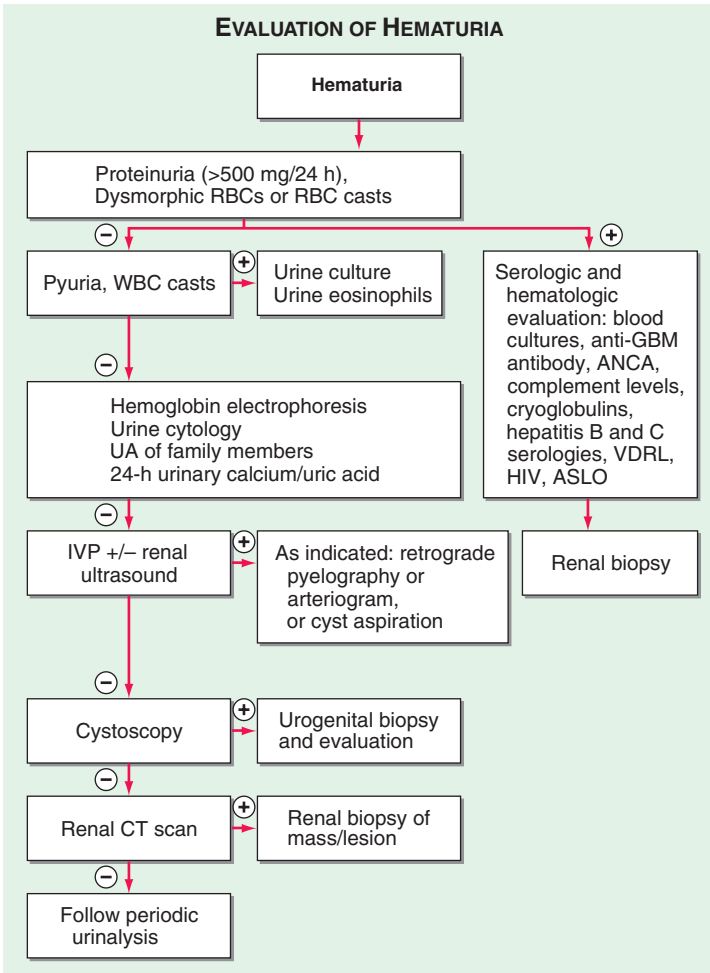


FIGURE 48-3 Approach to the pt with hematuria. ANCA, antineutrophil cytoplasmic antibody; ASLO, antistreptolysin O; GBM, glomerular basement membrane; VDRL, Venereal Disease Research Laboratory. (From Lin J, Denker BM: Azotemia and urinary abnormalities, in Kasper DL et al (eds). *Harrison's Principles of Internal Medicine*, 19th ed. New York, NY: McGraw-Hill; 2014.)

and postpharyngitic flares of IgA nephropathy are exceptions. Microscopic hematuria (>1–2 red blood cells [RBCs] per high-powered field), accompanied by proteinuria, hypertension, and an active urinary sediment (the “nephritic syndrome”) is most likely related to an inflammatory glomerulonephritis, classically poststreptococcal glomerulonephritis (Chap. 145).

Free hemoglobin and myoglobin are detected by dipstick; a negative urinary sediment with strongly heme-positive dipstick is characteristic of either hemolysis or rhabdomyolysis, which can be differentiated by clinical history

and laboratory testing. RBC casts are not a sensitive finding but when seen are highly specific for glomerular bleeding, usually, but not exclusively, caused by glomerular inflammation. Specificity of urinalysis can be enhanced by examining urine with a phase contrast microscope capable of detecting dysmorphic red cells (“acanthocytes”) associated with glomerular disease.

The approach to the pt with hematuria is shown in [Fig. 48-3](#).

■ PYURIA

This may accompany hematuria in inflammatory glomerular diseases. Isolated pyuria is most commonly observed in association with an infection of the upper or lower urinary tract. Pyuria may also occur with allergic interstitial nephritis (often with a preponderance of eosinophils), transplant rejection, and non-infectious, nonallergic tubulointerstitial diseases, including atheroembolic renal disease. The finding of “sterile” pyuria (i.e., urinary white blood cells without bacteria) in the appropriate clinical setting should raise suspicion of renal tuberculosis.

49

Pain and Swelling of Joints



Musculoskeletal complaints are extremely common in outpatient medical practice and are among the leading cause of disability and absenteeism from work. Pain in the joints must be evaluated in a uniform, thorough, and logical fashion to ensure the best chance of accurate diagnosis and to plan appropriate follow-up testing and therapy. Joint pain and swelling may be manifestations of disorders affecting primarily the musculoskeletal system or may reflect systemic disease.

■ INITIAL ASSESSMENT OF A MUSCULOSKELETAL COMPLAINT

([FIG. 49-1](#))

1. *Articular versus nonarticular*: Is the pain located in a joint or in a periarticular structure such as soft tissue or muscle?
2. *Inflammatory versus noninflammatory*: Inflammatory disease is suggested by local signs of inflammation (erythema, warmth, swelling); systemic features (morning stiffness, fatigue, fever, weight loss); or laboratory evidence of inflammation (thrombocytosis, elevated ESR or C-reactive protein).
3. *Acute (≤ 6 weeks) versus chronic*.
4. *Localized versus systemic*.

■ HISTORIC FEATURES

- Age, sex, race, and family history
- Symptom onset (abrupt or gradual), evolution (constant, intermittent, migratory, additive), and duration (acute versus chronic)
- Number and distribution of involved structures: monoarticular (one joint), oligoarticular (two to three joints), polyarticular (more than three joints); symmetry

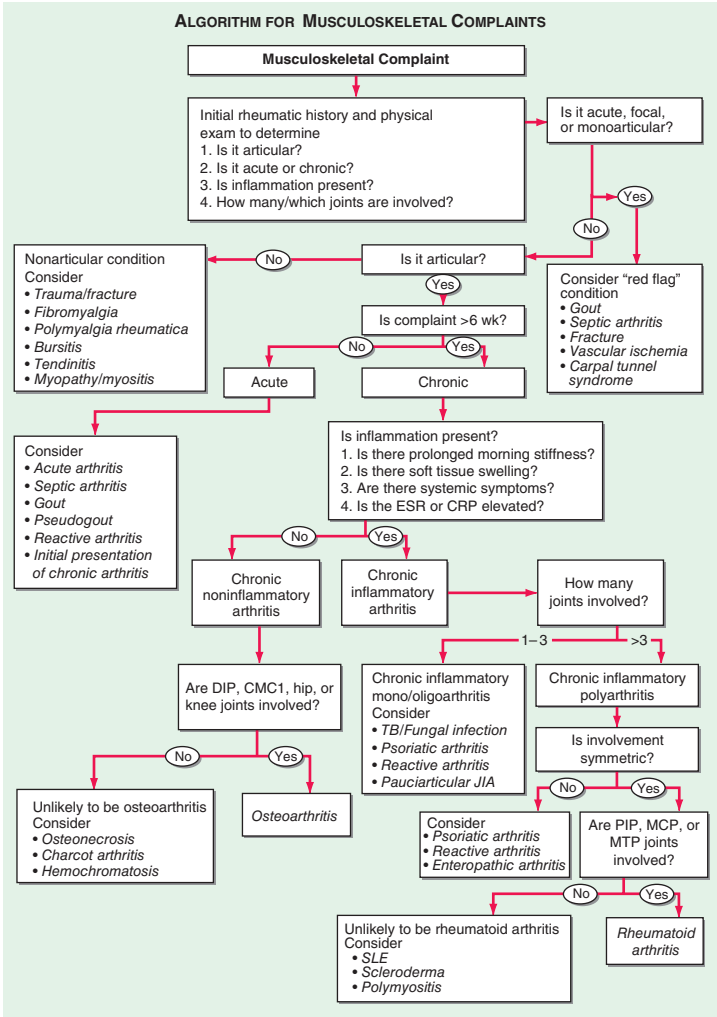


FIGURE 49-1 Algorithm for the diagnosis of musculoskeletal complaints. An approach to formulating a differential diagnosis (shown in italics). CMC, carpometacarpal; CRP, C-reactive protein; DIP, distal interphalangeal; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal; PMR, polymyalgia rheumatica; SLE, systemic lupus erythematosus.

- Other articular features: morning stiffness, effect of movement, features that improve/worsen Sx
- Extraarticular Sx: e.g., fever, rash, weight loss, visual change, dyspnea, diarrhea, dysuria, numbness, weakness
- Recent events: e.g., trauma, drug administration, travel, other illnesses

■ PHYSICAL EXAMINATION

Complete examination is essential: particular attention to skin, mucous membranes, nails (may reveal characteristic pitting in psoriasis), eyes. Careful and thorough examination of involved and uninvolved joints and periarticular structures; this should proceed in an organized fashion from head to foot or from extremities inward toward axial skeleton; special attention should be paid to identifying the presence or absence of:

- Warmth and/or erythema
- Swelling
- Synovial thickening
- Subluxation, dislocation, joint deformity
- Joint instability
- Limitations to active and passive range of motion
- Crepitus
- Periarticular changes
- Muscular changes including weakness, atrophy

■ LABORATORY INVESTIGATIONS

Additional evaluation usually indicated for monoarticular, traumatic, inflammatory, or chronic conditions or for conditions accompanied by neurologic changes or systemic manifestations.

- *For all evaluations:* include CBC, ESR, or C-reactive protein
- *Where there are suggestive clinical features:* include rheumatoid factor, antibodies to cyclic citrullinated peptides (anti-CCPs), ANA, antineutrophil cytoplasmic antibodies (ANCA), antistreptolysin O titer, Lyme antibodies
- *Where systemic disease is present or suspected:* renal/hepatic function tests, UA
- *Uric acid:* useful only when gout diagnosed and therapy contemplated
- *CPK, aldolase:* consider with muscle pain, weakness
- *Synovial fluid aspiration and analysis:* always indicated for acute monoarthritis or when infectious or crystal-induced arthropathy is suspected. Should be examined for (1) appearance, viscosity; (2) cell count and differential (suspect septic joint if WBC count $>50,000/\mu\text{L}$); (3) crystals using polarizing microscope; (4) Gram's stain, cultures (Fig. 49-2).

■ DIAGNOSTIC IMAGING

Conventional radiography using plain x-rays is a valuable tool in the diagnosis and staging of articular disorders (Table 49-1).

Additional imaging procedures, including ultrasound, radionuclide scintigraphy, CT, and MRI, may be helpful in selected clinical settings.

■ SPECIAL CONSIDERATIONS IN THE ELDERLY PT

The evaluation of joint and musculoskeletal disorders in the elderly pt presents a special challenge given the frequently insidious onset and chronicity of disease in this age group, the confounding effect of other medical conditions, and the increased variability of many diagnostic tests in the geriatric population. Although virtually all musculoskeletal conditions may afflict the elderly, certain disorders are especially frequent. Special attention should be paid to identifying the potential rheumatic consequences of intercurrent medical conditions and therapies when evaluating the geriatric pt with musculoskeletal complaints.

INTERPRETATION OF SYNOVIAL FLUID ASPIRATION

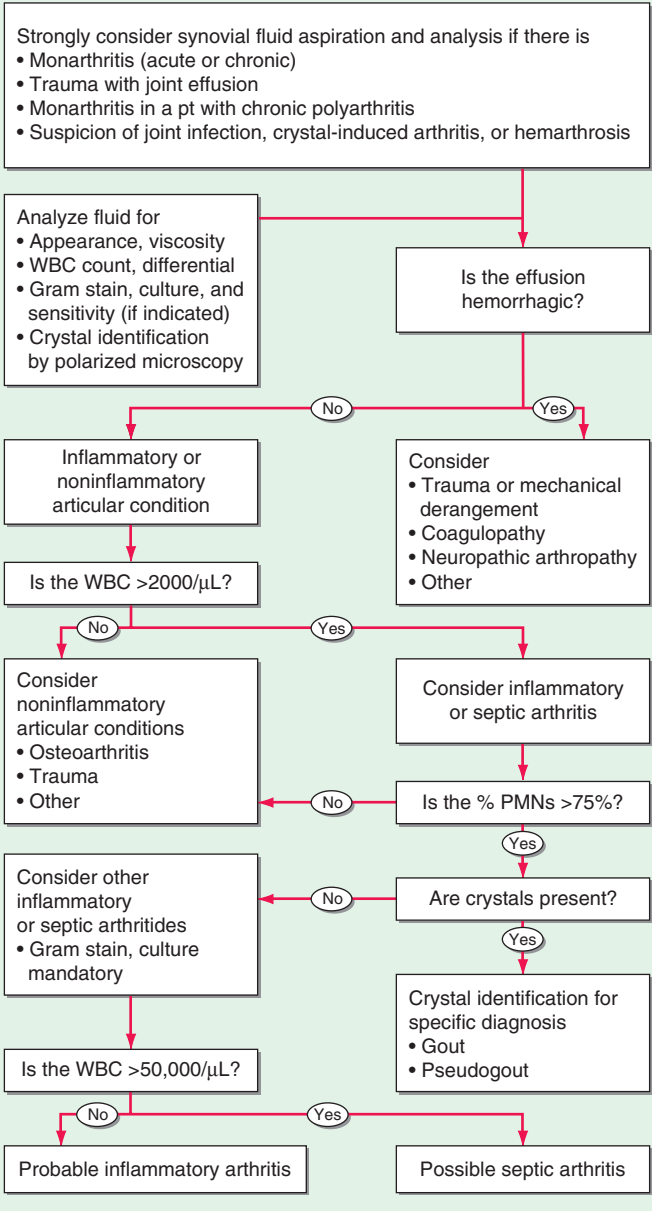


FIGURE 49-2 Algorithmic approach to the use and interpretation of synovial fluid aspiration and analysis. PMNs, polymorphonuclear leukocytes; WBC, white blood cell count.

TABLE 49-1 Applications for Conventional Radiography in Articular Disease

Trauma
Suspected chronic joint or bone infection
Progressive joint disability
Monarticular involvement
Baseline assessment of a chronic articular process
When therapeutic alterations are considered (such as for rheumatoid arthritis)

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Back and Neck Pain

**LOW BACK PAIN**

Cost of low back pain (LBP) in the United States is estimated at \$177 billion annually. Back symptoms are the most common cause of disability in those <45 years; LBP is the second most common cause of visiting a physician in the United States; >80% of people will have LBP at some point in their lives.

■ TYPES OF LOW BACK PAIN

- *Local pain*: caused by injury to pain-sensitive structures that compress or irritate sensory nerve endings; pain located near the affected part of the back.
- *Pain referred to the back*: abdominal or pelvic origin; back pain unaffected by posture.
- *Pain of spine origin*: restricted to the back or referred to lower limbs or buttock. Diseases of upper lumbar spine refer pain to upper lumbar region, groin, or anterior thighs. Diseases of lower lumbar spine refer pain to buttocks, posterior thighs, calves, or feet.
- *Radicular back pain*: radiates from spine to leg in specific nerve root territory. Coughing, sneezing, lifting heavy objects, or straining may elicit pain.
- *Pain associated with muscle spasm*: diverse causes; accompanied by tense paraspinal muscles, dull or aching pain in the paraspinal region, and abnormal posture.

■ EXAMINATION

Include abdomen and rectum to search for visceral sources of pain. Inspection may reveal scoliosis or muscle spasm. Palpation may elicit pain over a diseased spine segment. Pain from hip may be confused with spine pain; manual internal/external rotation of leg at hip (with knee and hip in flexion) reproduces the hip pain.

Straight leg raising (SLR) sign—elicited by passive flexion of leg at the hip with pt in supine position; maneuver stretches L5/S1 nerve roots and sciatic nerve passing posterior to the hip; SLR sign is positive if maneuver reproduces the pain. Crossed SLR sign—positive when SLR on one leg reproduces symptoms in opposite leg or buttocks; nerve/nerve root lesion is on the painful side. Reverse SLR sign—passive extension of leg backward with pt standing; maneuver stretches L2–L4 nerve roots, lumbosacral plexus, and femoral nerve passing anterior to the hip.

Neurologic examination—search for focal atrophy, weakness, reflex loss, diminished sensation in a dermatomal distribution. Findings with radiculopathy are summarized in [Table 50-1](#).

■ LABORATORY EVALUATION

“Routine” laboratory studies and lumbar spine x-rays are rarely needed for nonspecific acute LBP (<3 months) but indicated when risk factors for serious underlying disease are present ([Table 50-2](#)). MRI and CT-myelography are tests of choice for anatomic definition of spine disease. Electromyography (EMG) and nerve conduction studies are useful for functional assessment of peripheral nervous system.

■ ETIOLOGY

Lumbar Disk Disease

Common cause of low back and leg pain; usually at L4–L5 or L5–S1 levels. Dermatoma sensory loss, reduction or loss of deep tendon reflexes, or myotomal pattern of weakness more informative than pain pattern for localization. Usually unilateral; can be bilateral with large central disk herniations compressing multiple nerve roots and causing cauda equina syndrome ([Chap. 191](#)).

Indications for lumbar disk surgery:

- Progressive motor weakness on examination or progressive nerve root injury demonstrated on EMG.
- Cauda equina syndrome or spinal cord compression; usually indicated by urinary retention or abnormal bowel function.
- Incapacitating nerve root pain despite conservative treatment for at least 6–8 weeks: Trials indicate surgery leads to more rapid pain relief but no difference at 1–2 years compared with nonsurgical treatment.

Spinal Stenosis

A narrowed spinal canal producing neurogenic claudication, i.e., back, buttock, and/or leg pain induced by walking or standing and relieved by sitting. Symptoms are usually bilateral. Unlike vascular claudication, symptoms are provoked by standing without walking. Unlike lumbar disk disease, symptoms are relieved by sitting. Focal neurologic deficits common; severe neurologic deficits (paralysis, incontinence) rare. Stenosis results from acquired (75%), congenital, or mixed acquired/congenital factors.

- Symptomatic treatment adequate for mild disease
- Surgery indicated when medical therapy does not allow for activities of daily living or if focal neurologic signs are present. Most pts treated surgically experience relief of back and leg pain; 25% develop recurrent stenosis within 7–10 years.

Trauma

Low back strain or *sprain* used to describe minor, self-limited injuries associated with LBP. *Vertebral fractures* from trauma result in anterior wedging or compression of vertebral bodies; burst fractures involving vertebral body and posterior spine elements can occur. Neurologic impairment common with vertebral fractures; early surgical intervention indicated. CT scans used to screen for spine disease in moderate to severe trauma; superior to routine x-rays for bony disease. Most common cause of *nontraumatic fracture* is osteoporosis; others include osteomalacia, hyperparathyroidism, hyperthyroidism, multiple myeloma, or metastatic carcinoma.

TABLE 50-1 Lumbosacral Radiculopathy: Neurologic Features

LUMBOSACRAL NERVE ROOTS	EXAMINATION FINDINGS			PAIN DISTRIBUTION
	REFLEX	SENSORY	MOTOR	
L2 ^a	—	Upper anterior thigh	Psoas (hip flexors)	Anterior thigh
L3 ^a	—	Lower anterior thigh Anterior knee	Psoas (hip flexors) Quadriceps (knee extensors) Thigh adductors	Anterior thigh, knee
L4 ^a	Quadriceps (knee)	Medial calf	Quadriceps (knee extensors) ^b Thigh adductors	Knee, medial calf Anterolateral thigh
L5 ^c	—	Dorsal surface—foot Lateral calf	Peronei (foot evertors) ^b Tibialis anterior (foot dorsiflexors) Gluteus medius (hip abductors) Toe dorsiflexors	Lateral calf, dorsal foot, posterolateral thigh, buttocks
S1 ^c	Gastrocnemius/ soleus (ankle)	Plantar surface—foot Lateral aspect—foot	Gastrocnemius/soleus (foot plantar flexors) ^b Abductor hallucis (toe flexors) ^b Gluteus maximus (hip extensors)	Bottom foot, posterior calf, posterior thigh, buttocks

^aReverse straight leg–raising sign present.

^bThese muscles receive the majority of innervation from this root.

^cStraight leg–raising sign present.

TABLE 50-2 Acute Low Back Pain: Risk Factors for an Important Structural Cause**History**

Pain worse at rest or at night
 Prior history of cancer
 History of chronic infection (especially lung, urinary tract, skin)
 History of trauma
 Incontinence
 Age >70 years
 Intravenous drug use
 Glucocorticoid use
 History of a rapidly progressive neurologic deficit

Examination

Unexplained fever
 Unexplained weight loss
 Percussion tenderness over the spine
 Abdominal, rectal, or pelvic mass
 Internal/external rotation of the leg at the hip; heel percussion sign
 Straight leg- or reverse straight leg-raising signs
 Progressive focal neurologic deficit

Spondylolisthesis

Slippage of anterior spine forward, leaving posterior elements behind; L4–L5 > L5–S1 levels; can produce LBP or radiculopathy/cauda equina syndrome ([Chap. 191](#)).

Osteoarthritis (Spondylosis)

Back pain induced by spine movement and associated with stiffness. Increases with age; radiologic findings do not correlate with severity of pain. Osteophytes or combined disc-osteophytes may cause or contribute to central spinal canal stenosis, lateral recess stenosis, or neural foraminal narrowing.

Vertebral Metastases ([Chap. 22](#))

Back pain most common neurologic symptom in pts with systemic cancer and may be presenting complaint (20%); pain typically not relieved by rest. Early diagnosis is crucial. MRI or CT-myelography demonstrates vertebral body metastasis; disk space is spared.

Vertebral Osteomyelitis

Back pain unrelieved by rest; focal spine tenderness, elevated ESR. Primary source of infection usually urinary tract, skin, or lung; IV drug abuse a risk factor. Destruction of the vertebral bodies and disk space common. Lumbar spinal epidural abscess presents as back pain and fever; examination may be normal or show radicular findings, spinal cord involvement, or cauda equina syndrome. Extent of abscess best defined by MRI.

Lumbar Adhesive Arachnoiditis

May follow inflammation within subarachnoid space; fibrosis results in clumping of nerve roots, best seen by MRI; treatment is unsatisfactory.

Immune Disorders

Ankylosing spondylitis, rheumatoid arthritis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease.

Osteoporosis

Loss of bone substance resulting from immobilization, hyperparathyroidism, chronic glucocorticoid use, other medical disorders, or increasing age (particularly in females). Sole manifestation may be back pain exacerbated by movement. Can also occur in the upper back.

Visceral Diseases

Pelvis refers pain to sacral region, lower abdomen to mid-lumbar region, upper abdomen to lower thoracic, or upper lumbar region. Local signs are absent; normal movements of the spine are painless. Rupture of an abdominal aortic aneurysm may produce isolated back pain.

Other

Chronic LBP with no clear cause; psychiatric disorders, substance abuse may be associated.

TREATMENT**Low Back Pain****ACUTE LOW BACK PAIN (ALBP)**

- Pain of <3 months duration.
- Spine infections, fractures, tumors, or rapidly progressive neurologic deficits require urgent diagnostic evaluation.
- If “risk factors” (Table 50-2) are absent, initial treatment is symptomatic and no diagnostic tests are necessary.
- When leg pain absent, prognosis is excellent; full recovery in 85%.
- Clinical trials do not show benefit from bed rest >2 days. Possible benefits of early activity—cardiovascular conditioning, disk and cartilage nutrition, bone and muscle strength, increased endorphin levels.
- Proof lacking to support physical therapy, spinal manipulation, massage, acupuncture, ultrasound, laser therapy, corsets, or traction.
- Self-application of ice or heat or use of shoe insoles is optional given low cost and risk.
- Drug treatment of ALBP includes NSAIDs and acetaminophen (**Chap. 6**).
- Muscle relaxants (cyclobenzaprine) may be useful but sedation is a common side effect.
- Opioids are not clearly superior to NSAIDs or acetaminophen for ALBP.
- No evidence to support oral or injected epidural glucocorticoids.

CHRONIC LOW BACK PAIN (CLBP)

- Pain lasting >12 weeks; differential diagnosis includes most conditions described earlier.
- Cause can be clarified by neuroimaging and EMG/nerve conduction studies; diagnosis of radiculopathy secure when results concordant with findings on neurologic examination. Treatment should not be based on neuroimaging alone: up to one-third of asymptomatic young adults have a herniated lumbar disk by CT or MRI.
- Management based on identification of underlying cause; when specific cause not found, conservative management necessary.
- Treatment measures include acetaminophen, NSAIDs, and tricyclic antidepressants.

- Evidence supports the use of exercise therapy; effective in returning some pts to work, diminishing pain, and improving walking distances.
- Cognitive-behavioral therapy may have value; long-term results unclear.
- Alternative therapies including spinal manipulation, acupuncture, and massage are frequently tried; trials are mixed as to their effectiveness.
- Epidural glucocorticoids and facet joint injections are not effective in the absence of radiculopathy.
- Surgical intervention for chronic LBP without radiculopathy is controversial, and clinical trials do not support its use.

NECK AND SHOULDER PAIN

Usually arises from diseases of the cervical spine and soft tissues of the neck; typically precipitated by movement and may be accompanied by focal tenderness and limitation of motion.

■ ETIOLOGY

Trauma to the Cervical Spine

Trauma to the cervical spine (fractures, subluxation) places spine at risk for compression; immediate immobilization of the neck is essential to minimize movement of unstable cervical spine segments.

Whiplash injury is due to trauma (usually automobile accidents) causing cervical musculoligamentous injury due to hyperflexion or hyperextension. This diagnosis is not applied to pts with fractures, disk herniation, head injury, focal neurologic findings, or altered consciousness.

Cervical Disk Disease

Herniation of a lower cervical disk is a common cause of neck, shoulder, arm, or hand pain or tingling. Neck pain (worse with movement), stiffness, and limited range of motion are common. With nerve root compression, pain may radiate into shoulder or arm. Extension and lateral rotation of the neck narrows the intervertebral foramen and may reproduce radicular symptoms (Spurling's sign). In young individuals, acute radiculopathy from a ruptured disk is often traumatic. *Subacute radiculopathy* is less likely to be related to a specific traumatic incident and may involve both disk disease and spondylosis. Clinical features of cervical nerve root lesions are summarized in [Table 50-3](#).

Cervical Spondylosis

Osteoarthritis of the cervical spine may produce neck pain that radiates into the back of the head, shoulders, or arms; can also be source of headaches in the posterior occipital region. A combined radiculopathy and myelopathy may occur. An electrical sensation elicited by neck flexion and radiating down the spine from the neck (Lhermitte's symptom) usually indicates spinal cord involvement. MRI or CT can define the anatomic abnormalities, and EMG and nerve conduction studies can quantify the severity and localize the levels of nerve root injury.

Other Causes of Neck Pain

Includes *rheumatoid arthritis* of the cervical facet joints, ankylosing spondylitis, *herpes zoster* (shingles), *neoplasms* metastatic to the spine, *infections* (osteomyelitis and epidural abscess), and *metabolic bone diseases*. Neck pain may also be referred from the heart with coronary artery ischemia (cervical angina syndrome).

Thoracic Outlet

An anatomic region containing the first rib, subclavian artery and vein, brachial plexus, clavicle, and lung apex. Injury may result in posture- or movement-induced pain around the shoulder and supraclavicular region. *True neurogenic*

TABLE 50-3 Cervical Radiculopathy: Neurologic Features

CERVICAL NERVE ROOTS	EXAMINATION FINDINGS			PAIN DISTRIBUTION
	REFLEX	SENSORY	MOTOR	
C5	Biceps	Lateral deltoid	Rhomboids ^a (elbow extends backward with hand on hip) Infraspinatus ^a (arm rotates externally with elbow flexed at the side) Deltoid ^a (arm raised laterally 30–45° from the side)	Lateral arm, medial scapula
C6	Biceps	Thumb/index finger Dorsal hand/lateral forearm	Biceps ^a (arm flexed at the elbow in supination) Pronator teres (forearm pronated)	Lateral forearm, thumb/index fingers
C7	Triceps	Middle fingers Dorsal forearm	Triceps ^a (forearm extension, flexed at elbow) Wrist/finger extensors ^a	Posterior arm, dorsal forearm, dorsal hand
C8	Finger flexors	Palmar surface of little finger Medial hand and forearm	Abductor pollicis brevis (abduction of thumb) First dorsal interosseous (abduction of index finger) Abductor digiti minimi (abduction of little finger)	Fourth and fifth fingers, medial hand and forearm
T1	Finger flexors	Axilla and medial arm	Abductor pollicis brevis (abduction of thumb) First dorsal interosseous (abduction of index finger) Abductor digiti minimi (abduction of little finger)	Medial arm, axilla

^aThese muscles receive the majority of innervation from this root.

thoracic outlet syndrome is uncommon and results from compression of the lower trunk of the brachial plexus by an anomalous band of tissue; treatment is surgical division of the band. *Arterial thoracic outlet syndrome* results from compression of the subclavian artery by a cervical rib; treatment is thrombolysis or anticoagulation, plus surgical excision of the cervical rib. *Venous thoracic outlet syndrome* is due to subclavian vein thrombosis producing swelling of the arm and pain. The vein may be compressed by a cervical rib or anomalous scalene muscle. *Disputed thoracic outlet syndrome* includes a large number of pts with chronic arm and shoulder pain of unclear cause; surgery is controversial and treatment is often unsuccessful.

Brachial Plexus and Nerves

Pain from injury to the brachial plexus or peripheral nerves can mimic pain of cervical spine origin. *Neoplastic infiltration* can produce this syndrome, as can *postradiation fibrosis* (pain less often present). *Acute brachial neuritis* consists of acute onset of severe shoulder or scapular pain followed over days by weakness of proximal arm and shoulder girdle muscles innervated by the upper brachial plexus; onset often preceded by an infection or immunization. Recovery may take up to 3 years, and full functional recovery can be expected in the majority of pts.

Shoulder

If signs of radiculopathy are absent, differential diagnosis includes mechanical shoulder pain (tendinitis, bursitis, rotator cuff tear, dislocation, adhesive capsulitis, and cuff impingement under the acromion) and referred pain (subdiaphragmatic irritation, angina, Pancoast [apical lung] tumor). Mechanical pain is often worse at night, associated with shoulder tenderness, and aggravated by abduction, internal rotation, or extension of the arm.

TREATMENT

Neck and Shoulder Pain

- Indications for cervical disk surgery are similar to those for lumbar disk; however, with cervical disease, an aggressive approach is indicated if spinal cord injury is threatened.

NECK PAIN WITHOUT RADICULOPATHY

- Spontaneous improvement is expected for most acute neck pain.
- Symptomatic treatment includes a combination of NSAIDs, acetaminophen, cold packs, or heat while awaiting spontaneous recovery. For pts kept awake by symptoms, cyclobenzaprine (5–10 mg) at night can help relieve muscle spasm and promote drowsiness.
- If not related to trauma, supervised exercise appears to be effective.
- No valid clinical evidence to support cervical fusion or cervical disk arthroplasty.
- Low-level laser therapy may be effective but additional trials are needed.
- No evidence to support radiofrequency neurotomy or cervical facet injections.

NECK PAIN WITH RADICULOPATHY

- Natural history is favorable and many will improve without specific therapy.
- NSAIDs, acetaminophen, or both with or without muscle relaxants is appropriate initial therapy. For severe symptoms, opioid analgesics can be used in the emergency room and for short courses as an outpatient.
- A short course of high dose oral glucocorticoids with a rapid taper, or epidural steroids administered under imaging guidance can be effective for acute or

subacute disk-related cervical radiculopathy, but have not been subjected to rigorous trials.

- Soft cervical collars are modestly helpful in limiting movements that exacerbate pain.
- Indications for surgery include a progressive radicular motor deficit, pain that limits function and fails to respond to conservative management, or spinal cord compression.
- *Cervical spondylosis* with bony, compressive cervical radiculopathy is generally treated with surgical decompression to interrupt the progression of neurologic signs although it is unclear if long-term outcomes are improved over medical therapy.
- Surgical options for *cervical herniated disks* consist of anterior cervical discectomy alone, laminectomy with discectomy, or discectomy with fusion. The cumulative risk of subsequent radiculopathy or myelopathy at cervical segments adjacent to the fusion is ~3% per year and 26% per decade.

51

Headache



APPROACH TO THE PATIENT

Headache

Among the most common reasons that pts seek medical attention; can be either primary or secondary (Table 51-1). First step—distinguish serious from benign etiologies. Symptoms that raise suspicion for a serious cause are listed in Table 51-2. Intensity of head pain rarely has diagnostic value; most pts who present with worst headache of their lives have migraine. Headache location can suggest involvement of local structures (temporal pain in giant cell arteritis, facial pain in sinusitis). Ruptured aneurysm (instant onset), cluster headache (peak over 3–5 min), and migraine (pain increases over minutes to hours) differ in time to peak intensity. Provocation by environmental factors suggests a benign cause.

Complete neurologic examination is important in evaluation of headache. If examination is abnormal or if serious underlying cause is suspected, an imaging study (CT or MRI) is indicated as a first step. Lumbar puncture (LP) is required

TABLE 51-1 Common Causes of Headache

PRIMARY HEADACHE		SECONDARY HEADACHE	
TYPE	%	TYPE	%
Tension-type	69	Systemic infection	63
Migraine	16	Head injury	4
Idiopathic stabbing	2	Vascular disorders	1
Exertional	1	Subarachnoid hemorrhage	<1
Cluster	0.1	Brain tumor	0.1

Source: Data from Olesen J et al: *The Headaches*. Philadelphia, Lippincott Williams & Wilkins, 2005.

TABLE 51-2 Headache Symptoms That Suggest a Serious Underlying Disorder

Sudden-onset headache
First severe headache
“Worst” headache ever
Vomiting that precedes headache
Subacute worsening over days or weeks
Pain induced by bending, lifting, cough
Pain that disturbs sleep or presents immediately upon awakening
Known systemic illness
Onset after age 55
Fever or unexplained systemic signs
Abnormal neurologic examination
Pain associated with local tenderness, e.g., region of temporal artery

when meningitis (stiff neck, fever) or subarachnoid hemorrhage (following negative imaging) is a possibility. The psychological state of the pt should also be evaluated because a relationship exists between pain and depression.

■ MIGRAINE

A benign, episodic syndrome of headache associated with other symptoms of neurologic dysfunction in varying admixtures. Second to tension-type as most common cause of headache; afflicts ~15% of women and 6% of men annually. Diagnostic criteria are listed in [Table 51-3](#). Onset usually in childhood, adolescence, or early adulthood; however, initial attack may occur at any age. Family history is often present. Women may have increased sensitivity to attacks during menstrual cycle. Classic triad: premonitory visual (scotoma or scintillations), sensory, or motor symptoms; unilateral throbbing headache; and nausea and vomiting. Most pts do not have visual aura or other premonitory symptoms. Photophobia and phonophobia are common. Vertigo may occur. Focal neurologic disturbances without headache or vomiting (migraine equivalents) may

TABLE 51-3 Simplified Diagnostic Criteria for Migraine

Repeated attacks of headache lasting 4–72 h in pts with a normal physical examination, no other reasonable cause for the headache, and:

AT LEAST 2 OF THE FOLLOWING FEATURES:

Unilateral pain
Throbbing pain
Aggravation by movement
Moderate or severe intensity

PLUS AT LEAST 1 OF THE FOLLOWING FEATURES:

Nausea/vomiting
Photophobia and phonophobia

Source: Data from the International Headache Society Classification (Headache Classification Committee of the International Headache Society, *Cephalalgia* 38:1–211, 2018).

also occur. An attack lasting 4–72 h is typical, as is relief after sleep. Attacks may be triggered by glare, bright lights, sounds, hunger, stress, physical exertion, hormonal fluctuations, lack of sleep, alcohol, or other chemical stimulation.

TREATMENT

Migraine

- *Three approaches to migraine treatment:* nonpharmacologic (such as the avoidance of pt-specific triggers; information for pts is available at www.american-migraine-foundation.org); drug treatment of acute attacks (Tables 51-4 and 51-5); and prophylaxis (Table 51-6).

TABLE 51-4 Treatment of Acute Migraine

DRUG	TRADE NAME	DOSAGE
Simple analgesics		
Acetaminophen, aspirin, caffeine	Excedrin Migraine	2 tablets or caplets q6h (max 8 per day)
NSAIDs		
Naproxen	Aleve, Anaprox, generic	220–550 mg PO bid
Ibuprofen	Advil, Motrin, Nuprin, generic	400 mg PO q3–4h
Tolfenamic acid	Clotam Rapid	200 mg PO; may repeat ×1 after 1–2 h
Diclofenac K	Cambia	50 mg PO with water
5-HT_{1B/1D} receptor agonists		
Oral		
Ergotamine 1 mg, caffeine 100 mg	Cafergot	1 or 2 tablets at onset, then one tablet q ¹ / ₂ h (max 6 per day, 10 per week)
Naratriptan	Amerge	2.5-mg tablet at onset; may repeat once after 4 h
Rizatriptan	Maxalt Maxalt-MLT	5–10-mg tablet at onset; may repeat after 2 h (max 30 mg/d)
Sumatriptan	Imitrex	50–100-mg tablet at onset; may repeat after 2 h (max 200 mg/d)
Frovatriptan	Frova	2.5-mg tablet at onset, may repeat after 2 h (max 5 mg/d)
Almotriptan	Axert	12.5-mg tablet at onset, may repeat after 2 h (max 25 mg/d)
Eletriptan	Relpax	40 or 80 mg
Zolmitriptan	Zomig Zomig Rapimelt	2.5-mg tablet at onset; may repeat after 2 h (max 10 mg/d)
Nasal		
Dihydroergotamine	Migranal Nasal Spray	Prior to nasal spray, the pump must be primed 4 times; 1 spray (0.5 mg) is administered, followed in 15 min by a second spray

(Continued)

TABLE 51-4 Treatment of Acute Migraine (Continued)

DRUG	TRADE NAME	DOSAGE
Sumatriptan	Imitrex Nasal Spray	5–20 mg intranasal spray as 4 sprays of 5 mg or a single 20 mg spray (may repeat once after 2 h, not to exceed a dose of 40 mg/d)
Zolmitriptan	Zomig	5 mg intranasal spray as one spray (may repeat once after 2 h, not to exceed a dose of 10 mg/d)
Parenteral		
Dihydroergotamine	DHE-45	1 mg IV, IM, or SC at onset and q1h (max 3 mg/d, 6 mg per week)
Sumatriptan	Imitrex Injection Alsuma Sumavel DosePro	6 mg SC at onset (may repeat once after 1 h for max of 2 doses in 24 h)
Dopamine receptor antagonists		
Oral		
Metoclopramide	Reglan, ^a generic ^a	5–10 mg/d
Prochlorperazine	Compazine, ^a generic ^a	1–25 mg/d
Parenteral		
Chlorpromazine	Generic ^a	0.1 mg/kg IV at 2 mg/min; max 35 mg/d
Metoclopramide	Reglan, ^a generic	10 mg IV
Prochlorperazine	Compazine, ^a generic ^a	10 mg IV
Other		
Oral		
Acetaminophen, 325 mg, <i>plus</i> dichloralphenazone, 100 mg, <i>plus</i> isometheptene, 65 mg	Midrin, generic	Two capsules at onset followed by 1 capsule q1h (max 5 capsules)
Parenteral		
Opioids	Generic ^a	Multiple preparations and dosages; see Table 6-2
Other		
Neuromodulation Noninvasive Vagus Nerve Stimulation (nVNS) Single pulse transcranial magnetic stimulation (sTMS)	SpringTMS gammaCore	Two pulses at onset followed by two further pulses Two doses each of 120 seconds

^aNot all drugs are specifically indicated by the FDA for migraine. Local regulations and guidelines should be consulted.

Note: Antiemetics (e.g., domperidone 10 mg or ondansetron 4 or 8 mg) or prokinetics (e.g., metoclopramide 10 mg) are sometimes useful adjuncts.

Abbreviations: 5-HT, 5-hydroxytryptamine; NSAIDs, nonsteroidal anti-inflammatory drugs.

TABLE 51-5 Clinical Stratification of Acute Specific Migraine Treatments

CLINICAL SITUATION	TREATMENT OPTIONS
Failed NSAIDs/analgesics	<p>First tier</p> <p>Sumatriptan 50 mg or 100 mg PO Almotriptan 12.5 mg PO Rizatriptan 10 mg PO Eletriptan 40 mg PO Zolmitriptan 2.5 mg PO</p> <p>Slower effect/better tolerability</p> <p>Naratriptan 2.5 mg PO Frovatriptan 2.5 mg PO</p> <p>Infrequent headache</p> <p>Ergotamine/caffeine 1–2/100 mg PO Dihydroergotamine nasal spray 2 mg</p>
Early nausea or difficulties taking tablets	<p>Zolmitriptan 5 mg nasal spray Sumatriptan 20 mg nasal spray Rizatriptan 10 mg MLT wafer</p>
Headache recurrence	<p>Ergotamine 2 mg (most effective PR/usually with caffeine) Naratriptan 2.5 mg PO Almotriptan 12.5 mg PO Eletriptan 40 mg</p>
Tolerating acute treatments poorly	<p>Naratriptan 2.5 mg Almotriptan 12.5 mg Single pulse transcranial magnetic stimulation Noninvasive vagus nerve stimulation</p>
Early vomiting	<p>Zolmitriptan 5 mg nasal spray Sumatriptan 25 mg PR Sumatriptan 6 mg SC</p>
Menses-related headache	<p>Prevention</p> <p>Ergotamine PO at night Estrogen patches</p> <p>Treatment</p> <p>Triptans Dihydroergotamine nasal spray</p>
Very rapidly developing symptoms	<p>Zolmitriptan 5 mg nasal spray Sumatriptan 6 mg SC Dihydroergotamine 1 mg IM</p>

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

- Drug treatment necessary for most migraine pts, but avoidance or management of environmental triggers alone is sufficient for some.
- General principles of pharmacologic treatment:
 - Response rates vary from 50% to 70%.
 - Initial drug choice is empirical and individualized—influenced by age, coexisting illnesses, and side effect profile.

TABLE 51-6 Preventive Treatments in Migraine^a

DRUG	DOSE	SELECTED SIDE EFFECTS
Beta blocker Propranolol Metoprolol	40–120 mg bid 25–100 mg bid	Reduced energy Tiredness Postural symptoms Contraindicated in asthma
Antidepressants Amitriptyline Dosulepin Nortriptyline	10–75 mg at night 25–75 mg at night 25–75 mg at night	Drowsiness Note: Some pts may only need a total dose of 10 mg, although generally 1–1.5 mg/kg body weight is required
Venlafaxine	75–150 mg/d	
Anticonvulsants Topiramate	25–200 mg/d	Paresthesias Cognitive symptoms Weight loss Glaucoma Caution with nephrolithiasis
Valproate	400–600 mg bid	Drowsiness Weight gain Tremor Hair loss Fetal abnormalities Hematologic or liver abnormalities
Calcitonin gene-related peptide (CGRP) monoclonal antibodies Erenumab-aooe Fremanezumab	140 mg monthly SQ injection 675 mg quarterly SQ injection or 225 mg monthly SQ injection	Injection site reactions Injection site reactions
Serotonergic drugs Pizotifen ^b	0.5–2 mg qd	Weight gain Drowsiness
Other classes Flunarizine ^b	5–15 mg qd	Drowsiness Weight gain Depression Parkinsonism
Candesartan	4–24 mg daily	Dizziness

(Continued)

TABLE 51-6 Preventive Treatments in Migraine^a (Continued)

DRUG	DOSE	SELECTED SIDE EFFECTS
Neuromodulation Single pulse transcranial magnetic stimulation (sTMS)	4–24 pulses per day	Lightheadedness Tingling Tinnitus
Chronic migraine Onabotulinum toxin type A	155 U	Loss of brow furrow
No convincing evidence from controlled trials Verapamil		
Controlled trials demonstrate <i>no effect</i> Nimodipine Clonidine Selective serotonin reuptake inhibitors: fluoxetine		

^aCommonly used preventives are listed with typical doses and common side effects. Not all listed medicines are approved by the U.S. Food and Drug Administration; local regulations and guidelines should be consulted.

^bNot available in the United States.

- Efficacy of prophylactic treatment may take several months to assess with each drug.
- When an acute attack requires additional medication 60 min after the first dose, then the initial drug dose should be increased for subsequent attacks or another class of drug tried.
- Mild to moderate acute migraine attacks often respond to over-the-counter (OTC) NSAIDs when taken early.
- Triptans are widely used and have many formulations.
- There is likely less frequent headache recurrence when using ergots, but more frequent nausea.
- For prophylaxis, tricyclic antidepressants are a good first choice for young people with difficulty falling asleep; verapamil is often a first choice for prophylaxis in the elderly.
- Monoclonal antibodies to calcitonin gene-related peptide (CGRP) or its receptor have been reported to be effective and well-tolerated in chronic migraine and have recently been approved for this purpose.

Tension-Type Headache

Common in all age groups. Pain is described as bilateral tight, bandlike discomfort. May persist for hours or days; usually builds slowly.

- Pain can be managed generally with simple analgesics such as acetaminophen, aspirin, or NSAIDs.
- Often related to stress; responds to behavioral approaches including relaxation.
- Amitriptyline may be helpful for chronic tension-type headache prophylaxis.

Cluster Headache

Rare form of primary headache; population frequency ~0.1%. Characterized by episodes of recurrent, deep, unilateral, retroorbital searing pain. Unilateral lacrimation and nasal and conjunctival congestion may be present. Visual complaints, nausea, or vomiting is rare. Unlike migraine, pts with cluster tend to move about during attacks. A core feature is periodicity. Typically, daily bouts of one to two attacks of relatively short-duration unilateral pain for 8–10 weeks a year; usually followed by a pain-free interval that averages a little less than a year. Alcohol may provoke attacks.

- Prophylaxis with verapamil (40–80 mg twice daily to start; effective doses may be as high as 960 mg/d), lithium (400–800 mg/d), or prednisone (1 mg/kg up to 60 mg/d for 7 days followed by a taper over 21 days).
- High-flow oxygen (10–12 L/min for 15–20 min) or sumatriptan (6 mg SC or 20-mg nasal spray) is useful for the acute attack.
- Deep-brain stimulation of the posterior hypothalamic gray matter is successful for refractory cases as is the less-invasive approaches of occipital nerve stimulation and sphenopalatine ganglion stimulation with an implanted battery-free stimulator.

Post-Traumatic Headache

Common following motor vehicle accidents, other head trauma; severe injury or loss of consciousness often not present. Symptoms of headache, dizziness, vertigo, impaired memory, poor concentration, irritability; typically remits after several weeks to months. Neurologic examination and neuroimaging studies normal. Not a functional disorder; cause unknown and treatment usually not satisfactory.

Lumbar Puncture Headache

Typical onset within 48 h after LP but may be delayed for up to 12 days; follows 10–30% of LPs. Positional: onset when pt sits or stands, relief by lying flat. Most cases remit spontaneously in ≤ 1 week. Oral or IV caffeine (500 mg IV over 2 h) successful in many; epidural blood patch effective immediately in refractory cases.

Indomethacin-Responsive Headaches

A diverse set of disorders that respond often exquisitely to indomethacin (25 mg two to three times daily). Includes:

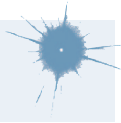
- *Paroxysmal hemicrania*: Frequent unilateral, severe, short-lasting episodes of headache that are often retroorbital and associated with autonomic phenomena such as lacrimation and nasal congestion.
- *Hemicrania continua*: Moderate and continuous unilateral pain associated with fluctuations of severe pain that may be associated with autonomic features.
- *Primary stabbing headache*: Stabbing pain confined to the head or rarely the face lasting from 1 to many seconds or minutes.
- *Primary cough headache*: Transient severe head pain with coughing, bending, lifting, sneezing, or stooping; lasts for several minutes. Usually benign, but posterior fossa mass lesion in some pts; therefore consider brain MRI.
- *Primary exertional headache*: Features similar to cough headache and migraine, but precipitated by any form of exercise.

■ FACIAL PAIN

Most common cause of facial pain is dental; triggered by hot, cold, or sweet foods. Exposure to cold repeatedly induces dental pain. Trigeminal neuralgia consists of paroxysmal, electric shock—like episodes of pain in the distribution of trigeminal nerve; occipital neuralgia presents as lancinating occipital pain. These disorders are discussed in [Chap. 190](#).

52

Syncope



Syncope is a transient, self-limited loss of consciousness due to acute global impairment of cerebral blood flow. It may occur suddenly, without warning, or may be preceded by presyncopal symptoms such as light-headedness or faintness, weakness, fatigue, nausea, dimming vision, ringing in ears, or sweating. The syncopal pt appears pale and has a faint, rapid, or irregular pulse. Breathing may be almost imperceptible; brief myoclonic or clonic movements may occur. Recovery of consciousness is prompt and complete if pt is maintained in a horizontal position and cerebral perfusion is restored.

APPROACH TO THE PATIENT

Syncope

The cause may be apparent only at the time of the event, leaving few, if any, clues when the pt is seen by the physician. Other disorders must be distinguished from syncope, including seizures, vertebrobasilar ischemia, hypoxemia, and hypoglycemia (see below). First consider serious underlying etiologies; among these are massive internal hemorrhage, myocardial infarction (can be painless), and cardiac arrhythmias. In elderly pts, a sudden faint without obvious cause should raise the question of complete heart block or a tachyarrhythmia. Loss of consciousness in particular situations, such as during venipuncture or micturition, suggests a benign abnormality of vascular tone. The position of the pt at the time of the syncopal episode is important; syncope in the supine position is unlikely to be vasovagal and suggests arrhythmia or seizure. Medications must be considered, including nonprescription drugs or health store supplements, with particular attention to recent changes. Symptoms of impotence, bowel and bladder difficulties, disturbed sweating, or an abnormal neurologic examination suggest a primary neurogenic cause. An algorithmic approach is presented in [Fig. 52-1](#).

■ ETIOLOGY

Syncope is usually due to a neurally mediated disorder, orthostatic hypotension, or an underlying cardiac condition ([Table 52-1](#)). Not infrequently the cause is multifactorial.

Neurocardiogenic (Vasovagal and Vasodepressor) Syncope

The common faint, experienced by normal persons, accounts for approximately half of all episodes of syncope. It is frequently recurrent and may be provoked by hot or crowded environment, alcohol, fatigue, pain, hunger, prolonged standing, or stressful situations.

Postural (Orthostatic) Hypotension

Sudden rising from a recumbent position or standing quietly is a precipitating circumstance. Cause of syncope in many elderly and incidence rises with age; polypharmacy with antihypertensive or antidepressant drugs often a contributor; physical deconditioning may also play a role. Also occurs with autonomic nervous system disorders, either peripheral (diabetes mellitus, nutritional, or amyloid polyneuropathy) or central (multiple system atrophy, Parkinson's disease). Some cases are idiopathic.

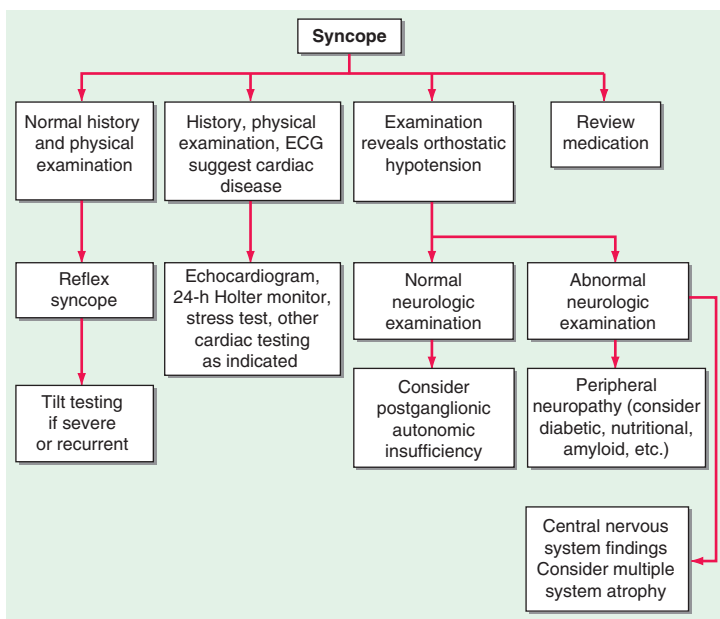


FIGURE 52-1 Approach to the pt with syncope.

TABLE 52-1 Causes of Syncope

A. Neurally Mediated Syncope

Vasovagal syncope

Provoked fear, pain, anxiety, intense emotion, sight of blood, unpleasant sights and odors, orthostatic stress

Situational reflex syncope

Pulmonary

Cough syncope, wind instrument player's syncope, weightlifter's syncope, "mess trick"^a and "fainting lark,"^b sneeze syncope, airway instrumentation

Urogenital

Postmicturition syncope, urogenital tract instrumentation, prostatic massage

Gastrointestinal

Swallow syncope, glossopharyngeal neuralgia, esophageal stimulation, gastrointestinal tract instrumentation, rectal examination, defecation syncope

Cardiac

Bezold-Jarisch reflex, cardiac outflow obstruction

Carotid sinus

Carotid sinus sensitivity, carotid sinus massage

Ocular

Ocular pressure, ocular examination, ocular surgery

(Continued)

TABLE 52-1 Causes of Syncope (Continued)**B. Orthostatic Hypotension**

Primary autonomic failure due to idiopathic central and peripheral neurodegenerative diseases—the “synucleinopathies”

Lewy body diseases

Parkinson's disease

Lewy body dementia

Pure autonomic failure

Multiple system atrophy (Shy-Drager syndrome)

Secondary autonomic failure due to autonomic peripheral neuropathies

Diabetes

Hereditary amyloidosis (familial amyloid polyneuropathy)

Primary amyloidosis (AL amyloidosis; immunoglobulin light chain associated)

Hereditary sensory and autonomic neuropathies (HSAN) (especially type III—familial dysautonomia)

Idiopathic immune-mediated autonomic neuropathy

Autoimmune autonomic ganglionopathy

Sjögren's syndrome

Paraneoplastic autonomic neuropathy

HIV neuropathy

Postprandial hypotension

Iatrogenic (drug-induced)

Volume depletion

C. Cardiac Syncope

Arrhythmias

Sinus node dysfunction

Atrioventricular dysfunction

Supraventricular tachycardias

Ventricular tachycardias

Inherited channelopathies

Cardiac structural disease

Valvular disease

Myocardial ischemia

Obstructive and other cardiomyopathies

Atrial myxoma

Pericardial effusions and tamponade

^aHyperventilation for ~1 min, followed by sudden chest compression.

^bHyperventilation (~20 breaths) in a squatting position, rapid rise to standing, then Valsalva.

DIFFERENTIAL DIAGNOSIS**Seizures**

The differential diagnosis is often between syncope and a generalized seizure. Syncope is more likely if the event was provoked by acute pain or emotion or occurred immediately after arising from a lying or sitting position; seizures are typically not related to posture. Pts with syncope often describe a stereotyped transition from consciousness to unconsciousness that develops over a few seconds.

Seizures either occur very abruptly without a transition or are preceded by premonitory symptoms such as an epigastric rising sensation, perception of odd odors, or racing thoughts. Pallor is seen during syncope; cyanosis is usually seen during a seizure. The duration of unconsciousness is usually very brief (i.e., seconds) in syncope and more prolonged (i.e., >5 min) in a seizure. Injury from falling and incontinence are common in seizure, rare in syncope. Whereas tonic-clonic movements are the hallmark of a generalized seizure, myoclonic and other movements also occur in up to 90% of syncopal episodes and eyewitnesses will often have a difficult time distinguishing between the two etiologies.

Hypoglycemia

Severe hypoglycemia is usually due to a serious disease or insulin use. Hunger is a premonitory feature that is not typical in syncope. The glucose level at the time of a spell is diagnostic.

Cataplexy

Abrupt partial or complete loss of muscular tone triggered by strong emotions; occurs in 60–75% of narcolepsy pts. Unlike syncope, consciousness is maintained throughout the attacks that typically last between 30 s and 2 min. No premonitory symptoms.

Psychiatric Disorders

Apparent loss of consciousness can be present in generalized anxiety, panic disorders, major depression, and somatization disorder. Frequently resembles presyncope, although the symptoms are not accompanied by prodromal symptoms and are not relieved by recumbency. Attacks can often be reproduced by hyperventilation and have associated symptoms of panic attacks such as a feeling of impending doom, air hunger, palpitations, and tingling of the fingers and perioral region. Such pts are rarely injured despite numerous falls. There are no clinically significant hemodynamic changes.

TREATMENT

Syncope

Therapy is determined by the underlying cause.

- Pts with neurally mediated syncope should be reassured and instructed to avoid situations or stimuli that provoke attacks. Plasma volume expansion should occur with fluid and salt.
- Drug therapy may be necessary for resistant neurally-mediated syncope. Fludrocortisone, vasoconstricting agents, and β -adrenergic antagonists are widely used although there is no consistent evidence from randomized trials.
- Pts with orthostatic hypotension should first be treated with removal of vasoactive medications. Then consider nonpharmacologic (pt education regarding moves from supine to upright, increasing fluids and salt in diet) and finally pharmacologic methods such as fludrocortisone and vasoconstricting agents such as midodrine, L-dihydroxyphenylserine, and pseudoephedrine.
- Management of cardiac causes depends in the underlying disorder. Cardiac pacing or cardioverter-defibrillator implantation is sometimes necessary.
- Management of refractory orthostatic hypotension is discussed in [Chap. 189](#).

53

Dizziness and Vertigo



APPROACH TO THE PATIENT

Dizziness or Vertigo

The term *dizziness* is used by pts to describe a variety of common sensations that include vertigo, light-headedness, faintness, and imbalance. With a careful history, distinguishing between *faintness* (presyncope; [Chap. 52](#)) and *vertigo* (a sense of movement of the body or the environment, most often a feeling of spinning) is usually possible.

When the meaning of *dizziness* is uncertain, provocative tests to reproduce the symptoms may be helpful. Valsalva maneuver, hyperventilation, or postural changes leading to orthostasis may reproduce faintness. Rapid rotation in a swivel chair is a simple provocative test to reproduce vertigo.

Benign positional vertigo is identified by the Dix-Hallpike maneuver to elicit vertigo and the characteristic nystagmus; the pt begins in a sitting position with head turned 45°; holding the back of the head, the examiner gently lowers the pt to supine position with head extended backward 20° and observes for nystagmus; after 30 s the pt is raised to sitting position and after 1 min rest the maneuver is repeated on other side.

The most useful bedside test of peripheral vestibular function is the *head impulse test*, in which the vestibuloocular reflex (VOR) is assessed with small-amplitude (~20 degrees) rapid head rotations. While the pt fixates on a target, the head is rotated to the left or right. If the VOR is deficient (e.g., in peripheral vertigo), the rotation is followed by a catch-up saccade in the opposite direction (e.g., a leftward saccade after a rightward rotation).

If a central cause for the vertigo is suspected (e.g., no signs of peripheral vertigo, no hearing loss, no ear sensations, or the presence of other neurologic abnormalities indicating central nervous system [CNS] disease), then prompt evaluation for central pathology is required. The initial test is usually an MRI scan of the posterior fossa. Distinguishing between central and peripheral etiologies can be accomplished with vestibular function tests, including videonystagmography and simple bedside examinations including the head impulse test and *dynamic visual acuity* (measure acuity at rest and with head rotated back and forth by the examiner; a drop in acuity of more than one line on a near card or Snellen chart indicates vestibular dysfunction).

■ FAINTNESS

Faintness is usually described as light-headedness followed by visual blurring and postural swaying along with a feeling of warmth, diaphoresis, and nausea. It is a symptom of insufficient blood, oxygen, or, rarely, glucose supply to the brain. It can occur prior to a syncopal event of any etiology ([Chap. 52](#)) and with hyperventilation or hypoglycemia. Light-headedness can rarely occur during an aura before a seizure. Chronic light-headedness is a common somatic complaint with depression.

■ VERTIGO

Usually due to a disturbance in the vestibular system; abnormalities in the visual or somatosensory systems may also contribute to vertigo. Frequently accompanied by nausea, postural unsteadiness, and gait ataxia; may be provoked or worsened by head movement.

TABLE 53-1 Features of Peripheral and Central Vertigo

- Nystagmus from an acute peripheral lesion is unidirectional, with fast phases beating away from the ear with the lesion. Nystagmus that changes direction with gaze is due to a central lesion.
- Transient mixed vertical-torsional nystagmus occurs in benign paroxysmal positional vertigo (BPPV), but pure vertical or pure torsional nystagmus is a central sign.
- Nystagmus from a peripheral lesion may be inhibited by visual fixation, whereas central nystagmus is not suppressed.
- Absence of a head impulse sign in a pt with acute prolonged vertigo should suggest a central cause.
- Unilateral hearing loss suggests peripheral vertigo. Findings such as diplopia, dysarthria, and limb ataxia suggest a central disorder.

Physiologic vertigo results from unfamiliar head movement (seasickness) or a mismatch between visual-proprioceptive-vestibular system inputs (height vertigo, visual vertigo during motion picture chase scenes). *Pathologic vertigo* may be caused by a peripheral (labyrinth or eighth nerve) or central CNS lesion. Distinguishing between these causes is the essential first step in diagnosis (Table 53-1) as only central lesions require urgent imaging, usually with MRI.

Peripheral Vertigo

Usually severe, accompanied by nausea and emesis. Tinnitus, a feeling of ear fullness, or hearing loss may occur. A characteristic jerk nystagmus is almost always present. The nystagmus does not change direction with a change in direction of gaze; it is usually horizontal with a torsional component and has its fast phase away from the side of the lesion. It is inhibited by visual fixation. The pt senses spinning motion away from the lesion and tends to have difficulty walking, with falls toward the side of the lesion, particularly in the darkness or with eyes closed. No other neurologic abnormalities are present.

Acute prolonged vertigo may be caused by infection, trauma, or ischemia. Often no specific etiology is found, and the term *acute labyrinthitis* (or *vestibular neuritis*) is used to describe the event. Acute bilateral labyrinthine dysfunction is usually due to drugs (aminoglycoside antibiotics), alcohol, or a neurodegenerative disorder. Recurrent labyrinthine dysfunction with signs and symptoms of cochlear disease is usually due to *Ménière's disease* (recurrent vertigo accompanied by tinnitus and deafness). Positional vertigo is usually precipitated by a recumbent head position; *benign paroxysmal positional vertigo* (BPPV) of the posterior semicircular canal is particularly common; the pattern of nystagmus is distinctive. BPPV may follow trauma but is usually idiopathic; it generally abates spontaneously after weeks or months. *Vestibular schwannomas* of the eighth cranial nerve (acoustic neuroma) usually present with hearing loss and tinnitus, sometimes accompanied by facial weakness and sensory loss due to involvement of cranial nerves VII and V. *Psychogenic vertigo* should be suspected in pts with chronic incapacitating vertigo who also have agoraphobia, panic attacks, a normal neurologic examination, and no nystagmus.

Central Vertigo

Identified by associated brainstem or cerebellar signs such as dysarthria, diplopia, dysphagia, hiccups, other cranial nerve abnormalities, weakness, or limb ataxia; depending on the cause, headache may be present. The nystagmus can take almost any form (i.e., vertical or multidirectional) but is often purely horizontal without a torsional component and changes direction with different directions

of gaze. Central nystagmus is not inhibited by fixation. Central vertigo may be chronic, mild, and is usually not accompanied by tinnitus or hearing loss. It may be due to vascular, demyelinating, neurodegenerative, or neoplastic disease. Vertigo may be a manifestation of migraine or, rarely, of temporal lobe epilepsy.

TREATMENT

Vertigo

- Treatment of acute vertigo consists of vestibular suppressant drugs for short-term relief (Table 53-2). They may hinder central compensation, prolonging the duration of symptoms, and therefore should be used sparingly and for a short period of time.
- Vestibular rehabilitation promotes central adaptation processes and may habituate motion sensitivity and other symptoms of psychosomatic dizziness. The general approach is to use a graded series of exercises that progressively challenge gaze stabilization and balance.

TABLE 53-2 Treatment of Vertigo

AGENT ^a	DOSE ^b
Antihistamines	
Meclizine	25–50 mg 3 times daily
Dimenhydrinate	50 mg 1–2 times daily
Promethazine	25 mg 2–3 times daily (also can be given rectally and IM)
Benzodiazepines	
Diazepam	2.5 mg 1–3 times daily
Clonazepam	0.25 mg 1–3 times daily
Anticholinergic	
Scopolamine transdermal ^c	Patch
Physical therapy	
Repositioning maneuvers ^d	
Vestibular rehabilitation	
Other	
Diuretics and/or low-sodium (1000 mg/d) diet ^e	
Antimigrainous drugs ^f	
Methylprednisolone ^g	100 mg daily days 1–3; 80 mg daily days 4–6; 60 mg daily days 7–9; 40 mg daily days 10–12; 20 mg daily days 13–15; 10 mg daily days 16–18, 20, 22
Selective serotonin reuptake inhibitors ^h	

^aAll listed drugs are approved by the U.S. Food and Drug Administration, but most are not approved for the treatment of vertigo.

^bUsual oral (unless otherwise stated) starting dose in adults; a higher maintenance dose can be reached by a gradual increase.

^cFor motion sickness only.

^dFor benign paroxysmal positional vertigo.

^eFor Ménière's disease.

^fFor vestibular migraine.

^gFor acute vestibular neuritis (started within 3 days of onset).

^hFor persistent postural-perceptual vertigo and anxiety.

- BPPV may respond dramatically to repositioning exercises such as the Epley maneuver designed to empty particulate debris from the posterior semicircular canal (<http://www.dizziness-and-balance.com/disorders/bppv/movies/Epley-480x640.avi>).
- For vestibular neuritis, antiviral medications are of no proven benefit unless herpes zoster oticus is present. Some data suggest that glucocorticoids improve the likelihood of recovery in vestibular neuritis if given within 3 days of symptom onset.
- Ménière's disease may respond to a low-salt diet (1 g/d) or to a diuretic. Otolaryngology referral is recommended.
- Recurrent episodes of migraine-associated vertigo should be treated with anti-migraine therapy (**Chap. 51**).

54

Acute Visual Loss and Double Vision



APPROACH TO THE PATIENT

Acute Visual Loss or Double Vision

Accurate measurement of visual acuity in each eye (with glasses or contact lenses) is of primary importance. Additional assessments include testing of pupils, eye movements, ocular alignment, and visual fields. Slit-lamp examination can exclude corneal infection, trauma, glaucoma, uveitis, and cataract. Ophthalmoscopic examination to inspect the optic disc and retina often requires pupillary dilation using 1% tropicamide and 2.5% phenylephrine; risk of provoking an attack of narrow-angle glaucoma is remote.

Visual field mapping by finger confrontation localizes lesions in the visual pathway (**Fig. 54-1**); formal testing using a perimeter may be necessary. The goal is to determine whether the lesion is anterior to, at, or posterior to the optic chiasm. A scotoma confined to one eye is caused by an anterior lesion affecting the optic nerve or globe; swinging flashlight test may reveal an afferent pupil defect (APD). History and ocular examination are usually sufficient for diagnosis. If a bitemporal hemianopia is present, lesion is located at optic chiasm (e.g., pituitary adenoma, meningioma). Homonymous visual field loss signals a retrochiasmatic lesion affecting the optic tract, lateral geniculate body, optic radiations, or visual cortex (e.g., stroke, tumor, abscess). Neuroimaging is recommended for any pt with a bitemporal or homonymous hemianopia.

■ TRANSIENT OR SUDDEN VISUAL LOSS

Amaurosis fugax (*transient monocular blindness*; a TIA of the retina) usually occurs from a retinal embolus often arising from ipsilateral carotid stenosis or the heart. Prolonged occlusion of the central retinal artery results in classic fundus appearance of a milky, infarcted retina with cherry red fovea. Any pt with compromise of the retinal circulation should be evaluated promptly for stroke risk factors (e.g., carotid atheroma, structural heart disease, atrial fibrillation). *Occipital*

OPTIC NERVE OR RETINA



Central
scotoma

(Optic neuritis;
macular degeneration)



Arcuate
scotoma

(AION, glaucoma, branch retinal
artery or vein occlusion)



Altitudinal
field
defect

(AION; retinal artery branch
occlusion; optic neuritis)



Centrocecal
scotoma

(Optic neuritis; toxic, nutritional,
or hereditary optic neuropathy)



Generalized
constriction

(Papilledema,
retinitis pigmentosa)

OPTIC CHIASM

Left

Right



Bitemporal
hemianopia

(Optic chiasm
compression by
pituitary tumor,
meningioma)

RETRO-CHIASMAL PATHWAY



Right homonymous
hemianopia

(Lesion of left optic tract,
lateral geniculate
body, optic radiations,
or visual cortex)



Superior right
quadrantanopia
("Pie in the Sky")

(Lesion of left optic
radiations in
temporal lobe)



Macular
sparing

(Bilateral visual
cortex lesions)

FIGURE 54-1 Deficits in visual fields caused by lesions affecting visual pathways.

cortex lesions can be confused with amaurosis fugax because many pts mistakenly ascribe symptoms to their left or right eye when in fact they are occurring in the left or right hemifield of both eyes. Interruption of blood flow to the visual cortex causes sudden graying of vision, occasionally with flashing lights or other symptoms that mimic *migraine*. The history may be the only guide to the correct diagnosis. Pts should be questioned about the precise pattern and duration of visual loss and other neurologic symptoms, especially those of posterior circulation dysfunction such as diplopia, vertigo, numbness, or weakness.

Marked *systemic hypertension* can cause visual loss from exudates, hemorrhages, cotton-wool spots (focal nerve fiber layer infarcts), and optic disc edema.

In central or branch *retinal vein occlusion*, the fundus examination reveals engorged, phlebitic veins with extensive retinal hemorrhages.

In age-related *macular degeneration*, characterized by extensive drusen and scarring of the pigment epithelium, leakage of blood or fluid from subretinal neovascular membranes can produce sudden central visual loss.

Flashing lights and floaters may indicate a fresh *vitreous detachment*. Separation of the vitreous from the retina is a frequent involuntional event in the elderly. It is not harmful unless it creates sufficient traction to produce a *retinal detachment*. *Vitreous hemorrhage* may occur in diabetic pts from retinal neovascularization.

Papilledema refers to optic disc edema from raised intracranial pressure. Transient visual obscurations are common, but visual acuity is not affected unless the papilledema is severe, long-standing, or accompanied by macular exudates or hemorrhage. Enlarged blind spots and peripheral constriction are typical. Neuroimaging should be obtained to exclude an intracranial mass. If negative, an LP is required to confirm elevation of the intracranial pressure. *Pseudotumor cerebri* (idiopathic intracranial hypertension) is a diagnosis of exclusion. Most pts are female and obese; some are found to have occult cerebral venous sinus thrombosis. Treatment is with acetazolamide, repeated LPs, and weight loss (via bariatric surgery if necessary); some pts require lumboperitoneal shunting to prevent blindness.

Optic neuritis is a common cause of monocular optic disc swelling and visual loss. If site of inflammation is retrobulbar, fundus will appear normal on initial examination. The typical pt is female, age 15–45, with pain provoked by eye movements. Glucocorticoids, typically IV methylprednisolone (1 g daily for 3 days) followed by oral prednisone (1 mg/kg per day for 11 days), may hasten recovery in severely affected pts but make no difference in final acuity (measured 6 months after the attack). If an MRI shows multiple demyelinating lesions, treatment for multiple sclerosis ([Chap. 192](#)) should be considered. Optic neuritis involving both eyes simultaneously or sequentially suggests neuromyelitis optica ([Chap. 193](#)).

Anterior ischemic optic neuropathy (AION) is an infarction of the optic nerve head due to inadequate perfusion via the posterior ciliary arteries. Pts have sudden visual loss, often noted on awakening, and painless swelling of the optic disc. It is important to differentiate between nonarteritic (idiopathic) AION and arteritic AION. There is no treatment for nonarteritic AION and glucocorticoids should not be prescribed. In contrast, arteritic AION is caused by *giant cell (temporal) arteritis* and requires immediate glucocorticoid therapy to prevent blindness; temporal artery biopsy establishes the diagnosis. The ESR and C-reactive protein should be checked in any elderly pt with acute optic disc swelling or symptoms suggestive of polymyalgia rheumatica (associated with arteritic AION).

■ DOUBLE VISION (DIPLOPIA)

First step: clarify whether diplopia persists in either eye after covering the opposite eye; if it does, the diagnosis is monocular diplopia usually caused by disease intrinsic to the eye with no dire implications for the pt. Occasionally it is a symptom of malingering or psychiatric disease.

If the pt has diplopia while being examined, motility testing will usually reveal an abnormality in ocular excursions. However, if the degree of angular separation between the double images is small, the limitation of eye movements may be subtle and difficult to detect. In this situation, the cover test is useful. While the pt is fixating upon a distant target, one eye is covered while observing the other eye for a movement of redress as it takes up fixation. If none is seen, the

TABLE 54-1 Common Causes of Diplopia

Brainstem stroke (skew deviation, nuclear or fascicular palsy)
Microvascular infarction (III, IV, VI nerve palsy)
Tumor (brainstem, cavernous sinus, superior orbital fissure, orbit)
Multiple sclerosis (internuclear ophthalmoplegia, ocular motor nerve palsy)
Aneurysm (III nerve)
Raised intracranial pressure (VI nerve)
Postviral inflammation
Meningitis (bacterial, fungal, granulomatous, neoplastic)
Carotid-cavernous fistula or thrombosis
Herpes zoster
Tolosa-Hunt syndrome
Wernicke-Korsakoff syndrome
Botulism
Myasthenia gravis
Guillain-Barré or Fisher syndrome
Graves' disease
Orbital pseudotumor
Orbital myositis
Trauma
Orbital cellulitis

procedure is repeated with the other eye. With genuine diplopia, this test should reveal ocular malalignment, especially if the head is turned or tilted in the position that gives rise to the worst symptoms.

Common causes of diplopia are summarized in [Table 54-1](#). The physical findings in isolated ocular motor nerve palsies are:

- **CN III:** Ptosis and deviation of the eye down and outwards, causing vertical and horizontal diplopia. A dilated pupil suggests direct compression of the third nerve; if present, the possibility of an aneurysm of the posterior communicating artery must be considered urgently. If pupil is spared, a microvascular infarction is likely the cause, especially in pts with diabetes or hypertension.
- **CN IV:** Vertical diplopia with cyclotorsion; the affected eye is slightly elevated, and limitation of depression is seen when the eye is held in adduction. The pt may assume a head tilt to the opposite side (e.g., left head tilt in right fourth nerve paresis).
- **CN VI:** Horizontal diplopia worse on gaze to the side of the lesion; the affected eye cannot abduct.

The development of multiple ocular motor nerve palsies, or diffuse ophthalmoplegia, raises the possibility of myasthenia gravis. In this disease, the pupils are always normal. Systemic weakness may be absent. Multiple ocular motor nerve palsies should be investigated with neuroimaging focusing on the cavernous sinus, superior orbital fissure, and orbital apex where all three nerves are in close proximity. Diplopia that cannot be explained by a single ocular motor nerve palsy may also be caused by meningitis (often carcinomatous or fungal), Graves' disease, Guillain-Barré syndrome (especially Miller Fisher syndrome), or Tolosa-Hunt syndrome (painful granulomatous inflammation of the cavernous sinus).

55

Weakness and Paralysis



APPROACH TO THE PATIENT

Weakness or Paralysis

Weakness is a reduction of power in one or more muscles. *Paralysis* indicates weakness that is so severe that the muscle cannot be contracted at all, whereas *paresis* refers to less severe weakness. The prefix *hemi-* refers to one half of the body, *para-* to both legs, and *quadri-* to all four limbs. The suffix *-plegia* signifies severe weakness or paralysis.

Increased *fatigability* or limitation in function due to pain or articular stiffness is often confused with weakness by pts. Increased time is sometimes required for full power to be exerted, and this *bradykinesia* may be misinterpreted as weakness. Severe proprioceptive sensory loss may also lead to complaints of weakness because adequate feedback information about the direction and power of movements is lacking. Finally, *apraxia*, a disorder of planning and initiating a skilled or learned movement, is sometimes mistaken for weakness.

The history should focus on the tempo of development of weakness, presence of sensory and other neurologic symptoms, medication history, predisposing medical conditions, and family history.

Weakness or paralysis is typically accompanied by other neurologic abnormalities that help to indicate the site of the responsible lesion (Table 55-1). It is important to distinguish weakness arising from disorders of upper motor neurons (i.e., motor neurons in the cerebral cortex and their axons that descend through the subcortical white matter, internal capsule, brainstem, and spinal cord) from disorders of the motor unit (i.e., lower motor neurons in the ventral horn of the spinal cord and their axons in the spinal roots and peripheral nerves, neuromuscular junction, and skeletal muscle).

Table 55-2 lists common causes of weakness by the primary site of pathology. Table 55-3 summarizes patterns with lesions of different parts of the nervous system.

An algorithm for the initial workup of weakness is shown in Fig. 55-1.

TABLE 55-1 Signs That Distinguish the Origin of Weakness

SIGN	UPPER MOTOR NEURON	LOWER MOTOR NEURON	MYOPATHIC	PSYCHOGENIC
Atrophy	None	Severe	Mild	None
Fasciculations	None	Common	None	None
Tone	Spastic	Decreased	Normal/ decreased	Variable/ paratonia
Distribution of weakness	Pyramidal/ regional	Distal/ segmental	Proximal	Variable/ inconsistent with daily activities
Muscle stretch reflexes	Hyperactive	Hypoactive/ absent	Normal/ hypoactive	Normal
Babinski sign	Present	Absent	Absent	Absent

TABLE 55-2 Common Causes of Weakness

Upper Motor Neuron

Cortex: Ischemia; hemorrhage; intrinsic mass lesion (primary or metastatic cancer, abscess); extrinsic mass lesion (subdural hematoma); degenerative (amyotrophic lateral sclerosis)

Subcortical white matter/internal capsule: Ischemia; hemorrhage; intrinsic mass lesion (primary or metastatic cancer, abscess); immunologic (multiple sclerosis); infectious (progressive multifocal leukoencephalopathy)

Brainstem: Ischemia, immunologic (multiple sclerosis)

Spinal cord: Extrinsic compression (cervical spondylosis, metastatic cancer, epidural abscess); immunologic (multiple sclerosis, transverse myelitis); infectious (AIDS-associated myelopathy, HTLV-I-associated myelopathy, tabes dorsalis); nutritional deficiency (subacute combined degeneration)

Motor Unit

Spinal motor neuron: Degenerative (amyotrophic lateral sclerosis), infectious (poliomyelitis)

Spinal root: Compressive (degenerative disk disease); immunologic (Guillain-Barré syndrome); infectious (AIDS-associated polyradiculopathy, Lyme disease)

Peripheral nerve: Metabolic (diabetes mellitus, uremia, porphyria); toxic (ethanol, heavy metals, many drugs, diphtheria); nutritional (B_{12} deficiency); inflammatory (polyarteritis nodosa); hereditary (Charcot-Marie-Tooth); immunologic (paraneoplastic, paraproteinemia); infectious (AIDS-associated polyneuropathies and mononeuritis multiplex); compressive (entrapment)

Neuromuscular junction: Immunologic (myasthenia gravis); toxic (botulism, aminoglycosides)

Muscle: Inflammatory (polymyositis, inclusion body myositis); degenerative (muscular dystrophy); toxic (glucocorticoids, ethanol, AZT); infectious (trichinosis); metabolic (hypothyroid, periodic paralyses); congenital (central core disease)

Abbreviation: AZT, azidothymidine.

TABLE 55-3 Clinical Differentiation of Weakness Arising from Different Areas of the Nervous System

LOCATION OF LESION	PATTERN OF WEAKNESS	ASSOCIATED SIGNS
Upper Motor Neuron		
Cerebral cortex	Hemiparesis (face and arm predominantly, or leg predominantly)	Hemisensory loss, seizures, homonymous hemianopia or quadrantanopia, aphasia, apraxias, gaze preference
Internal capsule	Hemiparesis (face, arm, leg may be equally affected)	Hemisensory deficit; homonymous hemianopia or quadrantanopia
Brainstem	Hemiparesis (arm and leg; face may not be involved at all)	Vertigo, nausea and vomiting, ataxia and dysarthria, eye movement abnormalities, cranial nerve dysfunction, altered level of consciousness, Horner's syndrome
Spinal cord	Quadriparesis if midcervical or above Paraparesis if low cervical or thoracic Hemiparesis below level of lesion (Brown-Séquard)	Sensory level; bowel and bladder dysfunction Contralateral pain/temperature loss below level of lesion

(Continued)

TABLE 55-3 Clinical Differentiation of Weakness Arising from Different Areas of the Nervous System (Continued)

LOCATION OF LESION	PATTERN OF WEAKNESS	ASSOCIATED SIGNS
Motor Unit		
Spinal motor neuron	Diffuse weakness, may involve control of speech and swallowing	Muscle fasciculations and atrophy; no sensory loss
Spinal root	Radicular pattern of weakness	Dermatomal sensory loss; radicular pain common with compressive lesions
Peripheral nerve	Polyneuropathy	Distal sensory loss, usually feet more than hands
	Mononeuropathy	Sensory loss in distribution of single nerve
Neuromuscular junction	Fatigable weakness, usually with ocular involvement producing diplopia and ptosis	No sensory loss; no reflex changes
Muscle	Proximal weakness	No sensory loss; diminished reflexes only when severe; may have muscle tenderness

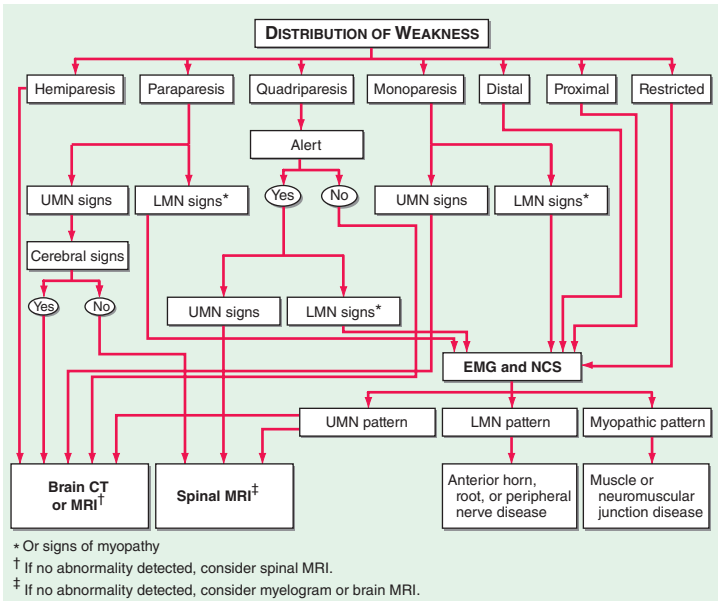


FIGURE 55-1 An algorithm for the initial workup of a pt with weakness. CT, computed tomography; EMG, electromyography; LMN, lower motor neuron; MRI, magnetic resonance imaging; NCS, nerve conduction studies; UMN, upper motor neuron.

56

Tremor and Movement Disorders



APPROACH TO THE PATIENT

Movement Disorders

Divided into akinetic rigid forms, with muscle rigidity and slowness of movement, and hyperkinetic forms, with involuntary movements. In both types, preservation of strength is the rule. Most movement disorders arise from disruption of basal ganglia circuits; common causes are degenerative diseases (hereditary and idiopathic), drug induced, organ system failure, CNS infection, and ischemia. Clinical features of the various movement disorders are summarized below.

■ BRADYKINESIA

Inability to initiate changes in activity or perform ordinary volitional movements rapidly and easily. There is a slowness of movement and a paucity of automatic motions such as eye blinking and arm swinging while walking. Usually due to Parkinson's disease or other causes of parkinsonism ([Chap. 186](#)).

■ TREMOR

Rhythmic oscillation of a part of the body due to intermittent muscle contractions, usually involving the distal limbs and less commonly the head, tongue, or jaw. A coarse tremor at rest, 4–5 beats/s, is usually due to Parkinson's disease. A fine postural tremor of 8–10 beats/s may be an exaggeration of normal physiologic tremor or indicate familial essential tremor (ET). An intention tremor, most pronounced during voluntary movement toward a target, is found with cerebellar pathway disease.

■ ESSENTIAL TREMOR

This is the most common movement disorder, affecting approximately 5% of the population. It can present in childhood but dramatically increases in prevalence over the age of 70 years. The tremor is most often manifest as a postural or action tremor and, in severe cases, can interfere with functions such as eating and drinking. It is typically bilateral and symmetric but may begin on one side and remain asymmetric. Tremor involves the head in ~30% of cases, voice in ~20%, tongue in ~20%, face/jaw in ~10%, and lower limbs in ~10%. Multiple body parts are involved in at least 50%. The tremor is characteristically improved by alcohol and worsened by stress. The tremor of ET must be distinguished from dystonic tremor and early Parkinson's disease ([Table 56-1](#)). The pathophysiology of ET is unknown. Approximately 50% of cases have a positive family history with autosomal dominant inheritance.

- Many pts with ET have mild symptoms and require no treatment.
- When activities of daily living such as eating and writing are impaired, therapy with propranolol (20–120 mg/d) or primidone (12.5–250 mg tid) benefits ~50% of pts; hand tremor tends to be most improved, while head tremor is often refractory.
- Botulinum toxin injections may be helpful for limb or voice tremor.
- Surgical therapies targeting the ventro-intermediate (VIM) nucleus of the thalamus may be effective in refractory cases.
- Focal ultrasound, a procedure that does not require surgery, has also been shown to be effective.

TABLE 56-1 Advanced Examination Pearls: Differentiating Essential Tremor from Parkinsonian Tremor

	ESSENTIAL TREMOR	PARKINSONIAN TREMOR
Speed	5–10 Hz	4–6 Hz
Symmetry	Bilateral	Usually asymmetric
Most common component	Postural	Rest
Other parkinsonian symptoms	Absent	Present
Helped with alcohol	Usually	Rarely
Family history	Present often	Usually absent

■ DYSTONIA

Consists of sustained or repetitive involuntary muscle contractions, frequently causing twisting movements and abnormal posture. May be generalized or focal; frequency estimated at 16 per 100,000 (approximately 50,000 cases in the United States), but is likely to be much higher because many cases are not recognized.

Focal dystonia is by far the most frequent form. It typically presents in the fourth to sixth decade; women affected about twice as often as men. *Major forms:* (1) *Cervical dystonia*—contractions of neck muscles causing the head to deviate to one side (*laterocollis*), twist (*torticollis*), or move in a forward (*anterocollis*), or backward (*retrocollis*) direction. (2) *blepharospasm*—contractions of the eyelids with increased blinking that can interfere with reading, watching television, working on a computer, and driving. (3) *Oromandibular dystonia* (OMD)—contractions of the lower face, lips, tongue, and jaw (opening or closing). Meige's syndrome, a combination of OMD and blepharospasm, predominantly affects women aged >60. (4) *Spasmodic dysphonia*—contractions of the vocal cords during phonation, causing impaired speech. Speech can sound choking and strained, or breathy and whispering. (5) *Limb dystonias*—can be present in arms or legs and often brought out by specific activities such as handwriting (writer's cramp), playing a musical instrument (musician's cramp), or putting in golf (the yips). Most pts have dystonia of the neck (cervical dystonia; ~50%) or eyelid (blepharospasm; ~20%). Focal dystonias can extend to involve other body regions (about 30% of cases) and are frequently misdiagnosed as psychiatric or orthopedic in origin. The cause is usually not known, but genetic factors, autoimmunity, and trauma have been suggested.

Generalized dystonia is often hereditary and, unlike focal dystonia, generally has an onset in childhood or adolescence. At least four well-established genes for *isolated dystonia*; *TOR1A*, *THAP1*, *ANO3*, and *GNAL*. Dopa-responsive dystonia (DRD; also known as Segawa syndrome) is caused by mutations in the *GCH1* gene (*GTP cyclohydrolase-1*) encoding the rate-limiting enzyme in the biosynthesis of dopamine. It is a childhood-onset dystonia with diurnal fluctuations and is important to recognize as the condition dramatically responds to low doses of levodopa. Parkinsonism can be a major, or even the only finding. Other generalized dystonias occur as a consequence of drugs such as antiemetics, neuroleptics, and treatments for Parkinson's disease.

- Therapy for focal dystonias usually involves botulinum toxin injections into the affected musculature.
- All forms of dystonia may respond to anticholinergics (e.g., trihexyphenidyl 20–120 mg/d), baclofen (20–120 mg/d), or tetrabenazine (initial dose 12.5 mg/d, usual maintenance 25–75 mg/d).
- Surgical therapies, including deep brain stimulation (DBS), may be effective in refractory cases.

■ CHOREOATHETOSIS

A combination of chorea (rapid, graceful, dance-like movements) and athetosis (slow, distal, writhing movements). The two usually exist together, though one may be more prominent. Choreic movements predominate in rheumatic (Sydenham's) chorea and Huntington's disease (HD). Systemic lupus erythematosus is the most common systemic disorder that causes chorea, but it can also be seen with hyperthyroidism, various autoimmune disorders including Sjogren's, infections including HIV, NMDA antibody positive encephalitis, metabolic alterations, and with a variety of medications (especially anticonvulsants, cocaine, CNS stimulants, estrogens, and lithium). Chorea-acanthocytosis (neuroacanthocytosis) is a progressive autosomal recessive disorder characterized by chorea coupled with red cell abnormalities on peripheral blood smear (acanthocytes). The chorea can be severe and associated with self-mutilating behavior, dystonia, tics, seizures, and a polyneuropathy. Hemiballismus is a violent form of chorea that comprises wild, flinging movements on one side of the body; the most common cause is a lesion (often infarct or hemorrhage) of the subthalamic nucleus. Athetosis (slow, distal, writhing movements) is prominent in some forms of cerebral palsy. Chronic neuroleptic use may lead to tardive dyskinesia, in which choreoathetotic movements are usually restricted to the buccal, lingual, and mandibular areas.

■ HUNTINGTON'S DISEASE (HD)

A progressive, fatal, autosomal dominant disorder characterized by motor, behavioral, and cognitive dysfunction. Onset is typically between 25 and 45 years. Rapid, nonpatterned, semipurposeful, involuntary choreiform movements are the hallmark feature; dysarthria, gait disturbance, oculomotor abnormalities, and behavioral and cognitive disturbances also occur, and the latter can be a major source of disability. In late stages, chorea becomes less prominent, and the picture is dominated by dystonia, rigidity, bradykinesia, myoclonus, and spasticity. HD is caused by an expansion in the number of polyglutamine (cytosine-adenine-guanine [CAG]) repeats in coding sequence of the *HTT* gene encoding the protein huntingtin.

- Treatment involves a multidisciplinary approach with medical, neuropsychiatric, social, and genetic counseling for pts and families.
- Dopamine-blocking agents may control the chorea; tetrabenazine may also treat chorea but can cause secondary parkinsonism.
- Depression and anxiety should be treated with appropriate antidepressant and anti-anxiety drugs such as clozapine (50–600 mg/d), quetiapine (50–600 mg/d), and risperidone (2–8 mg/d).
- Psychosis can be treated with atypical neuroleptic agents.
- No disease-modifying agents currently exist.

■ TICS

Brief, rapid, recurrent, and seemingly purposeless stereotyped muscle contractions. Tourette syndrome (TS) is a neurobehavioral, multiple tic disorder that may involve motor tics (especially twitches of the face, neck, and shoulders) and phonic tics (grunts, words, coprolalia, echolalia). Pts may experience an irresistible urge to express tics but characteristically can voluntarily suppress them for short periods of time. Onset is usually between 2 and 15 years of age, and tics often lessen or even disappear in adulthood.

- Drug treatment is only indicated when tics are disabling and interfere with quality of life.
- Therapy is generally initiated with clonidine, starting at low dose, or guanfacine (0.5–2 mg/d). If these agents are not effective, atypical neuroleptics (risperidone, olanzapine, ziprasidone) may be used.

■ MYOCLONUS

Brief, rapid (<100 ms), shock-like, jerky, movements, usually multifocal. Like asterixis, often occurs in a diffuse encephalopathy. Following cardiac arrest, diffuse cerebral hypoxia may produce multifocal myoclonus. Metabolic disturbances or spinal cord injury can also cause myoclonus. Myoclonus occurs in normal individuals when waking up or falling asleep.

- Treatment, indicated only when function is impaired, consists of treating the underlying condition or removing an offending agent.
- Drug therapies include valproic acid (800–3000 mg/d), piracetam (8–20 g/d), clonazepam (2–15 mg/d), levetiracetam (1000–3000 mg/d), or primidone (500–1000 mg/d).

■ ASTERIXIS

Brief, arrhythmic interruptions of sustained voluntary muscle contraction, usually observed as a brief lapse of posture of wrists in dorsiflexion with arms outstretched, “negative myoclonus.” This “liver flap” may be seen in any encephalopathy related to drug intoxication, organ system failure, or CNS infection. Therapy is correction of the underlying disorder.

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Aphasia



Aphasias are disturbances in the comprehension or production of spoken or written language. Clinical examination should assess spontaneous speech (fluency), comprehension, repetition, naming, reading, and writing. A classification scheme is presented in [Table 57-1](#). In nearly all right-handed individuals and many left-handed pts, language localization is in the left hemisphere.

■ CLINICAL FEATURES

Wernicke's Aphasia

Although speech sounds grammatical, melodic, and effortless (fluent), it is virtually incomprehensible due to errors in word usage, structure, and tense and the presence of paraphasic errors and neologisms (“jargon”). Comprehension of written and spoken material is severely impaired, as are reading, writing, and repetition. The pt usually seems unaware of the deficit and is not frustrated. Associated symptoms can include parietal lobe sensory deficits and homonymous hemianopia. Motor disturbances are rare.

Lesion is located in posterior perisylvian region. Most common cause is embolism to the inferior division of dominant middle cerebral artery (MCA); less commonly intracerebral hemorrhage, severe head trauma, or tumor is responsible.

Broca's Aphasia

Speech output is sparse (nonfluent), slow, labored, interrupted by many word-finding pauses, and usually dysarthric; output may be reduced to a grunt or single word. Naming and repetition also impaired. Most pts have severe writing impairment. Comprehension of written and spoken language is relatively preserved. The pt is often aware of and visibly frustrated by deficit. With large lesions, a dense hemiparesis may occur, and eyes may deviate toward side

TABLE 57-1 Clinical Features of Aphasias and Related Conditions Commonly Seen in Cerebrovascular Accidents

	COMPREHENSION	REPETITION OF SPOKEN LANGUAGE	NAMING	FLUENCY
Wernicke's	Impaired	Impaired	Impaired	Preserved or increased
Broca's	Preserved (except grammar)	Impaired	Impaired	Decreased
Global	Impaired	Impaired	Impaired	Decreased
Conduction	Preserved	Impaired	Impaired	Preserved
Nonfluent (anterior) transcortical	Preserved	Preserved	Impaired	Impaired
Fluent (posterior) transcortical	Impaired	Preserved	Impaired	Preserved
Isolation	Impaired	Echolalia	Impaired	No purposeful speech
Anomic	Preserved	Preserved	Impaired	Preserved except for word-finding pauses
Pure word deafness	Impaired only for spoken language	Impaired	Preserved	Preserved
Pure alexia	Impaired only for reading	Preserved	Preserved	Preserved

of lesion. More commonly, lesser degrees of contralateral face and arm weakness are present. Sensory loss is rarely found, and visual fields are intact.

Lesion involves dominant inferior frontal gyrus (Broca's area), although cortical and subcortical areas along superior sylvian fissure and insula are often involved. Commonly caused by vascular lesions involving the superior division of the MCA; less commonly due to tumor, intracerebral hemorrhage, or abscess.

Global Aphasia

All aspects of speech and language are impaired. Pt cannot read, write, or repeat and has poor auditory comprehension. Speech output is minimal and nonfluent. Hemiplegia, hemisensory loss, and homonymous hemianopia are usually present. Syndrome represents the combined dysfunction of Wernicke's and Broca's areas, usually resulting from proximal occlusion of MCA supplying dominant hemisphere (less commonly hemorrhage, trauma, or tumor).

Conduction Aphasia

Speech output is fluent but paraphasic, comprehension of spoken language is intact, and repetition is severely impaired, as are naming and writing. Lesion spares, but functionally disconnects, Wernicke's and Broca's areas. Most cases are embolic strokes, involving temporoparietal or dorsal perisylvian region.

LABORATORY EVALUATION

CT scan or MRI usually identifies the location and nature of the causative lesion.

TREATMENT**Aphasia**

- Speech therapy may be helpful in treatment of certain types of aphasia; more effective in Broca's aphasia than in Wernicke's.
- When the lesion is caused by a stroke, recovery of language function generally peaks within 2–6 months, after which further progress is limited.

58**Sleep Disorders**

Disorders of sleep are among the most common problems seen by clinicians. More than one-half of adults experience at least intermittent sleep disturbances, and 50–70 million Americans suffer from a chronic sleep disturbance which can adversely affect daytime functioning as well as physical and mental health.

APPROACH TO THE PATIENT**Sleep Disorders**

Pts may complain of (1) difficulty in initiating and maintaining sleep at night (insomnia); (2) excessive daytime sleepiness or tiredness; (3) unusual behaviors during sleep (parasomnias); or (4) circadian rhythm disorders associated with jet lag, shift work, and delayed sleep phase syndrome. Careful history of sleep habits is a cornerstone of diagnosis (e.g., ask when pt typically goes to bed, falls asleep, and wakes up; also note if he/she awakens during sleep, feels rested in the morning, and naps during the day). Reports from the sleep partner (e.g., heavy snoring, falling asleep while driving) are also important. Pts with excessive sleepiness should be advised to avoid driving until effective therapy is achieved. Completion of a day-by-day sleep-work-drug log for 1–2 weeks is often helpful. Work and sleep times (including daytime naps and nocturnal awakenings) as well as drug and alcohol use, including caffeine and hypnotics, should be noted each day. The physical examination may show a small airway, large tonsils, or a neurologic or medical disorder that contributes to the complaint. Objective sleep laboratory recording is necessary to evaluate specific disorders such as sleep apnea, periodic limb movements, and narcolepsy.

INSOMNIA

Insomnia is the complaint of poor sleep and usually presents as difficulty initiating or maintaining sleep. People with insomnia are dissatisfied with their sleep and feel it impairs their ability to function well. Affected individuals often experience fatigue, decreased mood, irritability, malaise, and cognitive impairment. *Chronic insomnia*, lasting >3 months, occurs in about 10% of adults. *Acute or short-term insomnia* affects over 30% of adults and is often precipitated by stressful life events. Most insomnia begins in adulthood, but many pts may be predisposed and report easily disturbed sleep predating the insomnia, suggesting that their sleep is lighter than usual.

All insomnias can be exacerbated and perpetuated by behaviors that are not conducive to initiating or maintaining sleep. *Inadequate sleep hygiene* is characterized by a behavior pattern prior to sleep, and/or a bedroom environment, that is not conducive to sleep. In preference to hypnotic medications, the pt should attempt to avoid stressful activities before bed, reserve the bedroom environment for sleeping, and maintain regular rising times.

Psychophysiological Insomnia

These pts are preoccupied with a perceived inability to sleep adequately at night. Rigorous attention should be paid to sleep hygiene and correction of counterproductive, arousing behaviors before bedtime. Behavioral therapies are the treatment of choice.

Drugs and Medications

Caffeine is the most common pharmacologic cause of insomnia although a wide range of psychoactive drugs can interfere with sleep, including alcohol and nicotine. Numerous medications, including antidepressants, stimulants, and glucocorticoids, can produce insomnia. Severe rebound insomnia can result from the acute withdrawal of hypnotics, especially following the use of short-acting benzodiazepines.

Movement Disorders

Pts with *restless legs syndrome* (RLS) complain of creeping dysesthesias deep within the calves or feet associated with an irresistible urge to move the affected limbs; symptoms are typically worse at night. RLS is very common, affecting 5–10% of adults and is more common in women and older adults. Iron deficiency, renal failure, and peripheral neuropathies can cause secondary RLS, and symptoms can worsen by pregnancy, caffeine, alcohol, antidepressants, lithium, neuroleptics, and antihistamines. One-third of pts have multiple affected family members. Treatment is with dopaminergic drugs (pramipexole 0.25–0.5 mg daily at 7 PM or ropinirole 0.5–4.0 mg daily at 7 PM). *Periodic limb movements of sleep* (PLMS) consist of stereotyped extensions of the great toe and dorsiflexion of the foot recurring every 20–40 s during non-REM sleep. Treatment options include dopaminergic medications.

Other Neurologic Disorders

A variety of neurologic disorders produce sleep disruption through both indirect, nonspecific mechanisms (e.g., neck or back pain) or by impairment of central neural structures involved in the generation and control of sleep itself. Common disorders to consider include *dementia* from any cause, *epilepsy*, *Parkinson's disease*, and *migraine*.

Psychiatric Disorders

Approximately 80% of pts with mental disorders complain of impaired sleep. The underlying diagnosis may be depression, mania, an anxiety disorder, or schizophrenia.

Medical Disorders

In *asthma*, daily variation in airway resistance results in marked increases in asthmatic symptoms at night, especially during sleep. Treatment of asthma with theophylline-based compounds, adrenergic agonists, or glucocorticoids can independently disrupt sleep. Inhaled glucocorticoids that do not disrupt sleep may provide a useful alternative to oral drugs. *Chronic obstructive pulmonary disease*, pain from rheumatologic disorders or neuropathy, *cystic fibrosis*, *hyperthyroidism*, *menopause*, and *gastroesophageal reflux* are other causes.

TREATMENT

Insomnia

Primary insomnia is a diagnosis of exclusion.

- Treatment of a medical or psychiatric disease that may be contributing should be addressed first.
- Attention should be paid to improving sleep hygiene and avoiding counterproductive behaviors before bedtime (Table 58-1).
- Cognitive behavioral therapy emphasizes understanding the nature of normal sleep, the circadian rhythm, the use of light therapy, and visual imagery to block unwanted thought intrusions.
- Pharmacotherapy is reserved for instances when insomnia persists after treatment of contributing factors. Antihistamines are the primary active ingredient in most over-the-counter sleep aids. Benzodiazepine receptor agonists are effective and well tolerated; options include zaleplon (5–20 mg), zolpidem (5–10 mg), triazolam (0.125–0.25 mg), eszopiclone (1–3 mg), and temazepam (15–30 mg). Heterocyclic antidepressants such as trazodone (25–100 mg) are often used due to their lack of abuse potential and lower cost. Limit use to a short period of time for acute insomnia or intermittent use for chronic insomnia. All sedatives increase the risk of falls and confusion in the elderly, and therefore if required these medications should be used at the lowest effective dose.

■ DISORDERS OF EXCESSIVE DAYTIME SLEEPINESS

Differentiation of sleepiness from subjective complaints of fatigue may be difficult. Quantification of daytime sleepiness can be performed in a sleep laboratory using a multiple sleep latency test (MSLT), the repeated daytime measurement of sleep latency under standardized conditions. An approach to the evaluation is summarized in Table 58-2.

TABLE 58-1 Methods to Improve Sleep Hygiene in Insomnia Pts

HELPFUL BEHAVIORS	BEHAVIORS TO AVOID
Use the bed only for sleep and sex <ul style="list-style-type: none"> • If you cannot sleep within 20 min, get out of bed and read or do other relaxing activities in dim light before returning to bed 	Avoid behaviors that interfere with sleep physiology, including: <ul style="list-style-type: none"> • Napping, especially after 3:00 PM • Attempting to sleep too early • Caffeine after lunchtime
Make quality sleep a priority <ul style="list-style-type: none"> • Go to bed and get up at the same time each day • Ensure a restful environment (comfortable bed, bedroom quiet and dark) 	In the 2–3 h before bedtime, avoid: <ul style="list-style-type: none"> • Heavy eating • Smoking or alcohol • Vigorous exercise
Develop a consistent bedtime routine. For example: <ul style="list-style-type: none"> • Prepare for sleep with 20–30 min of relaxation (e.g., soft music, meditation, yoga, pleasant reading) • Take a warm bath 	When trying to fall asleep, avoid: <ul style="list-style-type: none"> • Solving problems • Thinking about life issues • Reviewing events of the day

TABLE 58-2 Evaluation of the Pt with Excessive Daytime Sleepiness

FINDINGS ON HISTORY AND PHYSICAL EXAMINATION	DIAGNOSTIC EVALUATION	DIAGNOSIS	THERAPY
Difficulty waking in the morning, rebound sleep on weekends, and vacations with improvement in sleepiness	Sleep log	Insufficient sleep	Sleep education and behavioral modification to increase amount of sleep
Obesity, snoring, hypertension	Polysomnogram	Obstructive sleep apnea (Chap. 140)	Continuous positive airway pressure; upper airway surgery; dental appliance; weight loss
Cataplexy, hypnagogic hallucinations, sleep paralysis	Polysomnogram and multiple sleep latency test	Narcolepsy	Stimulants (e.g., modafinil, methylphenidate); REM sleep-suppressing antidepressants (e.g., venlafaxine); sodium oxybate
Restless legs, kicking movements during sleep	Assessment for predisposing medical conditions (e.g., iron deficiency or renal failure)	Restless legs syndrome with or without periodic limb movements	Treatment of predisposing condition if possible; dopamine agonists (e.g., pramipexole, ropinirole)
Sedating medications, stimulant withdrawal, head trauma, systemic inflammation, Parkinson's disease, and other neurodegenerative disorders, hypothyroidism, encephalopathy	Thorough medical history and examination including detailed neurologic examination	Sleepiness due to a drug or medical condition	Change medications, treat underlying condition, consider stimulants

Sleep Apnea Syndromes

Respiratory dysfunction during sleep is a common cause of excessive daytime sleepiness and/or disturbed nocturnal sleep, affecting an estimated 24% of middle-aged men and 9% of middle-aged women. Episodes may be due to occlusion of the airway (*obstructive sleep apnea*), absence of respiratory effort (*central sleep apnea*), or a combination of these factors (*mixed sleep apnea*). Obstruction is exacerbated by obesity, supine posture, sedatives (especially alcohol), nasal obstruction, and hypothyroidism. Sleep apnea is particularly prevalent in overweight men and in the elderly and is undiagnosed in most affected

individuals. Treatment consists of correction of the above factors, positive airway pressure devices, oral appliances, and sometimes surgery or neurostimulation (Chap. 140).

Narcolepsy

A disorder of excessive daytime sleepiness and intrusion of REM-related sleep phenomena into wakefulness (cataplexy, hypnagogic hallucinations, and sleep paralysis). *Cataplexy*, the abrupt loss of muscle tone in arms, legs, or face, is precipitated by emotional stimuli such as laughter or sadness. Symptoms of narcolepsy typically begin in the second decade. The prevalence is 1 in 2000. Narcolepsy has a genetic basis; almost all narcoleptics with cataplexy are positive for HLA DQB1*06:02. Hypothalamic neurons containing the neuropeptide hypocretin (orexin) regulate the sleep/wake cycle and loss of these cells, possibly due to autoimmunity, has been implicated in narcolepsy. Diagnosis is made with sleep studies confirming a short daytime sleep latency and a rapid transition to REM sleep.

TREATMENT

Narcolepsy

- Somnolence is treated with modafinil (200–400 mg/d given as a single dose each morning).
- Older stimulants such as methylphenidate (10–20 mg bid) or dextroamphetamine (10 mg bid) are alternatives, particularly in refractory pts.
- Cataplexy usually responds to antidepressants that increase noradrenergic or serotonergic tone. Venlafaxine (37.5–150 mg each morning) and fluoxetine (10–40 mg each morning) are often effective. The tricyclic antidepressants, such as protriptyline (10–40 mg/d) or clomipramine (25–50 mg/d), are potent suppressors of cataplexy, but their anticholinergic effects, including sedation and dry mouth, make them less attractive. Alternatively, sodium oxybate, given at bedtime and 3–4 h later, is also effective.
- Adequate nocturnal sleep time and the use of short naps are other useful preventative measures.

■ CIRCADIAN RHYTHM SLEEP DISORDERS

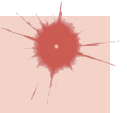
Insomnia or hypersomnia may occur in disorders of sleep timing rather than sleep generation. Such conditions may be (1) organic—due to a defect in the circadian pacemaker, or (2) environmental—due to a disruption of exposure to entraining stimuli (light/dark cycle). Examples of the latter include jet-lag disorder and shift work. Shift work sleepiness can be treated with modafinil (200 mg) or armodafinil (150 mg) taken 30–60 min before the start of each night shift as well as properly timed exposure to bright light. Safety programs should promote education about sleep and increase awareness of hazards associated with night work.

Delayed sleep-wake phase syndrome is characterized by late sleep onset and awakening with otherwise normal sleep architecture. Bright-light phototherapy in the morning hours or melatonin therapy during the evening hours may be effective.

Advanced sleep-wake phase syndrome moves sleep onset to the early evening hours with early morning awakening. These pts may benefit from bright-light phototherapy during the evening hours. Some autosomal dominant cases result from mutations in genes (*PER2* or casein kinase I delta) involved in regulation of the circadian clock.

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Sore Throat, Earache, and Upper Respiratory Symptoms



- URIs are among the leading causes of lost time from work or school.
- Distinguishing pts with primary viral URI from those with primary bacterial URI is difficult since the signs and symptoms are the same.
- URIs are often treated with antibiotics even though bacteria cause only 25% of cases. Inappropriate prescribing of antibiotics for URIs is a leading cause of antibiotic resistance in common community-acquired pathogens such as *Streptococcus pneumoniae*.

NONSPECIFIC URIs

- **Definition:** Nonspecific URIs (the “common cold”) have no prominent localizing features.
- **Etiology:** A wide variety of viruses (e.g., rhinoviruses, coronaviruses, parainfluenza viruses, influenza viruses, adenoviruses) can cause nonspecific URIs.
- **Clinical manifestations:** an acute, mild, self-limited catarrhal syndrome, typically characterized by rhinorrhea, nasal congestion, cough, and sore throat
 - Hoarseness, malaise, sneezing, and fever are more variable.
 - The median duration of symptoms is ~1 week (range, 2–10 days). Cough secondary to upper respiratory inflammation may last 2–3 weeks and does not necessarily indicate a need for antibiotics.
 - Secondary bacterial infections complicate 0.5–2% of colds and are associated with a prolonged course and/or increased severity of illness, often with localization of signs and symptoms. Purulent nasal and throat secretions are poor predictors of bacterial infection.
- **Treatment:** Symptom-based treatment (e.g., with decongestants, NSAIDs) is typically all that is required. Antibiotics are not indicated.

SINUS INFECTIONS

- Rhinosinusitis is an inflammatory condition most commonly involving the maxillary sinus; next, in order of frequency, are the ethmoid, frontal, and sphenoid sinuses.
- Sinusitis accounts for millions of visits to primary care physicians each year and is the fifth most common diagnosis for which antibiotics are prescribed.

■ ACUTE SINUSITIS

- **Definition:** sinusitis of <4 weeks’ duration
- **Etiology:** Infectious and noninfectious causes lead to sinus ostial obstruction and retention of mucus.
 - Infectious causes include viruses (e.g., rhinovirus, parainfluenza virus, influenza virus) and bacteria (e.g., *S. pneumoniae*, nontypable *Haemophilus influenzae*, and—in children—*Moraxella catarrhalis*).
 - In immunocompromised pts, fungi (e.g., *Rhizopus*, *Mucor*, and occasionally *Aspergillus*) can be involved.
 - Nosocomial cases are often polymicrobial and involve *Staphylococcus aureus* and gram-negative bacilli.
 - Noninfectious causes include allergic rhinitis, barotrauma, and exposure to chemical irritants.

- **Clinical manifestations:** Common manifestations include nasal drainage and congestion, facial pain or pressure, and headache.
 - Tooth pain and halitosis can be associated with bacterial sinusitis.
 - Pain localizes to the involved sinus and is often worse when the pt bends over or is supine.
 - Advanced frontal sinusitis can present as *Pott's puffy tumor*: swelling and pitting edema over the frontal bone from a communicating subperiosteal abscess.
 - Life-threatening complications include meningitis, epidural abscess, and brain abscess.
- **Diagnosis:** It is difficult to distinguish viral from bacterial sinusitis clinically, although viral cases greatly outnumber bacterial cases.
 - Only 40–50% of pts with symptoms of >10 days' duration, purulent nasal drainage, nasal obstruction, and facial pain have bacterial sinusitis.
 - If fungal sinusitis is a consideration, involved areas should be biopsied.
 - Except in nosocomial cases, sinus CT or radiography is not recommended for acute sinusitis. Nosocomial sinusitis should be confirmed by sinus CT, with sinus aspirates sent for culture and susceptibility testing (ideally before antimicrobial treatment is initiated).

TREATMENT

Acute Sinusitis

- Most pts improve without antibiotic treatment.
- For pts with mild to moderate symptoms, treatment should focus on symptom relief and facilitation of sinus drainage (e.g., oral and topical decongestants, nasal saline lavage).
- Antibiotics should be given to pts with severe disease at presentation and considered for pts without improvement after 10–14 days.
 - See [Table 59-1](#) for recommended regimens for adults.
 - For pts who do not respond to initial antimicrobial treatment, consultation with an otolaryngologist about possible sinus aspiration and/or lavage should be considered.
- Surgery should be considered for pts with severe disease, intracranial complications, or invasive fungal sinusitis.

■ CHRONIC SINUSITIS

- **Definition:** sinusitis of >12 weeks' duration
- **Etiology:** commonly associated with bacterial or fungal infection
- **Chronic bacterial sinusitis:** Impaired mucociliary clearance leads to repeated infections as opposed to one persistent infection.
 - Pts have constant nasal congestion and sinus pressure, with periods of increased severity.
 - Sinus CT can define the extent of disease, detect an underlying anatomic defect or obstructing process, and assess response to treatment.
 - Endoscopy-derived tissue samples for histology and culture should be obtained to guide treatment.
 - Repeated antibiotic courses are required, often for 3–4 weeks at a time. Adjunctive measures include intranasal administration of glucocorticoids, sinus irrigation, and surgical evaluation.

TABLE 59-1 Guidelines for the Diagnosis and Treatment of Acute Bacterial Sinusitis in Adults

DIAGNOSTIC CRITERIA	TREATMENT RECOMMENDATIONS ^a
Moderate symptoms (e.g., nasal purulence/congestion or cough) for >10 d or Severe symptoms of any duration, including unilateral/focal facial swelling or tooth pain	<i>Initial therapy:</i> Amoxicillin/clavulanate, 500/125 mg PO tid or 875/125 mg PO bid ^b <i>Penicillin allergy:</i> Doxycycline, 100 mg PO bid; or An antipneumococcal fluoroquinolone (e.g., moxifloxacin, 400 mg/d PO daily) ^c <i>Exposure to antibiotics within 30 d or >30% prevalence of penicillin-resistant Streptococcus pneumoniae:</i> Amoxicillin/clavulanate (extended release), 2000/125 mg PO bid; or Doxycycline, 100 mg PO bid; or An antipneumococcal fluoroquinolone (e.g., moxifloxacin, 400 mg PO daily) ^c <i>Recent treatment failure:</i> Amoxicillin/clavulanate (extended release), 2000 mg PO bid; or An antipneumococcal fluoroquinolone (e.g., moxifloxacin, 400 mg PO daily) ^c

^aThe duration of therapy is 5–7 days if symptoms improve within the first few days of treatment but can be up to 7–10 days, with appropriate follow-up. Severe disease may warrant IV antibiotics and consideration of hospital admission.

^bIn areas where the prevalence of antibiotic resistance is low, amoxicillin can be considered as initial therapy in pts without recent antibiotic exposure.

^cFluoroquinolones carry a risk of tendinitis and neuropathy and should be used only if other options are not reasonable, with consideration of risks and benefits.

- **Chronic fungal sinusitis:** a noninvasive disease in immunocompetent hosts, typically due to *Aspergillus* and dematiaceous molds. Recurrence is common.
 - Mild, indolent disease is usually cured with endoscopic surgery and without antifungal agents.
 - Unilateral disease with a mycetoma (fungus ball) in the sinus is treated with surgery and—if bony erosion has occurred—antifungal agents.
 - Allergic fungal sinusitis, seen in pts with nasal polyps and asthma, presents as pansinusitis and thick, eosinophil-laden mucus with the consistency of peanut butter.

INFECTIONS OF THE EAR AND MASTOID

■ EXTERNAL EAR INFECTIONS

In the absence of local or regional adenopathy, consider noninfectious causes of inflammation, among which trauma, insect bites, and environmental exposures are more commonly implicated than are autoimmune diseases (e.g., lupus) or vasculitides (e.g., granulomatosis with polyangiitis).

- **Auricular cellulitis:** Tenderness, erythema, swelling, and warmth of the external ear, particularly the lobule, follow minor trauma. Treat with warm compresses and antibiotics active against *S. aureus* and streptococci (e.g., cephalexin, dicloxacillin).

- **Perichondritis:** Infection of the perichondrium of the auricular cartilage follows local trauma (e.g., ear piercing). The infection may closely resemble auricular cellulitis, although the lobule is less often involved in perichondritis.
 - Treatment requires systemic antibiotics active against the most common etiologic agents, *Pseudomonas aeruginosa* and *S. aureus*, and typically consists of an antipseudomonal penicillin (e.g., piperacillin) or a penicillinase-resistant penicillin (e.g., nafcillin) plus an antipseudomonal quinolone (e.g., ciprofloxacin). Surgical drainage may be needed; resolution can take weeks.
 - If perichondritis fails to respond to adequate treatment, consider noninfectious inflammatory etiologies (e.g., relapsing polychondritis).
- **Otitis externa:** a collection of diseases involving primarily the auditory meatus and resulting from a combination of heat and retained moisture, with desquamation and maceration of the epithelium of the outer ear canal. All forms are predominantly bacterial in origin; *P. aeruginosa* and *S. aureus* are the most common pathogens.
 - *Acute localized otitis externa:* furunculosis in the outer third of the ear canal, usually due to *S. aureus*. Treatment consists of an oral antistaphylococcal penicillin (e.g., dicloxacillin, cephalexin), with surgical drainage in cases of abscess formation.
 - *Acute diffuse otitis externa (swimmer's ear):* infection in macerated, irritated canals that is typically due to *P. aeruginosa* and is characterized by severe pain, erythema, and swelling of the canal and white clumpy discharge from the ear. Treatment includes cleansing of the canal to remove debris and use of topical agents (e.g., hypertonic saline, mixtures of alcohol and acetic acid, antibiotic preparations combining neomycin and polymyxin), with or without glucocorticoids to reduce inflammation.
 - *Chronic otitis externa:* erythematous, scaling, pruritic dermatitis that usually arises from persistent drainage from a chronic middle-ear infection, other causes of repeated irritation, or rare chronic infections such as tuberculosis or leprosy. Treatment consists of identifying and eliminating the offending process; successful resolution is frequently difficult.
 - *Malignant or necrotizing otitis externa:* a slowly progressive infection characterized by purulent otorrhea, an erythematous swollen ear and external canal, and severe otalgia out of proportion to exam findings, with granulation tissue present in the posteroinferior wall of the canal, near the junction of bone and cartilage
 - This potentially life-threatening disease, which occurs primarily in elderly diabetic or immunocompromised pts, can involve the base of the skull, meninges, cranial nerves, and brain.
 - *P. aeruginosa* is the most common etiologic agent, but other gram-negative bacilli, *S. aureus*, *Staphylococcus epidermidis*, *Actinomyces*, and *Aspergillus* have been reported.
 - A biopsy specimen of granulation tissue (or deeper tissues) should be obtained for culture.
 - Treatment involves systemic antibiotics for 6–8 weeks and consists of an antipseudomonal agent (e.g., piperacillin, ceftazidime), sometimes in combination with an aminoglycoside or a fluoroquinolone; antibiotic drops active against *Pseudomonas*, combined with glucocorticoids, are used as adjunctive treatment.
 - Recurs in up to 20% of cases. Aggressive glycemic control in diabetic pts helps with treatment and prevention of recurrence.

■ MIDDLE-EAR INFECTIONS

Eustachian tube dysfunction, often in association with URIs, causes inflammation with a sterile transudate. Viral or bacterial superinfection often occurs.

- **Acute otitis media:** typically follows a viral URI, which can directly cause viral otitis media or, more commonly, predispose to bacterial otitis media
 - *Etiology:* *S. pneumoniae* is isolated in up to 35% of cases; nontypable *H. influenzae* and *M. catarrhalis* are other common causes of bacterial otitis media. Concern is increasing about community-acquired methicillin-resistant *S. aureus* (MRSA) as an emerging etiologic agent. Viruses (e.g., respiratory syncytial virus, influenza virus, rhinovirus, enterovirus) have been recovered either alone or with bacteria in up to 40% of cases.
 - *Clinical manifestations:* The tympanic membrane is immobile, erythematous, bulging, or retracted and can perforate spontaneously.
 - Other findings may include otalgia, otorrhea, decreased hearing, and fever.
 - In isolation, erythema of the tympanic membrane is nonspecific as it is common in association with inflammation of the upper respiratory mucosa.
 - *Treatment:* Indications for antibiotic treatment and regimens are listed in [Table 59-2](#); antibiotic prophylaxis and surgical interventions offer little benefit in recurrent acute otitis media.
- **Serous otitis media:** Also known as otitis media with effusion, this condition can persist for weeks (e.g., acute effusions) or months (e.g., after an episode of acute otitis media) without signs of infection and is associated with significant hearing loss in the affected ear.
 - The majority of cases resolve spontaneously within 3 months without antibiotic treatment.
 - Antibiotic treatment or myringotomy with tympanostomy tubes is reserved for pts with bilateral effusions that have persisted for at least 3 months and are associated with significant bilateral hearing loss.
- **Chronic otitis media:** persistent or recurrent purulent otorrhea with tympanic membrane perforation, usually associated with conductive hearing loss
 - Inactive disease, characterized by a central perforation of the tympanic membrane, is treated with repeated courses of topical antibiotic drops during periods of drainage.
 - Active disease involves formation of a cholesteatoma that may enlarge and ultimately lead to erosion of bone, meningitis, and brain abscess; surgical treatment is required.
- **Mastoiditis:** accumulation of purulent exudate in the mastoid air cells that erodes surrounding bones and causes abscess-like cavities
 - Pts have pain, erythema, and mastoid process swelling causing displacement of the pinna along with the signs and symptoms of otitis media.
 - Rare complications include subperiosteal abscess, deep neck abscess, and septic thrombosis of the lateral sinus.
 - Broad-spectrum empirical IV antibiotic regimens targeting *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* can be narrowed once culture results are available; mastoidectomy is reserved for pts with complicated cases or pts in whom medical management fails.

INFECTIONS OF THE PHARYNX AND ORAL CAVITY

Sore throat is the most common presenting symptom and one of the most common reasons for ambulatory care visits by adults and children.

■ ACUTE PHARYNGITIS

- **Etiology:** Respiratory viruses are the most common identifiable cause, although ~30% of cases have no etiology identified.

TABLE 59-2 Guidelines for the Diagnosis and Treatment of Acute Otitis Media

ILLNESS SEVERITY	DIAGNOSTIC CRITERIA	TREATMENT RECOMMENDATIONS
Mild to moderate	<p>>2 yrs or 6 mo to 2 yrs without middle-ear effusion</p> <p><6 mo; or</p> <p>6 mo to 2 yrs with middle-ear effusion (fluid in the middle ear, evidenced by decreased TM mobility, air/fluid level behind TM, bulging TM, purulent otorrhea) and acute onset of signs and symptoms of middle-ear inflammation, including fever, otalgia, decreased hearing, tinnitus, vertigo, erythematous TM; or</p> <p>>2 yrs with bilateral disease, TM perforation, high fever, immunocompromise, emesis</p>	<p><i>Observation alone</i> (deferring antibiotic therapy for 48–72 h and limiting management to symptom relief)</p> <p><i>Initial therapy</i>^a:</p> <p>Amoxicillin, 80–90 mg/kg qd (up to 2 g) PO in divided doses (bid or tid); or</p> <p>Cefdinir, 14 mg/kg qd PO in 1 dose or divided doses (bid); or</p> <p>Cefuroxime, 30 mg/kg qd PO in divided doses (bid); or</p> <p>Azithromycin, 10 mg/kg qd PO on day 1 followed by 5 mg/kg qd PO for 4 d</p> <p><i>Exposure to antibiotics within 30 d or recent treatment failure</i>^{a,b}:</p> <p>Amoxicillin, 90 mg/kg qd (up to 2 g) PO in divided doses (bid), plus clavulanate, 6.4 mg/kg qd PO in divided doses (bid); or</p> <p>Ceftriaxone, 50 mg/kg IV/IM qd for 3 d; or</p> <p>Clindamycin, 30–40 mg/kg qd PO in divided doses (tid)</p>
Severe	<p>As above, with temperature $\geq 39.0^{\circ}\text{C}$ ($\geq 102^{\circ}\text{F}$); or</p> <p>Moderate to severe otalgia</p>	<p><i>Initial therapy</i>^a:</p> <p>Amoxicillin, 90 mg/kg qd (up to 2 g) PO in divided doses (bid), plus clavulanate, 6.4 mg/kg qd PO in divided doses (bid); or</p> <p>Ceftriaxone, 50 mg/kg IV/IM qd for 3 d</p> <p><i>Exposure to antibiotics within 30 d or recent treatment failure</i>^{a,b}:</p> <p>Ceftriaxone, 50 mg/kg IV/IM qd for 3 d; or</p> <p>Clindamycin, 30–40 mg/kg qd PO in divided doses (tid); or</p> <p>Consider tympanocentesis with culture</p>

^aDuration (unless otherwise specified): 10 days for pts <6 years old and pts with severe disease; 5–7 days (with consideration of observation only in previously healthy individuals with mild disease) for pts ≥ 6 years old.

^bFailure to improve and/or clinical worsening after 48–72 h of observation or treatment.

Abbreviation: TM, tympanic membrane.

Source: Data from American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media, 2004.

- **Viruses:** Rhinoviruses and coronaviruses cause ~20% and ~5% of cases, respectively; influenza and parainfluenza viruses are seasonal causes; HSV, coxsackievirus, CMV, EBV, and HIV are other important viral causes.
- **Bacteria:** Group A *Streptococcus* (GAS) accounts for 5–15% of adult cases. *Fusobacterium necrophorum*, which can cause Lemierre disease, is increasingly identified as a cause of pharyngitis in adolescents and is isolated nearly as often as GAS. Rare bacterial causes that should be considered in appropriate exposure groups include *Neisseria gonorrhoeae*, *Corynebacterium diphtheriae*, *Yersinia enterocolitica*, and *Treponema pallidum*.
- **Clinical manifestations:** Specific signs and symptoms sometimes suggest that one etiology is more likely than another.
 - **Respiratory viruses:** Symptoms usually are not severe and are associated with coryza without fever, tender cervical lymphadenopathy, or pharyngeal exudates.
 - **Influenza virus and adenovirus:** evidenced by severe exudative pharyngitis with fever, myalgias, and—for adenovirus—conjunctivitis
 - **HSV:** presents as pharyngeal inflammation and exudates with vesicles and ulcers on the palate
 - **Coxsackievirus (herpangina):** characterized by small vesicles on the soft palate and uvula that rupture to form shallow white ulcers
 - **EBV and CMV:** present as acute pharyngitis in association with other signs of infectious mononucleosis (e.g., fever, fatigue, generalized lymphadenopathy)
 - **HIV:** associated with fever, acute pharyngitis, myalgias, malaise, and sometimes a maculopapular rash
 - **Streptococci:** Presentation ranges from mild disease to profound pharyngeal pain, fever, chills, abdominal pain, and a hyperemic pharyngeal membrane with tonsillar hypertrophy and exudates; coryzal symptoms are absent.
 - **Other bacteria:** often present as exudative pharyngitis without other specific findings
- **Diagnosis:** The primary goal of diagnostic testing is to identify cases of GAS pharyngitis.
 - Rapid antigen-detection tests for GAS offer good specificity (>90%) but variable sensitivity (65–90%); throat cultures are recommended for children, but not adults, in the setting of negative rapid testing.
 - Samples for specific cultures for other bacterial and viral causes should be obtained if these diagnoses are suspected.
 - If HIV is being considered, testing for HIV RNA should be performed.
- **Treatment:** Antibiotic treatment for GAS infection (penicillin VK, 500 mg PO tid × 10 days; or benzathine penicillin G, 1.2 million units IM × 1 dose) is recommended for pts with a positive rapid antigen detection test or throat swab culture; treatment modestly reduces symptom duration and prevents the development of rheumatic fever.
 - Long-term penicillin prophylaxis (benzathine penicillin G, 1.2 million units IM every 3–4 weeks; or penicillin VK, 250 mg PO bid) is indicated for pts at risk of recurrent rheumatic fever.
 - Symptom-based treatment of viral pharyngitis is generally sufficient.
 - Specific antiviral treatment (e.g., oseltamivir, acyclovir) may be helpful in selected cases of influenza and HSV infection.

■ ORAL INFECTIONS

Oral–labial herpesvirus infections and oropharyngeal candidiasis are discussed in [Chaps. 102](#) and [108](#), respectively.

INFECTIONS OF THE LARYNX AND EPIGLOTTIS

- **Laryngitis:** Acute laryngitis is a common syndrome caused by nearly all the major respiratory viruses and by some bacteria (e.g., GAS, *C. diphtheriae*, and *M. catarrhalis*). Chronic cases of infectious laryngitis are much less common in developed countries than in low-income countries and are caused by *Mycobacterium tuberculosis*, endemic fungi (e.g., *Histoplasma*, *Blastomyces*, *Coccidioides*), and *Cryptococcus*.
 - Pts are hoarse, exhibit reduced vocal pitch or aphonia, and have coryzal symptoms.
 - Treatment of acute laryngitis consists of humidification, voice rest, and—if GAS is cultured—antibiotic administration. Treatment of chronic laryngitis depends on the pathogen, whose identification usually requires biopsy with culture.
- **Epiglottitis:** acute, rapidly progressive cellulitis of the epiglottis and adjacent structures that can result in complete—and sometimes fatal—airway obstruction
 - Epiglottitis is caused by GAS, *S. pneumoniae*, *Haemophilus parainfluenzae*, and *S. aureus*; pediatric cases due to *H. influenzae* type b are now rare because of vaccination.
 - Symptoms include fever, severe sore throat, and systemic toxicity, and pts often drool while sitting forward. Examination may reveal respiratory distress, inspiratory stridor, and chest wall retractions.
 - Direct visualization in the examination room (i.e., with a tongue blade) should not be performed, given the risk of complete airway obstruction. Direct fiberoptic laryngoscopy in a controlled environment (e.g., an operating room) may be performed for diagnosis, procurement of specimens for culture, and placement of an endotracheal tube.
 - Treatment focuses on airway protection. After blood and epiglottis samples are obtained for cultures, IV antibiotics active against *H. influenzae* (e.g., ampicillin/sulbactam or a second- or third-generation cephalosporin) should be given for 7–10 days.

INFECTIONS OF DEEP NECK STRUCTURES

These infections, which include Ludwig angina, Lemierre syndrome, and retropharyngeal abscess, are discussed in [Chap. 95](#).

60

General Examination of the Skin

As dermatologic evaluation relies heavily on the objective cutaneous appearance, physical examination is often performed prior to taking a complete history in pts presenting with a skin problem. A differential diagnosis can usually be generated on the basis of a thorough examination with precise descriptions of the skin lesion(s) and narrowed with pertinent facts from the history. Laboratory or diagnostic procedures are then used, when appropriate, to clarify the diagnosis.

PHYSICAL EXAMINATION

Examination of skin should take place in a well-illuminated room with pt completely disrobed. Helpful ancillary equipment includes a hand lens and a pocket flashlight to provide peripheral illumination of lesions. An ideal examination includes evaluation of the skin, hair, nails, and mucous membranes. The examination often begins with an assessment of the entire skin viewed at a distance, which is then narrowed down to focus on the individual lesions.

■ DISTRIBUTION

As illustrated in [Fig. 60-1](#), the distribution of skin lesions can provide valuable clues to the identification of the disorder: generalized (systemic diseases); sun-exposed (SLE, photoallergic, phototoxic, polymorphous light eruption, porphyria cutanea tarda); dermatomal (herpes zoster); extensor surfaces (elbows and knees in psoriasis); flexural surfaces (antecubital and popliteal fossae in atopic dermatitis).

■ ARRANGEMENT AND SHAPE

Can describe individual or multiple lesions: *Linear* (contact dermatitis such as poison ivy); *annular*—"ring-shaped" lesion (erythema chronicum migrans, erythema annulare centrifricum, tinea corporis); *iris* or *target lesion*—two or three concentric circles of differing hue (erythema multiforme); *nummular*—"coin-shaped" (nummular eczema); *morbilliform*—"measles-like" with small confluent papules coalescing into unusual shapes (measles, drug eruption); *herpetiform*—grouped vesicles, papules, or erosions (herpes simplex).

■ PRIMARY LESIONS

Cutaneous changes caused directly by disease process ([Table 60-1](#)).

■ SECONDARY LESIONS

Changes in area of primary pathology often due to secondary events, e.g., scratching, secondary infection, bleeding ([Table 60-2](#)).

■ OTHER DESCRIPTIVE TERMS

Color, e.g., violaceous, erythematous; physical characteristics, e.g., warm, tender; sharpness of edge, surface contour—flat-topped, pedunculated (on a stalk), verrucous (wartlike), umbilicated (containing a central depression).

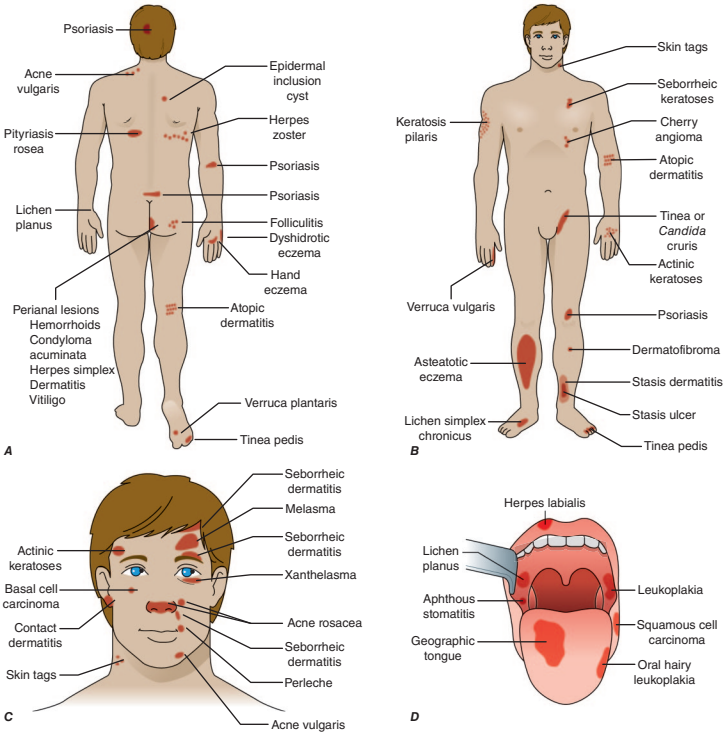


FIGURE 60-1 The distribution of some common dermatologic diseases and lesions.

HISTORY

A complete history should be obtained, with special attention being paid to the following points:

1. Evolution of the lesion—site of onset, manner in which eruption progressed or spread, duration, periods of resolution or improvement in chronic eruptions
2. Symptoms associated with the eruption—itching, burning, pain, numbness; what has relieved symptoms; time of day when symptoms are most severe
3. Current or recent medications—both prescription and over-the-counter
4. Associated systemic symptoms (e.g., malaise, fatigue, arthralgias)
5. Ongoing or previous illnesses
6. History of allergies
7. Presence of photosensitivity
8. Review of systems
9. Family history
10. Social, sexual, or travel history

ADDITIONAL DIAGNOSTIC PROCEDURES

■ SKIN BIOPSY

Minor surgical procedure. Choice of site very important.

TABLE 60-1 Description of Primary Skin Lesions

Macule: A flat, colored lesion, <2 cm in diameter, not raised above the surface of the surrounding skin. A “freckle,” or ephelid, is a prototype pigmented macule.

Patch: A large (>2 cm) flat lesion with a color different from the surrounding skin. This differs from a macule only in size.

Papule: A small, solid lesion, <0.5 cm in diameter, raised above the surface of the surrounding skin and hence palpable (e.g., a closed comedone, or whitehead, in acne).

Nodule: A larger (0.5–5.0 cm), firm lesion raised above the surface of the surrounding skin. This differs from a papule only in size (e.g., a dermal nevocmelanocytic nevus).

Tumor: A solid, raised growth >5 cm in diameter.

Plaque: A large (>1 cm), flat-topped, raised lesion; edges may either be distinct (e.g., in psoriasis) or gradually blend with surrounding skin (e.g., in eczematous dermatitis).

Vesicle: A small, fluid-filled lesion, <0.5 cm in diameter, raised above the plane of surrounding skin. Fluid is often visible, and the lesions are translucent [e.g., vesicles in allergic contact dermatitis caused by *Toxicodendron* (poison ivy)].

Pustule: A vesicle filled with leukocytes. **Note:** The presence of pustules does not necessarily signify the existence of an infection.

Bulla: A fluid-filled, raised, often translucent lesion >0.5 cm in diameter.

Wheal: A raised, erythematous, edematous papule or plaque, usually representing short-lived vasodilatation and vasopermeability.

Telangiectasia: A dilated, superficial blood vessel.

■ POTASSIUM HYDROXIDE PREPARATION

Useful for detection of dermatophyte or yeast. Scale is collected from advancing edge of a scaling lesion by gently scraping with side of a microscope slide or a scalpel blade. Nail lesions are best sampled by trimming back nail and scraping subungual debris. A drop of 10–20% potassium hydroxide is added to slide, and

TABLE 60-2 Description of Secondary Skin Lesions

Lichenification: A distinctive thickening of the skin that is characterized by accentuated skin-fold markings.

Scale: Excessive accumulation of stratum corneum.

Crust: Dried exudate of body fluids that may be either yellow (i.e., serous crust) or red (i.e., hemorrhagic crust).

Erosion: Loss of epidermis without an associated loss of dermis.

Ulcer: Loss of epidermis and at least a portion of the underlying dermis.

Excoriation: Linear, angular erosions that may be covered by crust and are caused by scratching.

Atrophy: An acquired loss of substance. In the skin, this may appear as a depression with intact epidermis (i.e., loss of dermal or subcutaneous tissue) or as sites of shiny, delicate, wrinkled lesions (i.e., epidermal atrophy).

Scar: A change in the skin secondary to trauma or inflammation. Sites may be erythematous, hypopigmented, or hyperpigmented depending on their age or character. Sites on hair-bearing areas may be characterized by destruction of hair follicles.

coverslip is applied. The slide may be gently heated and examined under microscope. This technique can be utilized to identify hyphae in dermatophyte infections, pseudohyphae and budding yeast in *Candida* infections, and “spaghetti and meatballs” yeast forms in tinea versicolor.

■ TZANCK PREPARATION

Useful for determining presence of herpes viruses (herpes simplex virus or herpes zoster virus). Optimal lesion to sample is an early vesicle. Lesion is gently unroofed with no. 15 scalpel blade, and base of vesicle is gently scraped with belly of blade (keep blade perpendicular to skin surface to prevent laceration). Scrapings are transferred to slide and stained with Wright’s or Giemsa stain. A positive preparation has multinucleated giant cells. Culture or immunofluorescence testing must be performed to identify the specific virus.

■ DIASCOPIY

Assesses whether a lesion blanches with pressure. Done by pressing a magnifying lens or microscope slide on lesion and observing changes in vascularity. For example, hemangiomas will usually blanch; purpuric lesions will not.

■ WOOD’S LIGHT EXAMINATION

Useful for detecting bacterial or fungal infection or accentuating features of some skin lesions.

■ PATCH TESTS

To document cutaneous sensitivity to specific antigen.

61

Common Skin Conditions



PAPULOSQUAMOUS DISORDERS

Disorders exhibiting papules and scale.

■ PSORIASIS

A chronic, recurrent disorder. Classic lesion is a well-margined, erythematous plaque with silvery-white surface scale. Distribution includes extensor surfaces (i.e., knees, elbows, and buttocks); may also involve palms and scalp (particularly anterior scalp margin). Associated findings include psoriatic arthritis (Chap. 163) and nail changes (onycholysis, pitting, or thickening of nail plate with accumulation of subungual debris).

TREATMENT

Psoriasis

Maintain cutaneous hydration; topical glucocorticoids; topical vitamin D analogue (calcipotriol) and retinoid (tazarotene); UV light (PUVA, when UV used in combination with psoralens); for severe disease methotrexate or cyclosporine; acitretin can also be used but is teratogenic. Ustekinumab (human monoclonal antibody that blocks IL-12 and IL-23), apremilast (phosphodiesterase 4 inhibitor), secukinumab (anti IL-17), or ixekizumab (anti IL-17) can be considered for chronic, moderate to severe plaque psoriasis and are also approved for

psoriatic arthritis. Guselkumab (anti IL-23) is approved for moderate to severe plaque psoriasis. Etanercept (dimeric fusion protein: TNF receptor/Fc human IgG1), infliximab, adalimumab, and certolizumab pegol (monoclonal antibodies directed against TNF) are approved for psoriasis and psoriatic arthritis.

■ PITYRIASIS ROSEA

A self-limited condition lasting 3–8 weeks. Initially, there is a single 2- to 6-cm annular salmon-colored patch (herald patch) with a peripheral rim of scale, followed in days to weeks by a generalized eruption involving the trunk and proximal extremities. Individual lesions are similar to but smaller than the herald patch and are arranged in symmetric fashion with long axis of each individual lesion along skin lines of cleavage. Appearance may be similar to that of secondary syphilis.

TREATMENT

Pityriasis Rosea

Disorder is self-limited, so treatment is directed at symptoms; oral antihistamines for pruritus; topical glucocorticoids; UV-B phototherapy in some cases.

LICHEN PLANUS

Disorder of unknown cause; can follow administration of certain drugs, chronic graft-versus-host disease, hepatitis C; lesions are pruritic, polygonal, flat-topped, and violaceous. Course is variable, but most pts have spontaneous remissions 6–24 months after onset of disease.

TREATMENT

Lichen Planus

Topical glucocorticoids.

ECZEMATOUS DISORDERS

■ ECZEMA

Eczema, or dermatitis, is a reaction pattern that presents with variable clinical and histologic findings; it is the final common expression for a number of disorders.

■ ATOPIC DERMATITIS

One aspect of atopic triad of hayfever, asthma, and eczema. Usually an intermittent, chronic, severely pruritic, eczematous dermatitis with scaly erythematous patches, vesiculation, crusting, and fissuring. Lesions are most commonly on flexures, with prominent involvement of antecubital and popliteal fossae; generalized erythroderma in severe cases.

TREATMENT

Eczema and Atopic Dermatitis

Avoidance of irritants; cutaneous hydration; topical glucocorticoids; treatment of infected lesions [often with *Staphylococcus aureus* (SA)]—consider

community-acquired methicillin-resistant strains (CA-MRSA)]. Systemic glucocorticoids only for severe exacerbations unresponsive to topical conservative therapy. Topical calcineurin inhibitors have been used for severe disease but may carry toxicity. Crisaborole (phosphodiesterase 4 inhibitor) is approved for topical treatment of mild to moderate atopic dermatitis.

■ ALLERGIC CONTACT DERMATITIS

A delayed hypersensitivity reaction that occurs after cutaneous exposure to an antigenic substance. Lesions occur at site of contact and are vesicular, weeping, crusting; linear arrangement of vesicles is common. Most frequent allergens are resin from plants of the genus *Toxicodendron* (poison ivy, oak, sumac), nickel, rubber, and cosmetics.

TREATMENT

Allergic Contact Dermatitis

Avoidance of sensitizing agent; topical glucocorticoids; consideration of systemic glucocorticoids over 2–3 weeks for widespread disease.

■ IRRITANT CONTACT DERMATITIS

Inflammation of the skin due to direct injury by an exogenous agent. The most common area of involvement is the hands, where dermatitis is initiated or aggravated by chronic exposure to water and detergents. Features may include skin dryness, cracking, erythema, and edema.

TREATMENT

Irritant Contact Dermatitis

Avoidance of irritants; barriers (use of protective gloves); topical glucocorticoids; treatment of secondary bacterial or dermatophyte infection.

■ SEBORRHEIC DERMATITIS

A chronic noninfectious process characterized by erythematous patches with greasy yellowish scale. Lesions are generally on scalp, eyebrows, nasolabial folds, axillae, central chest, and posterior auricular area.

TREATMENT

Seborrheic Dermatitis

Nonfluorinated topical glucocorticoids; shampoos containing coal tar, salicylic acid, or selenium sulfide.

INFECTIONS

■ IMPETIGO

A superficial infection of skin secondary to either *S. aureus* or group A β -hemolytic streptococci. The primary lesion is a superficial pustule that ruptures and forms a “honey-colored” crust. Tense bullae are associated with *S. aureus* infections

(bullous impetigo). Lesions may occur anywhere but commonly involve the face. Impetigo and *furunculosis* (painful erythematous nodule, or boil) have gained prominence because of increasing incidence of CA-MRSA.

TREATMENT

Impetigo

Gentle debridement of adherent crusts with soaks and topical antibiotics; appropriate oral antibiotics depending on organism.

■ ERYSIPELAS

Superficial cellulitis, most commonly on face, characterized by a bright red, sharply demarcated, intensely painful, warm plaque. Because of superficial location of infection and associated edema, surface of plaque may exhibit a *peau d'orange* (orange peel) appearance. Most commonly due to infection with group A β -hemolytic streptococci, occurring at sites of trauma or other breaks in skin.

TREATMENT

Erysipelas

Appropriate antibiotics depending on organism.

■ HERPES SIMPLEX (SEE ALSO CHAP. 102)

Recurrent eruption characterized by grouped vesicles on an erythematous base that progress to erosions; often secondarily infected with staphylococci or streptococci. Infections frequently involve mucocutaneous surfaces around the oral cavity, genitals, or anus. Can also cause severe visceral disease including esophagitis, pneumonitis, encephalitis, and disseminated herpes simplex virus infection. Tzanck preparation of an unroofed early vesicle reveals multinucleated giant cells. Confirmed by detection of virus, viral antigen, or viral DNA in scrapings from lesions.

TREATMENT

Herpes Simplex

Will differ based on disease manifestations and level of immune competence (Chap. 102); appropriate antibiotics for secondary infections, depending on organism.

■ HERPES ZOSTER (SEE ALSO CHAP. 102)

Eruption of grouped vesicles on an erythematous base usually limited to a single dermatome ("shingles"); disseminated lesions can also occur, especially in immunocompromised pts. Tzanck preparation reveals multinucleated giant cells; indistinguishable from herpes simplex except by culture. Detection of varicella zoster virus DNA by PCR is confirmatory but of limited availability. Postherpetic neuralgia, lasting months to years, may occur, especially in the elderly.

TREATMENT**Herpes Zoster**

Will differ based on disease manifestations and level of immune competence ([Chap. 102](#)).

■ DERMATOPHYTE INFECTION

Skin fungus, may involve any area of body; due to infection of stratum corneum, nail plate, or hair. Appearance may vary from mild scaliness to florid inflammatory dermatitis. Common sites of infection include the foot (tinea pedis), nails (tinea unguium), groin (tinea cruris), or scalp (tinea capitis). Classic lesion of tinea corporis (“ringworm”) is an erythematous papulosquamous patch, often with central clearing and scale along peripheral advancing border. Hyphae are often seen on KOH preparation, although tinea capitis and tinea corporis may require culture or biopsy.

TREATMENT**Dermatophyte Infection**

Depends on affected site and type of infection. Topical imidazoles, triazoles, and allylamines may be effective. Haloprogin, undecylenic acid, ciclopirox olamine, and tolnaftate are also effective, but nystatin is not active against dermatophytes. Griseofulvin, 500 mg/d, if systemic therapy required. Itraconazole or terbinafine may be effective for nail infections.

■ CANDIDIASIS

Fungal infection caused by a related group of yeasts. Manifestations may be localized to the skin or rarely systemic and life-threatening. Predisposing factors include diabetes mellitus, cellular immune deficiencies, and HIV ([Chap. 107](#)). Frequent sites include the oral cavity, chronically wet macerated areas, around nails, intertriginous areas. Diagnosed by clinical pattern and demonstration of yeast on KOH preparation or culture.

TREATMENT**Candidiasis**

(See also [Chap. 108](#)). Removal of predisposing factors; topical nystatin or azoles; systemic therapy reserved for immunosuppressed pts, unresponsive chronic or recurrent disease; vulvovaginal candidiasis may respond to a single dose of fluconazole, 150 mg.

■ WARTS

Cutaneous neoplasms caused by human papilloma viruses (HPVs). Typically dome-shaped lesions with irregular, filamentous surface. Propensity for the face, arms, and legs; often spread by shaving. HPVs are also associated with genital or perianal lesions and play a role in the development of cancer of the uterine cervix and anogenital skin ([Chap. 86](#)).

TREATMENT**Warts**

Cryotherapy with liquid nitrogen, keratinolytic agents (salicylic acid). For genital warts, application of podophyllin solution is effective but can be associated with marked local reactions; topical imiquimod also has been used. HPV vaccine reduces the incidence of anogenital and cervical carcinoma.

ACNE**■ ACNE VULGARIS**

Usually a self-limited disorder of teenagers and young adults. Comedones (small cysts formed in hair follicles) are clinical hallmark; often accompanied by inflammatory lesions of papules, pustules, or nodules; may scar in severe cases.

TREATMENT**Acne Vulgaris**

Careful cleaning and removal of oils; oral tetracycline or erythromycin; topical antibacterials (e.g., benzoyl peroxide), topical retinoic acid. Systemic isotretinoin only for unresponsive severe nodulocystic acne (risk of severe adverse events including teratogenicity and possible association with depression).

■ ACNE ROSACEA

Inflammatory disorder affecting predominantly the central face, rarely affecting pts <30 years of age. Tendency toward exaggerated flushing, with eventual superimposition of papules, pustules, and telangiectasias; may lead to rhinophyma and ocular problems.

TREATMENT**Acne Rosacea**

Oral tetracycline, 250–500 mg bid; doxycycline 100 mg bid, minocycline 50–100 mg bid, topical metronidazole and topical nonfluorinated glucocorticoids may be useful.

VASCULAR DISORDERS**■ ERYTHEMA NODOSUM**

Septal panniculitis characterized by erythematous, warm, tender subcutaneous nodular lesions typically over anterior tibia. Lesions are usually flush with skin surface but are indurated and have appearance of an erythematous/violaceous bruise. Lesions usually resolve spontaneously in 3–6 weeks without scarring. Commonly seen in sarcoidosis, administration of certain drugs (esp. sulfonamides, oral contraceptives, and estrogens), and a wide range of infections including streptococcal and tubercular; may be idiopathic.

TREATMENT**Erythema Nodosum**

Identification and treatment/removal of underlying cause. NSAIDs for severe or recurrent lesions; systemic glucocorticoids are effective but dangerous if underlying infection is not appreciated.

■ ERYTHEMA MULTIFORME

A reaction pattern of skin consisting of a variety of lesions but most commonly erythematous papules and bullae. “Target” or “iris” lesion is characteristic and consists of concentric circles of erythema and normal flesh-colored skin, often with a central vesicle or bulla.

Distribution of lesions classically acral, especially palms and soles. Three most common causes are drug reaction (particularly penicillins and sulfonamides) or concurrent herpetic or *Mycoplasma* infection. Can rarely affect mucosal surfaces and internal organs (erythema multiforme major or Stevens-Johnson syndrome).

TREATMENT**Erythema Multiforme**

Provocative agent should be sought and eliminated if drug-related. In mild cases limited to skin, only symptomatic treatment is needed (antihistamines, NSAID). For Stevens-Johnson syndrome, systemic glucocorticoids have been used but are controversial; prevention of secondary infection and maintenance of nutrition and fluid/electrolyte balance are critical.

■ URTICARIA

A common disorder, either acute or chronic, characterized by evanescent (individual lesions lasting <24 h), pruritic, edematous, pink to erythematous plaques with a whitish halo around margin of individual lesions. Lesions range in size from papules to giant coalescent lesions (10–20 cm in diameter). Often due to drugs, systemic infection, or foods (esp. shellfish). If individual lesions last >24 h, consider diagnosis of urticarial vasculitis.

TREATMENT**Urticaria**

See [Chap. 159](#).

■ VASCULITIS

Palpable purpura (nonblanching, elevated lesions) is the cutaneous hallmark of vasculitis. Other lesions include petechiae (esp. early lesions), necrosis with ulceration, bullae, and urticarial lesions (urticarial vasculitis). Lesions usually most prominent on lower extremities. Associations include infections, autoimmune diseases, primary systemic vasculitides, malignancy, hepatitis B and C, drugs, and inflammatory bowel disease. May occur as an idiopathic, predominantly cutaneous vasculitis.

TREATMENT**Vasculitis**

Will differ based on cause. Pursue identification and treatment/elimination of an exogenous cause or underlying disease. If part of a systemic vasculitis, treat based on major organ-threatening features (**Chap. 165**). Immunosuppressive therapy should be avoided in idiopathic, predominantly cutaneous vasculitis as disease frequently does not respond and rarely causes irreversible organ system dysfunction.

CUTANEOUS DRUG REACTIONS

Cutaneous reactions are among the most frequent medication toxicities. These can have a wide range of severity and manifestations including urticaria, photosensitivity, erythema multiforme, fixed drug reactions, erythema nodosum, vasculitis, lichenoid reactions, bullous drug reactions, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN). Diagnosis is usually made by appearance and careful medication history.

TREATMENT**Cutaneous Drug Reactions**

Withdrawal of the medication. Treatment based on nature and severity of cutaneous pathology.

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Examination of Blood Smears
and Bone Marrow**BLOOD SMEARS****ERYTHROCYTE (RBC) MORPHOLOGY**

- *Normal*: 7.5 μm diameter. Roughly the size of the nucleus of a small lymphocyte.
- *Reticulocytes* (Wright's stain): large, grayish-blue, admixed with pink (polychromasia).
- *Anisocytosis*: variation in RBC size; large cells imply delay in erythroid precursor DNA synthesis caused by folate or B₁₂ deficiency or drug effect; small cells imply a defect in hemoglobin synthesis caused by iron deficiency or abnormal hemoglobin genes. The automated red cell distribution width (RDW) is a measure of anisocytosis.
- *Poikilocytosis*: abnormal RBC shapes; the following are examples:
 1. *Acanthocytes* (*spur cells*): irregularly spiculated; abetalipoproteinemia, severe liver disease, rarely anorexia nervosa.
 2. *Echinocytes* (*burr cells*): regularly shaped, uniformly distributed spiny projections; uremia, RBC volume loss.
 3. *Elliptocytes*: elliptical; hereditary elliptocytosis.
 4. *Schistocytes* (*schizocytes*): fragmented cells of varying sizes and shapes; microangiopathic or macroangiopathic hemolytic anemia.
 5. *Sickled cells*: elongated, crescentic; sickle cell anemias.
 6. *Spherocytes*: small hyperchromic cells lacking normal central pallor; hereditary spherocytosis, extravascular hemolysis as in autoimmune hemolytic anemia, G6PD deficiency.
 7. *Target cells*: central and outer rim staining with intervening ring of pallor; liver disease, thalassemia, hemoglobin C, and sickle C diseases.
 8. *Teardrop cells*: myelofibrosis, other infiltrative processes of marrow (e.g., carcinoma).
 9. *Rouleaux formation*: alignment of RBCs in stacks; may be artifactual or due to paraproteinemia (e.g., multiple myeloma, macroglobulinemia).

RBC INCLUSIONS

- *Howell-Jolly bodies*: 1- μm -diameter basophilic cytoplasmic inclusion that represents a residual nuclear fragment, usually single; asplenic pts.
- *Basophilic stippling*: multiple, punctate basophilic cytoplasmic inclusions composed of precipitated mitochondria and ribosomes; lead poisoning, thalassemia, myelofibrosis.
- *Pappenheimer (iron) bodies*: iron-containing granules usually composed of mitochondria and ribosomes resemble basophilic stippling but also stain with Prussian blue; lead poisoning, other sideroblastic anemias.
- *Heinz bodies*: spherical inclusions of precipitated hemoglobin seen only with supravital stains, such as crystal violet; G6PD deficiency (after oxidant stress such as infection, certain drugs), unstable hemoglobin variants.
- *Parasites*: characteristic intracytoplasmic inclusions; malaria, babesiosis.

LEUKOCYTE INCLUSIONS AND NUCLEAR CONTOUR ABNORMALITIES

- *Toxic granulations*: dark cytoplasmic granules; bacterial infection.
- *Döhle bodies*: 1- to 2- μm blue, oval cytoplasmic inclusions; bacterial infection, Chédiak-Higashi anomaly.

- *Auer rods*: eosinophilic, rodlike cytoplasmic inclusions; acute myeloid leukemia (some cases).
- *Hypersegmentation*: neutrophil nuclei contain more than the usual 2–4 lobes; usually >5% have ≥ 5 lobes or a single cell with 7 lobes is adequate to make the diagnosis; folate or B₁₂ deficiency, drug effects.
- *Hyposegmentation*: neutrophil nuclei contain fewer lobes than normal, either one or two: Pelger-Huet anomaly, pseudo-Pelger-Huet or acquired Pelger-Huet anomaly in acute leukemia.

■ PLATELET ABNORMALITIES

- *Platelet clumping*: an in vitro artifact—is often readily detectable on smear; can lead to falsely low platelet count by automated cell counters.
- *Giant platelets*: can be a sign of a very young platelet or increased platelet production or abnormal karyocyte maturation; if the platelets are >5–6 μm in diameter, they may not be counted as platelets by electronic counters.

BONE MARROW

Aspiration assesses cell morphology. *Biopsy* assesses overall marrow architecture, including degree of cellularity. Biopsy should precede aspiration to avoid aspiration artifact (mainly hemorrhage) in the specimen.

■ INDICATIONS

Aspiration

Hypoproliferative or unexplained anemia, leukopenia, or thrombocytopenia, suspected leukemia or myeloma or marrow defect, evaluation of iron stores, workup of some cases of fever of unknown origin.

Special Tests

Histochemical staining (leukemias), cytogenetic studies (leukemias, lymphomas), microbiology (bacterial, mycobacterial, fungal cultures), Prussian blue (iron) stain (assessment of iron stores, diagnosis of sideroblastic anemias).

Biopsy

Performed in addition to aspiration for pancytopenia (aplastic anemia), metastatic tumor, granulomatous infection (e.g., mycobacteria, brucellosis, histoplasmosis), myelofibrosis, lipid storage disease (e.g., Gaucher's, Niemann-Pick), any case with "dry tap" on aspiration; evaluation of marrow cellularity. When biopsy and aspirate are both planned, the biopsy should be performed first because of the risk of bleeding artifact from biopsy of an aspiration site.

Special Tests

Histochemical staining (e.g., acid phosphatase for metastatic prostate carcinoma), immunoperoxidase staining (e.g., immunoglobulin or cell surface marker detection in multiple myeloma, leukemia, or lymphoma; lysozyme detection in monocytic leukemia), reticulin staining (increased in myelofibrosis), microbiologic staining (e.g., acid-fast staining for mycobacteria).

■ INTERPRETATION

Cellularity

Defined as percentage of space occupied by hematopoietic cells. The space that is not hematopoietic tissue is usually fat. Cellularity decreases with age after age 65 years from about 50% to 25–30% with a corresponding increase in fat.

Erythroid:Granulocytic (E:G) Ratio

Normally about 1:2, the E:G ratio is decreased in acute and chronic infection, leukemoid reactions (e.g., chronic inflammation, metastatic tumor), acute and chronic myeloid leukemia, myelodysplastic disorders ("preleukemia"), and pure

red cell aplasia; increased in agranulocytosis, anemias with erythroid hyperplasia (megaloblastic, iron-deficiency, thalassemia, hemorrhage, hemolysis, sideroblastic), and erythrocytosis (excessive RBC production); normal in aplastic anemia (though marrow hypocellular), myelofibrosis (marrow hypocellular), multiple myeloma, lymphoma, anemia of chronic disease. Some centers use the term M:E (myeloid to erythroid) ratio; normal value is 2:1 and increases with diseases that promote myeloid activity or inhibit erythroid activity and decreases with diseases that inhibit myeloid activity or promote erythroid activity.

63

Red Blood Cell Disorders



Anemia is a common clinical problem in medicine. A physiologic approach (outlined in [Chap. 47](#)) provides the most efficient path to diagnosis and management. Anemias arise either because red blood cell (RBC) production is inadequate or because RBC lifespan (normally 120 days) is shortened through loss from the circulation or destruction.

HYPOPROLIFERATIVE ANEMIAS

These are the most common anemias. Usually the RBC morphology is normal and the reticulocyte index (RI) is low. Marrow damage, early iron deficiency, and decreased erythropoietin production or action may produce anemia of this type.

Marrow damage may be caused by infiltration of the marrow with tumor or fibrosis that crowds out normal erythroid precursors or by the absence of erythroid precursors (aplastic anemia) as a consequence of exposure to drugs, radiation, chemicals, viruses (e.g., hepatitis), autoimmune mechanisms, or genetic factors, either hereditary (e.g., Fanconi's anemia) or acquired (e.g., paroxysmal nocturnal hemoglobinuria). Most cases of aplasia are idiopathic. The tumor or fibrosis that infiltrates the marrow may originate in the marrow (as in leukemia or myelofibrosis) or be secondary to processes originating outside the marrow (as in metastatic cancer or myelophthisis).

Early iron-deficiency anemia (or iron-deficient erythropoiesis) is associated with a decrease in serum ferritin levels ($<15 \mu\text{g/L}$), moderately elevated total iron-binding capacity (TIBC) ($>380 \mu\text{g/dL}$), serum iron (SI) level $<50 \mu\text{g/dL}$, and an iron saturation of $<30\%$ but $>10\%$ ([Fig. 63-1](#)). RBC morphology is generally normal until iron deficiency is severe (see below).

Decreased stimulation of erythropoiesis can be a consequence of inadequate erythropoietin production (e.g., renal disease destroying the renal tubular cells that produce it or hypometabolic states [endocrine deficiency or protein starvation]) in which insufficient erythropoietin is produced or of inadequate erythropoietin action. In older people, erythropoietin levels normally increase to maintain normal hemoglobin levels. If this increase does not happen, anemia may develop. About 11% of community-dwelling adults aged >65 and up to 45% of nursing home residents have this aging-related anemia. It is a relative erythropoietin deficiency without renal disease. The anemia of chronic disease is a common entity. It is multifactorial in pathogenesis: inhibition of erythropoietin production, inhibition of iron reutilization (which blocks the response to erythropoietin), and inhibition of erythroid colony proliferation by inflammatory

	Normal	Negative iron balance	Iron-deficient erythropoiesis	Iron-deficiency anemia
Iron stores				
Erythron iron				
Marrow iron stores	1–3+	0–1+	0	0
Serum ferritin (µg/L)	50–200	<20	<15	<15
TIBC (µg/dL)	300–360	>360	>380	>400
SI (µg/dL)	50–150	NL	<50	<30
Saturation (%)	30–50	NL	<20	<10
Marrow sideroblasts (%)	40–60	NL	<10	<10
RBC protoporphyrin (µg/dL)	30–50	NL	>100	>200
RBC morphology	NL	NL	NL	Microcytic/hypochromic

FIGURE 63-1 Measurements of marrow iron stores, serum ferritin, and total iron-binding capacity (TIBC) are sensitive to early iron-store depletion. Iron-deficient erythropoiesis is recognized from additional abnormalities in the serum iron (SI), percent transferrin saturation, the pattern of marrow sideroblasts, and the red cell protoporphyrin level. Pts with iron-deficiency anemia demonstrate all the same abnormalities plus hypochromic microcytic anemia. (From Hillman RS, Finch CA: *Red Cell Manual*, 7th Ed., Philadelphia, Davis, 1996, with permission.)

cytokines (e.g., tumor necrosis factor, interferon γ). Hepcidin, a small iron-binding molecule produced by the liver during an acute-phase inflammatory response, may bind iron and prevent its reutilization in hemoglobin synthesis. The laboratory tests shown in [Table 63-1](#) may assist in the differential diagnosis of hypoproliferative anemias. Measurement of hepcidin in the urine is not yet practical or widely available.

MATURATION DISORDERS

These result from either defective hemoglobin synthesis, leading to cytoplasmic maturation defects and small relatively empty red cells, or abnormally slow DNA replication, leading to nuclear maturation defects and large full red cells. Defects in hemoglobin synthesis usually result from insufficient iron supply (iron deficiency) or decreased globin production (thalassemia) or are idiopathic (sideroblastic anemia). Defects in DNA synthesis are usually due to nutritional problems (vitamin B₁₂ and folate deficiency), toxic (methotrexate or other cancer chemotherapeutic agent) exposure, or intrinsic marrow maturation defects (refractory anemia, myelodysplasia).

Laboratory tests useful in the differential diagnosis of the microcytic anemias are shown in [Table 63-2](#). Mean corpuscular volume (MCV) is generally 60–80 fL.

TABLE 63-1 Diagnosis of Hypoproliferative Anemias

TESTS	IRON DEFICIENCY	INFLAMMATION	RENAL DISEASE	HYPOMETABOLIC STATES	ANEMIA OF AGING
Anemia	Mild to severe	Mild	Mild to severe	Mild	Mild
MCV (fL)	60–90	80–90	90	90	80–90
Morphology	Normomicrocytic	Normocytic	Normocytic	Normocytic	Normocytic
SI	<30	<50	Normal	Normal	Normal
TIBC	>360	<300	Normal	Normal	Normal
Saturation (%)	<10	10–20	Normal	Normal	Normal
Serum ferritin (µg/L)	<15	30–200	115–150	Normal	Normal
Iron stores	0	2–4+	1–4+	Normal	Normal
Erythropoietin levels	High	Normal or High	Low	Normal or Low	Normal

Abbreviations: MCV, mean corpuscular volume; SI, serum iron; TIBC, total iron-binding capacity.

TABLE 63-2 Diagnosis of Microcytic Anemia

TESTS	IRON DEFICIENCY	INFLAMMATION	THALASSEMIA	SIDEROBLASTIC ANEMIA
Smear	Micro/hypo	Normal micro/hypo	Micro/hypo with targeting	Variable
SI	<30	<50	Normal to high	Normal to high
TIBC	>360	<300	Normal	Normal
Percent saturation	<10	10–20	30–80	30–80
Ferritin (µg/L)	<15	30–200	50–300	50–300
Hemoglobin pattern on electrophoresis	Normal	Normal	Abnormal with β thalassemia; can be normal with α thalassemia	Normal

Abbreviations: SI, serum iron; TIBC, total iron-binding capacity.

Increased lactate dehydrogenase (LDH) and indirect bilirubin levels suggest an increase in RBC destruction and favor a cause other than iron deficiency. Iron status is best assessed by measuring SI, TIBC, and ferritin levels. Macrocytic MCVs are >94 fL. Folate status is best assessed by measuring RBC folate levels. Vitamin B₁₂ status is best assessed by measuring serum B₁₂, homocysteine, and methylmalonic acid levels. Homocysteine and methylmalonic acid levels are elevated in the setting of B₁₂ deficiency.

ANEMIA DUE TO RBC DESTRUCTION OR ACUTE BLOOD LOSS

■ BLOOD LOSS

Trauma, GI hemorrhage (may be occult) are common causes; less common are genitourinary sources (menorrhagia, gross hematuria), internal bleeding such as intraperitoneal from spleen or organ rupture, retroperitoneal, iliopsoas hemorrhage (e.g., in hip fractures). Acute bleeding is associated with manifestations of hypovolemia, reticulocytosis, macrocytosis; chronic bleeding is associated with iron deficiency, hypochromia, microcytosis.

■ HEMOLYSIS

Causes are listed in [Table 63-3](#).

1. *Intracellular RBC abnormalities*: most are inherited enzyme defects [glucose-6-phosphate dehydrogenase (G6PD) deficiency $>$ pyruvate kinase deficiency], hemoglobinopathies, sickle cell anemia and variants, thalassemia, unstable hemoglobin variants.
2. *G6PD deficiency*: leads to episodes of hemolysis precipitated by ingestion of drugs that induce oxidant stress on RBCs. These include antimalarials (chloroquine), sulfonamides, analgesics (phenacetin), and other miscellaneous drugs ([Table 63-4](#)).
3. *Sickle cell anemia*: characterized by a single-amino-acid change in β globin (valine for glutamic acid in the 6th residue) that produces a molecule of decreased solubility, especially in the absence of O₂. Although anemia and

TABLE 63-3 Classification of Hemolytic Anemias^a

	INTRACORPUSCULAR DEFECTS	EXTRACORPUSCULAR FACTORS
Hereditary	Hemoglobinopathies Enzymopathies Membrane-cytoskeletal defects	Familial (atypical) hemolytic uremic syndrome
Acquired	Paroxysmal nocturnal hemoglobinuria (PNH)	Mechanical destruction (microangiopathic) Toxic agents Drugs Infectious Autoimmune

^aHereditary causes correlate with intracorporeal defects because these defects are due to inherited mutations. The one exception is PNH because the defect is due to an acquired somatic mutation. Similarly, acquired causes correlate with extracorporeal factors because mostly these factors are exogenous. The one exception is familial hemolytic uremic syndrome (HUS; often referred to as atypical HUS) because here an inherited abnormality allows complement activation to be excessive, with bouts of production of membrane attack complex capable of destroying normal red cells.

TABLE 63-4 Drugs That Carry Risk of Clinical Hemolysis in Persons with G6PD Deficiency

	DEFINITE RISK	POSSIBLE RISK	DOUBTFUL RISK
Antimalarials	Primaquine Dapsone/ chlorproguanil ^a	Chloroquine	Quinine
Sulphonamides/ sulphones	Sulfamethoxazole Others Dapsone	Sulfasalazine Sulfadimidine	Sulfisoxazole Sulfadiazine
Antibacterial/ antibiotics	Cotrimoxazole Nalidixic acid Nitrofurantoin Niridazole	Ciprofloxacin Norfloxacin	Chloramphenicol <i>p</i> -Aminosalicylic acid
Antipyretic/ analgesics	Acetanilide Phenazopyridine	Acetylsalicylic acid high dose (>3 g/d)	Acetylsalicylic acid (<3 g/d) Acetaminophen Phenacetin
Other	Naphthalene Methylene blue	Vitamin K analogues Ascorbic acid >1 g Rasburicase	Doxorubicin Probenecid

^aMarketed as Lapdap from 2003 to 2008.

chronic hemolysis are present, the major disease manifestations relate to vaso-occlusion from misshapen sickled RBCs. Infarcts in lung, bone, spleen, retina, brain, and other organs lead to symptoms and dysfunction (Fig. 63-2).

4. *Membrane abnormalities (rare)*: spur cell anemia (cirrhosis, anorexia nervosa), paroxysmal nocturnal hemoglobinuria, hereditary spherocytosis (increased RBC osmotic fragility, spherocytes), hereditary elliptocytosis (causes mild hemolytic anemia).
5. *Immunohemolytic anemia* (positive Coombs' test, spherocytes): Two types: (a) *warm antibody* (usually IgG): idiopathic, lymphoma, chronic lymphocytic leukemia, systemic lupus erythematosus, drugs (e.g., methyl dopa, penicillins, quinine, quinidine, isoniazid, sulfonamides); and (b) *cold antibody*—cold agglutinin disease (IgM) due to *Mycoplasma* infection, infectious mononucleosis, lymphoma, idiopathic; paroxysmal cold hemoglobinuria (IgG) due to syphilis, viral infections.
6. *Mechanical trauma (macro- and microangiopathic hemolytic anemias; schistocytes)*: prosthetic heart valves, vasculitis, malignant hypertension, eclampsia, renal graft rejection, giant hemangioma, scleroderma, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, march hemoglobinuria (e.g., marathon runners, bongo drummers).
7. *Direct toxic effect*: infections (e.g., malaria, *Clostridium perfringens* toxin, toxoplasmosis).
8. *Hypersplenism* (pancytopenia may be present).

■ LABORATORY ABNORMALITIES

Elevated RI, polychromasia and nucleated RBCs on smear; also spherocytes, elliptocytes, schistocytes, or target, spur, or sickle cells may be present depending on disorder; elevated unconjugated serum bilirubin and LDH, elevated

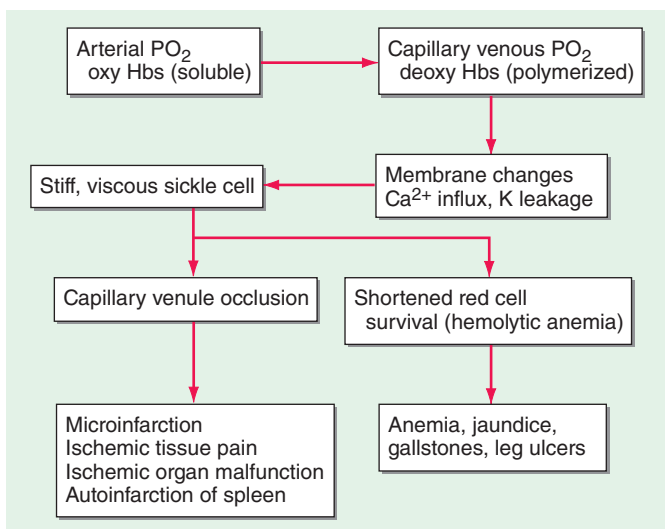


FIGURE 63-2 Pathophysiology of sickle cell crisis.

plasma hemoglobin, low or absent haptoglobin; urine hemosiderin present in intravascular but not extravascular hemolysis, Coombs' test (immuno-hemolytic anemias), osmotic fragility test (hereditary spherocytosis), hemoglobin electrophoresis (sickle cell anemia, thalassemia), G6PD assay (best performed after resolution of hemolytic episode to prevent false-negative result).

TREATMENT

Anemia

GENERAL APPROACHES

The acuteness and severity of the anemia determine whether transfusion therapy with packed RBCs is indicated. Rapid occurrence of severe anemia (e.g., after acute GI hemorrhage resulting in Hct <25%, following volume repletion) or development of angina or other symptoms is an indication for transfusion. Hct should increase 3–4% (Hb by 10 g/L [1 g/dL]) with each unit of packed RBCs, assuming no ongoing losses. Chronic anemia (e.g., vitamin B₁₂ deficiency), even when severe, may not require transfusion therapy if the pt is compensated and specific therapy (e.g., vitamin B₁₂) is instituted.

SPECIFIC DISORDERS

1. *Iron deficiency*: find and treat cause of blood loss, oral iron (e.g., FeSO₄ 300 mg tid).
2. *Folate deficiency*: common in malnourished, alcoholics; less common now than before folate food supplementation; folic acid 1 mg PO qd (5 mg qd for pts with malabsorption).
3. *Vitamin B₁₂ deficiency*: can be managed either with parenteral vitamin B₁₂ 100 µg IM qd for 7 d, then 100–1000 µg IM per month or with 2 mg oral crystalline vitamin B₁₂ per day. An inhaled formulation is also available.
4. *Anemia of chronic disease*: treat underlying disease; in uremia use recombinant human erythropoietin, 50–150 U/kg three times a week; role of erythropoietin

in other forms of anemia of chronic disease is less clear; response more likely if serum erythropoietin levels are low. Target Hb 9–10 g/dL. Iron administration is not useful.

5. *Sickle cell anemia*: hydroxyurea 10–30 mg/kg per day PO increases level of hemoglobin F (HbF) and prevents sickling, treat infections early, supplemental folic acid; painful crises treated with oxygen, analgesics (opioids), hydration, and hypertransfusion; consider allogeneic bone marrow transplantation in pts with increasing frequency of crises.
6. *Thalassemia*: transfusion to maintain Hb >90 g/L (>9 g/dL), folic acid, prevention of Fe overload with deferoxamine (parenteral) or deferasirox (oral) chelation; consider splenectomy and allogeneic bone marrow transplantation.
7. *Aplastic anemia*: antithymocyte globulin and cyclosporine leads to improvement in 70%, bone marrow transplantation in young pts with a matched donor.
8. *Autoimmune hemolysis*: glucocorticoids, sometimes immunosuppressive agents, danazol, plasmapheresis, rituximab.
9. *G6PD deficiency*: avoid agents known to precipitate hemolysis.

64

Leukocytosis and Leukopenia



LEUKOCYTOSIS

APPROACH TO THE PATIENT

Leukocytosis

Review smear (are abnormal cells present?) and obtain differential count. The normal values for concentration of blood leukocytes are shown in [Table 64-1](#).

■ NEUTROPHILIA

Absolute neutrophil count (polys and bands) >10,000/ μ L. The pathophysiology of neutrophilia involves increased production, increased marrow mobilization, or decreased margination (adherence to vessel walls).

Causes

(1) *Exercise, stress*; (2) *infections*—esp. bacterial; smear shows increased numbers of immature neutrophils (“left shift”), toxic granulations, Döhle bodies; (3) *burns*; (4) *tissue necrosis* (e.g., myocardial, pulmonary, renal infarction); (5) *chronic inflammatory disorders* (e.g., gout, vasculitis); (6) *drugs* (e.g., glucocorticoids, epinephrine, lithium); (7) *cytokines* (e.g., granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]); (8) *myeloproliferative disorders* ([Chap. 66](#)); (9) *metabolic* (e.g., ketoacidosis, uremia); (10) *other*—malignant neoplasms, acute hemorrhage or hemolysis, after splenectomy, smoking, obesity.

■ LEUKEMOID REACTION

Extreme elevation of leukocyte count (>50,000/ μ L) composed of mature and/or immature neutrophils.

TABLE 64-1 Normal Values for Leukocyte Concentration in Blood

CELL TYPE	MEAN, CELLS/ μ L	95% CONFIDENCE INTERVALS, CELLS/ μ L	TOTAL WBC, %
Neutrophil	3650	1830–7250	30–60
Lymphocyte	2500	1500–4000	20–50
Monocyte	430	200–950	2–10
Eosinophil	150	0–700	0.3–5
Basophil	30	0–150	0.6–1.8

Causes

(1) *Infection* (severe, chronic, e.g., tuberculosis), esp. in children; (2) *hemolysis* (severe); (3) *malignant neoplasms* (esp. carcinoma of the breast, lung, kidney); (4) *cytokines* (e.g., G-CSF, GM-CSF). May be distinguished from chronic myeloid leukemia (CML) by measurement of the leukocyte alkaline phosphatase (LAP) level: elevated in leukemoid reactions, depressed in CML.

■ LEUKOERYTHROBLASTIC REACTION

Similar to leukemoid reaction with addition of nucleated red blood cells (RBCs) and schistocytes on blood smear.

Causes

(1) *Myelophthisis*—invasion of the bone marrow by tumor, fibrosis, granulomatous processes; smear shows “teardrop” RBCs; (2) *myelofibrosis*—same pathophysiology as myelophthisis, but the fibrosis is a primary marrow disorder; (3) *hemorrhage* or *hemolysis* (rarely, in severe cases).

■ LYMPHOCYTOSIS

Absolute lymphocyte count $>5000/\mu$ L.

Causes

(1) *Infection*—infectious mononucleosis, hepatitis, cytomegalovirus, rubella, pertussis, tuberculosis, brucellosis, syphilis; (2) *endocrine disorders*—thyrotoxicosis, adrenal insufficiency; (3) *neoplasms*—chronic lymphocytic leukemia (CLL), most common cause of lymphocyte count $>10,000/\mu$ L.

■ MONOCYTOSIS

Absolute monocyte count $>800/\mu$ L.

Causes

(1) *Infection*—subacute bacterial endocarditis, tuberculosis, brucellosis, rickettsial diseases (e.g., Rocky Mountain spotted fever), malaria, leishmaniasis; (2) *granulomatous diseases*—sarcoidosis, Crohn’s disease; (3) *collagen vascular diseases*—rheumatoid arthritis, systemic lupus erythematosus (SLE), polyarteritis nodosa, polymyositis, temporal arteritis; (4) *hematologic diseases*—leukemias, lymphoma, myeloproliferative and myelodysplastic syndromes, hemolytic anemia, chronic idiopathic neutropenia; (5) *malignant neoplasms*.

■ EOSINOPHILIA

Absolute eosinophil count $>500/\mu$ L.

Causes

(1) *Drugs*, (2) *parasitic infections*, (3) *allergic diseases*, (4) *collagen vascular diseases*, (5) *malignant neoplasms*, (6) *hypereosinophilic syndromes*.

■ BASOPHILIA

Absolute basophil count $>100/\mu$ L.

Causes

(1) *Allergic diseases*, (2) *myeloproliferative disorders* (esp. CML), (3) *chronic inflammatory disorders* (rarely).

LEUKOPENIA

Total leukocyte count $<4300/\mu\text{L}$.

■ NEUTROPENIA

Absolute neutrophil count $<2000/\mu\text{L}$ (increased risk of bacterial infection with count $<1000/\mu\text{L}$). The pathophysiology of neutropenia involves decreased production or increased peripheral destruction.

Causes

(1) *Drugs*—cancer chemotherapeutic agents are most common cause, also phenytoin, carbamazepine, indomethacin, chloramphenicol, penicillins, sulfonamides, cephalosporins, propylthiouracil, phenothiazines, captopril, methyl dopa, procainamide, chlorpropamide, thiazides, cimetidine, allopurinol, colchicine, ethanol, penicillamine, and immunosuppressive agents; (2) *infections*—viral (e.g., influenza, hepatitis, infectious mononucleosis, HIV), bacterial (e.g., typhoid fever, miliary tuberculosis, fulminant sepsis), malaria; (3) *nutritional*— B_{12} , folate deficiencies; (4) *genetic*—benign ethnic neutropenia (BEN) seen in up to 25% of blacks, no associated risk of infection; inheritance of an allele of the Duffy antigen receptor for cytokines (DARC rs2814778) can be associated with constitutive neutropenia that is not associated with predilection to infection; more common in African Americans; (5) *hematologic diseases*—cyclic neutropenia (q21d, with recurrent infections common), leukemia, myelodysplasia (preleukemia), aplastic anemia, bone marrow infiltration (uncommon cause), Chédiak-Higashi syndrome; treatment with G-CSF is safe and effective over many years; (6) *hypersplenism*—e.g., Felty's syndrome, congestive splenomegaly, Gaucher's disease; (7) *autoimmune diseases*—idiopathic, SLE, lymphoma (may see positive antineutrophil antibodies).

TREATMENT**The Febrile, Neutropenic Pt**

See **Chap. 82**. In addition to usual sources of infection, consider paranasal sinuses, oral cavity (including teeth and gums), anorectal region; empirical therapy with broad-spectrum antibiotics (e.g., ceftazidime or cefepime) is indicated after blood and other appropriate cultures are obtained. Prolonged febrile neutropenia (>7 days) leads to increased risk of disseminated fungal infections; requires addition of antifungal chemotherapy (e.g., amphotericin B, liposomal amphotericin B, voriconazole). The duration of chemotherapy-induced neutropenia may be shortened by a few days by treatment with the cytokines G-CSF.

■ LYMPHOPENIA

Absolute lymphocyte count $<1000/\mu\text{L}$.

Causes

(1) *Acute stressful illness*—e.g., myocardial infarction, pneumonia, sepsis; (2) *glucocorticoid therapy*; (3) *lymphoma* (esp. Hodgkin's lymphoma); (4) *immunodeficiency syndromes*—ataxia telangiectasia and Wiskott-Aldrich and DiGeorge syndromes; (5) *immunosuppressive therapy*—e.g., antilymphocyte globulin, cyclophosphamide; (6) *large-field radiation therapy* (esp. for lymphoma); (7) *intestinal lymphangiectasia* (increased lymphocyte loss); (8) *chronic illness*—e.g.,

congestive heart failure, uremia, SLE, disseminated malignancies; (9) *bone marrow failure/replacement*—e.g., aplastic anemia, miliary tuberculosis.

■ MONOCYTOPENIA

Absolute monocyte count $<100/\mu\text{L}$.

Causes

(1) *Acute stressful illness*, (2) *glucocorticoid therapy*, (3) *aplastic anemia*, (4) *leukemia* (certain types, e.g., hairy cell leukemia), (5) *chemotherapeutic and immunosuppressive agents*.

■ EOSINOPENIA

Absolute eosinophil count $<50/\mu\text{L}$.

Causes

(1) *Acute stressful illness*, (2) *glucocorticoid therapy*.

65

Bleeding and Thrombotic Disorders



BLEEDING DISORDERS

Bleeding may result from abnormalities of (1) platelets, (2) blood vessel walls, or (3) coagulation. Platelet disorders characteristically produce petechial and purpuric skin lesions and bleeding from mucosal surfaces. Defective coagulation results in ecchymoses, hematomas, and mucosal and, in some disorders, recurrent joint bleeding (hemarthroses).

■ PLATELET DISORDERS

Thrombocytopenia

Normal platelet count is $150,000\text{--}350,000/\mu\text{L}$. Thrombocytopenia is defined as a platelet count $<100,000/\mu\text{L}$. Bleeding time, a measurement of platelet function, is abnormally increased if platelet count is $<100,000/\mu\text{L}$; injury or surgery may provoke excess bleeding. Spontaneous bleeding is unusual unless count $<20,000/\mu\text{L}$; platelet count $<10,000/\mu\text{L}$ may be associated with serious hemorrhage. Bone marrow examination shows increased number of megakaryocytes in disorders associated with accelerated platelet destruction; decreased number in disorders of platelet production. Evaluation of thrombocytopenia is shown in [Fig. 65-1](#).

Causes

(1) Production defects such as marrow injury (e.g., drugs, irradiation), marrow failure (e.g., aplastic anemia), marrow invasion (e.g., carcinoma, leukemia, fibrosis); (2) sequestration due to splenomegaly; (3) accelerated destruction—causes include:

- *Drugs* such as chemotherapeutic agents, thiazides, ethanol, estrogens, sulfonamides, quinidine, quinine, methyl dopa.
- *Heparin-induced thrombocytopenia (HIT)* is seen in 5% of pts receiving >5 days of therapy and is due to in vivo platelet aggregation often from anti-platelet factor 4 antibodies. Arterial and occasionally venous thromboses may result. Despite the low platelets, HIT is a hypercoagulable state.
- *Autoimmune destruction* by an antibody mechanism; may be idiopathic or associated with systemic lupus erythematosus (SLE), lymphoma, HIV.

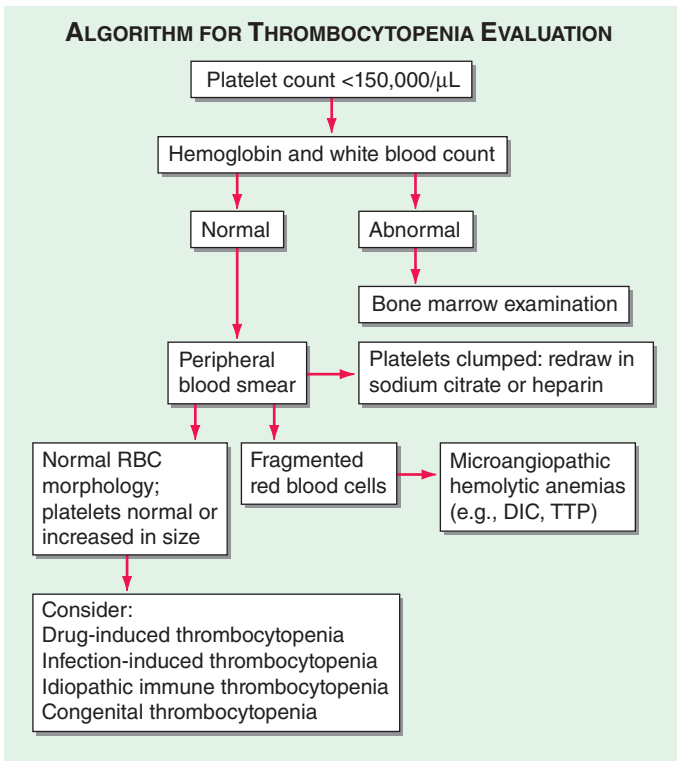


FIGURE 65-1 Algorithm for evaluating the thrombocytopenic pt. DIC, disseminated intravascular coagulation; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura.

- *Idiopathic thrombocytopenic purpura* (ITP) has two forms: an acute, self-limited disorder of childhood requiring no specific therapy, and a chronic disorder of adults (esp. women 20–40 years). Chronic ITP may be due to autoantibodies to glycoprotein IIb/IIIa or glycoprotein Ib-IX complexes.
- *Disseminated intravascular coagulation* (DIC): platelet consumption with coagulation factor depletion (prolonged prothrombin time [PT], partial thromboplastin time [PTT]) and stimulation of fibrinolysis (generation of fibrin split products [FSPs]). Blood smear shows microangiopathic hemolysis (schistocytes). Causes include infection (esp. meningococcal, pneumococcal, gram-negative bacteremias), extensive burns, trauma, or thrombosis; giant hemangioma, retained dead fetus, heat stroke, mismatched blood transfusion, metastatic carcinoma, acute promyelocytic leukemia.
- *Thrombotic thrombocytopenic purpura* (TTP): rare disorder characterized by microangiopathic hemolytic anemia, fever, thrombocytopenia, renal dysfunction (and/or hematuria), and neurologic dysfunction most commonly caused by antibodies to ADAMTS13, a protease that normally cleaves von Willebrand factor (vWF); when vWF is not cleaved, it spontaneously binds and activates adherence of platelets.
- *Hemorrhage with extensive transfusion.*

Pseudothrombocytopenia

Platelet clumping usually secondary to collection of blood in EDTA (0.3% of pts). Examination of blood smear establishes diagnosis.

Thrombocytosis

Platelet count $>350,000/\mu\text{L}$. Either primary (essential thrombocytosis; **Chap. 66**) or secondary (reactive); latter secondary to severe hemorrhage, iron deficiency, surgery, after splenectomy (transient), malignant neoplasms (esp. Hodgkin's lymphoma, polycythemia vera, ovarian cancer; possibly related to IL6 production by the tumor), chronic inflammatory diseases (e.g., inflammatory bowel disease), recovery from acute infection, vitamin B₁₂ deficiency, drugs (e.g., vincristine, epinephrine). Rebound thrombocytosis may occur after marrow recovery from cytotoxic agents, alcohol, vitamin B₁₂ replenishment. Primary thrombocytosis may be complicated by bleeding and/or thrombosis; generally problems not seen until the platelet count is >1.5 million/ μL ; secondary rarely causes hemostatic problems.

Disorders of Platelet Function

Suggested by the finding of prolonged bleeding time with normal platelet count. Defect is in platelet adhesion, aggregation, or granule release. Causes include (1) drugs— aspirin, other nonsteroidal anti-inflammatory drugs, dipyridamole, clopidogrel or prasugrel, heparin, penicillins, esp. carbenicillin, ticarcillin; (2) uremia; (3) cirrhosis; (4) dysproteinemias; (5) myeloproliferative and myelodysplastic disorders; (6) von Willebrand disease (vWD; see below); (7) cardiopulmonary bypass.

■ HEMOSTATIC DISORDERS DUE TO BLOOD VESSEL WALL DEFECTS

Causes include (1) aging; (2) drugs—e.g., glucocorticoids (chronic therapy), penicillins, sulfonamides; (3) vitamin C deficiency; (4) TTP; (5) hemolytic uremic syndrome; (6) Henoch-Schönlein purpura; (7) paraproteinemias; (8) hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease).

■ DISORDERS OF BLOOD COAGULATION**Congenital Disorders**

1. *Hemophilia A*: incidence 1:5000; sex-linked recessive deficiency of factor VIII (low plasma factor VIII coagulant activity, but normal amount of factor VIII-related antigen—vWF). Laboratory features: elevated PTT, normal PT.
2. *Hemophilia B (Christmas disease)*: incidence 1:30,000, sex-linked recessive, due to factor IX deficiency. Clinical and laboratory features similar to hemophilia A.
3. *von Willebrand disease*: most common inherited coagulation disorder (1:800–1000), usually autosomal dominant; primary defect is reduced synthesis or chemically abnormal factor VIII-related antigen produced by platelets and endothelium, resulting in abnormal platelet function.

Acquired Disorders

1. *Vitamin K deficiency*: impairs production of factors II (prothrombin), VII, IX, and X; vitamin K is a cofactor in the carboxylation of glutamate residues on prothrombin complex proteins; major source of vitamin K is dietary (esp. green vegetables), with minor production by gut bacteria. Laboratory features: elevated PT and PTT.
2. *Liver disease*: results in deficiencies of all clotting factors except VIII. Laboratory features: elevated PT, normal or elevated PTT.
3. *Other disorders*: DIC, fibrinogen deficiency (liver disease, L-asparaginase therapy, rattlesnake bites), other factor deficiencies, circulating anticoagulants (lymphoma, SLE, idiopathic), massive transfusion (dilutional coagulopathy).

TREATMENT**Bleeding Disorders****THROMBOCYTOPENIA CAUSED BY DRUGS**

Discontinue use of possible offending agents; expect recovery in 7–10 days. Platelet transfusions may be needed if platelet count $<10,000/\mu\text{L}$. Use of platelet stimulating agents is controversial.

HIT

Discontinue heparin promptly. A direct thrombin inhibitor such as lepirudin (0.4-mg/kg bolus, 0.15-mg/kg per hour infusion; PTT target $1.5\text{--}2.5 \times$ baseline) or argatroban (2- $\mu\text{g}/\text{kg}$ per min infusion; PTT target $1.5\text{--}3 \times$ baseline) should be used for treatment of thromboses. Do not use low-molecular-weight heparin (LMWH), as antibodies often cross-react. Fondaparinux is also effective.

CHRONIC ITP

Intervention may not be necessary in the absence of bleeding or platelet count $>40,000/\mu\text{L}$. Prednisone, initially 1–2 mg/kg per day, then slow taper to keep the platelet count $>60,000/\mu\text{L}$. Dexamethasone 40 mg/d for 4 days, q2–4 weeks may be even more effective. Intravenous immunoglobulin (IVIg) (2 g/kg in divided doses over 2–5 days) to block phagocytic destruction may be useful. Rituximab is effective in pts refractory to glucocorticoids. Eltrombopag (50 mg PO qd) boosts platelet production and allows delay or avoidance of splenectomy. Splenectomy, danazol (androgen), or other agents (e.g., vincristine, cyclophosphamide, fludarabine) are indicated for refractory pts or those requiring $>5\text{--}10$ mg prednisone daily.

DIC

Control of underlying disease most important; platelets, fresh-frozen plasma (FFP) to correct clotting parameters. Heparin may be beneficial in pts with acute promyelocytic leukemia.

TTP

Plasmapheresis and FFP infusions (plasma exchange), possibly IV IgG; recovery in two-thirds of cases. Plasmapheresis removes inhibitors of the vWF cleavage enzyme (ADAMTS13), and FFP replaces the enzyme. Caplacizumab is an anti-vWF single variable domain immunoglobulin (nanobody) that inhibits the interaction between vWF multimers and platelets and can accelerate normalization of the platelet count.

DISORDERS OF PLATELET FUNCTION

Remove or reverse underlying cause. Dialysis and/or cryoprecipitate infusions (10 bags/24 h) may be helpful for platelet dysfunction associated with uremia.

HEMOSTATIC DISORDERS

Withdraw offending drugs, replace vitamin C, plasmapheresis, and plasma infusion for TTP.

HEMOPHILIA A

Factor VIII replacement for bleeding or before surgical procedure; degree and duration of replacement depends on severity of bleeding. Give factor VIII (e.g., Recombinate) to obtain a 15% (for mild bleeding) to 50% (for severe bleeding) factor VIII level. The duration should range from a single dose of factor VIII to therapy bid for up to 2 weeks. Dose is calculated as follows:

$$\text{Factor VIII dose} = (\text{Target level} - \text{baseline level}) \times \text{weight (kg)} \times 0.5 \text{ unit/kg}$$

Up to 33% of pts may develop anti-factor VIII antibodies; activated factor VII or factor eight inhibitor bypass agent (FEIBA) may stop or prevent bleeding in these pts. In pts with or without anti-factor VIII antibodies, emicizumab (3 mg/kg every other week) may be effective. It is a bispecific antibody that bridges activated factor IX and factor X to replace the function of activated factor VIII.

Progress is noted in gene therapy of factor VIII deficiency using an adeno-associated virus 5 vector.

HEMOPHILIA B

Recombinant factor IX (e.g., Benefix), FFP or factor IX concentrates (e.g., Proplex, Konyne). Because of the longer half-life, once-daily treatment is sufficient. Dose is calculated as follows:

$$\text{Factor IX dose} = (\text{Target level} - \text{baseline level}) \times \text{weight (kg)} \times 1 \text{ unit/kg}$$

Gene therapy using a hyperfunctional factor IX variant (factor IX Padua, R338L) has made 8 of 10 factor IX-dependent pts independent of factor IX infusions.

VON WILLEBRAND DISEASE

Desmopressin (1-deamino-8-D-arginine vasopressin) increases release of vWF from endothelial stores in type 1 vWD. It is given IV (0.3 µg/kg) or by nasal spray (2 squirts of 1.5-mg/mL fluid in each nostril). For types 2A, 2M, and 3, cryoprecipitate (plasma product rich in factor VIII) or factor VIII concentrate (Humate-P, Koate HS) is used: up to 10 bags bid for 48–72 h, depending on the severity of bleeding.

VITAMIN K DEFICIENCY

Vitamin K, 10 mg SC or slow IV.

LIVER DISEASE

Fresh-frozen plasma.

THROMBOTIC DISORDERS

■ HYPERCOAGULABLE STATE

Consider in pts with recurrent episodes of venous thrombosis (i.e., deep-vein thrombosis [DVT], pulmonary embolism [PE]). Causes include (1) venous stasis (e.g., pregnancy, immobilization); (2) vasculitis; (3) cancer and myeloproliferative disorders; (4) oral contraceptives; (5) lupus anticoagulant—antibody to platelet phospholipid, stimulates coagulation; (6) HIT; (7) deficiencies of endogenous anti-coagulant factors—antithrombin III, protein C, protein S; (8) factor V Leiden—mutation in factor V (Arg → Glu at position 506) confers resistance to inactivation by protein C, accounts for 25% of cases of recurrent thrombosis; (9) prothrombin gene mutation—Glu → Arg at position 20210 results in increased prothrombin levels; accounts for about 6% of thromboses; (10) other—paroxysmal nocturnal hemoglobinuria, dysfibrinogenemias (abnormal fibrinogen).

The approach to the diagnosis of the pt with DVT and/or PE is discussed in [Chap. 135](#).

TREATMENT

Thrombotic Disorders

Correct underlying disorder whenever possible; long-term warfarin therapy is otherwise indicated.

ANTICOAGULANT AGENTS

1. *Heparin*: enhances activity of antithrombin III; parenteral agent of choice. LMWH is the preparation of choice (enoxaparin or dalteparin). It can be administered SC, monitoring of the PTT is unnecessary, and it is less likely to induce antibodies and thrombocytopenia. The usual dose is 100 U/kg SC bid. Unfractionated heparin should be given only if LMWH is unavailable. In adults, the dose of unfractionated heparin is 25,000–40,000 U continuous IV infusion over 24 h following initial IV bolus of 5000 U; monitor by following PTT; should be maintained between 1.5 and 2 times upper normal limit. Prophylactic anticoagulation to lower risk of venous thrombosis recommended in some pts (e.g., postoperative, immobilized). Prophylactic doses of unfractionated heparin are 5000 U SC bid or tid. Major complication of unfractionated heparin therapy is hemorrhage—manage by discontinuing heparin; for severe bleeding, administer protamine (1 mg/100 U heparin); results in rapid neutralization.
2. *Warfarin (Coumadin)*: vitamin K antagonist, decreases levels of factors II, VII, IX, X, and anticoagulant proteins C and S. Administered over 2–3 days; initial load of 5–10 mg PO qd followed by titration of daily dose to keep PT 1.5–2 times control PT or 2–3 times if the International Normalized Ratio (INR) method is used. Complications include hemorrhage, warfarin-induced skin necrosis (rare, occurs in persons deficient in protein C), teratogenic effects. Warfarin effect reversed by administration of vitamin K; FFP infused if urgent reversal necessary. Numerous drugs potentiate or antagonize warfarin effect. Potentiating agents include chlorpromazine, chloral hydrate, sulfonamides, chloramphenicol, other broad-spectrum antibiotics, allopurinol, cimetidine, tricyclic antidepressants, disulfiram, laxatives, high-dose salicylates, thyroxine, clofibrate. Some pts who are sensitive to warfarin effects have genetic defects metabolizing the drug. Antagonizing agents include vitamin K, barbiturates, rifampin, cholestyramine, oral contraceptives, thiazides.
3. *Fondaparinux*: a pentapeptide that directly inhibits factor Xa. It is given at a dose of 2.5 mg SC daily for prophylaxis and 7.5 mg SC daily for treatment of thrombosis and does not require monitoring. Unlike the heparins, it does not bind to platelet factor 4 and does not elicit the antibodies that produce HIT. *Apixaban* and *rivaroxaban* are oral factor Xa inhibitors. *Apixaban* (5 mg PO bid) as effective as warfarin in DVT and more effective in stroke prevention in atrial fibrillation (AF).
4. *Argatroban* and *lepirudin*: direct thrombin inhibitors. These agents are being compared to LMWH and are commonly used in pts with HIT. Both are monitored with the activated PTT. *Dabigatran* (150 mg PO bid) is an oral thrombin inhibitor and is non-inferior to warfarin in both DVT and stroke prevention in AF.
5. *DOACs*: direct oral anticoagulants. These include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors, rivaroxaban, apixaban, and edoxaban. **Table 65-1** shows the pharmacologic properties of these agents.

In-hospital anticoagulation is usually initiated with heparin for 4–10 days, with subsequent maintenance on warfarin after an overlap of 3 days. Duration of therapy depends on underlying condition; calf DVT with clear precipitating cause, 3 months; proximal or idiopathic DVT or PE, 6–12 months; recurrent idiopathic DVT, 12 months minimum; embolic disease with ongoing risk factor, long term, indefinite. The new oral Xa and thrombin inhibitors are easier to use than warfarin. They are at least comparably effective, have lower bleeding rates, and do not require laboratory monitoring. They are not effective in pts with heart

TABLE 65-1 Comparison of the Pharmacologic Properties of the New Oral Anticoagulants

CHARACTERISTIC	RIVAROXABAN	APIXABAN	EDOxabAN	DABIGATRAN
Target	Factor Xa	Factor Xa	Factor Xa	Thrombin
Prodrug	No	No	No	Yes
Bioavailability	80%	60%	50%	6%
Dosing	qd (bid)	bid	qd	bid (qd)
Half-life	7–11 h	12 h	9–11 h	12–17 h
Renal excretion	33% (66%)	25%	35%	80%
Interactions	CYP 3A4/P-gp	CYP 3A4/P-gp	P-gp	P-gp

Abbreviations: bid, twice a day; CYP, cytochrome P450; P-gp, P-glycoprotein; qd, once a day.

valve problems. Reversal agents include andexanet-alfa, a modified recombinant factor Xa that acts as a decoy for the factor Xa inhibitors, and idarucizumab, a monoclonal antibody fragment with high affinity for dabigatran.

FIBRINOLYTIC AGENTS

Tissue plasminogen activators (tPAs) mediate clot lysis by activating plasmin, which degrades fibrin. Currently available versions include streptokinase, urokinase, anistreplase (acylated plasminogen streptokinase activator complex), and three modestly distinct forms of recombinant tPA: alteplase, tenecteplase, and reteplase. Indications include treatment of DVT, with lower incidence of post-phlebotic syndrome (chronic venous stasis, skin ulceration) than with heparin therapy; massive PE, arterial embolic occlusion of an extremity, treatment of acute myocardial infarction (MI), unstable angina pectoris. Dosages for fibrinolytic agents: (1) tPA—for acute MI and massive PE (adult >65 kg), 10-mg IV bolus over 1–2 min, then 50 mg IV over 1 h, and 40 mg IV over next 2 h (total dose = 100 mg). tPA is slightly more effective but more expensive than streptokinase for treatment of acute MI. (2) Streptokinase—for acute MI, 1.5 million IU IV over 60 min; or 20,000 IU as a bolus intracoronary (IC) infusion, followed by 2000 IU/min for 60 min IC. For PE or arterial or DVT, 250,000 IU over 30 min, then 100,000 IU/h for 24 h (PE) or 72 h (arterial or DVT). (3) Urokinase—for PE, 4400 IU/kg IV over 10 min, then 4400 (IU/kg)/h IV for 12 h.

Fibrinolytic therapy is usually followed by a period of anticoagulant therapy with heparin. Fibrinolytic agents are contraindicated in pts with (1) active internal bleeding; (2) recent (<2–3 months) cerebrovascular accident; (3) intracranial neoplasm, aneurysm, or recent head trauma.

ANTIPLATELET AGENTS

Aspirin inhibits platelet function by blocking the ability of cyclooxygenase (COX-1) to synthesize thromboxane A₂. The thienopyridines (ticlopidine and clopidogrel) inhibit ADP-induced platelet aggregation by blocking its receptor (P2Y₁₂). Dipyridamole acts by inhibiting phosphodiesterase, which permits cAMP levels to increase and block activation. Glycoprotein IIb/IIIa (GPIIb/IIIa) antagonists block the integrin receptors on the platelet and prevent platelet aggregation. Three such agents are now in use: abciximab, an Fab antibody fragment that binds to the activated form of GPIIb/IIIa; eptifibatid, a cyclic heptapeptide that includes the KGD tripeptide motif that the GPIIb/IIIa receptor recognizes; and tirofiban, a tyrosine derivative that mimics the KGD motif.

Aspirin (160–325 mg/d) plus clopidogrel (400-mg loading dose then 75 mg/d) may be beneficial in lowering incidence of arterial thrombotic events (stroke, MI) in high-risk pts. Antiplatelet agents are useful in preventing strokes, complications from percutaneous coronary interventions, and progression of unstable angina.

66

Myeloid Leukemias, Myelodysplasia, and Myeloproliferative Syndromes



ACUTE MYELOID LEUKEMIA (AML)

AML is a clonal malignancy of myeloid bone marrow precursors in which poorly differentiated cells accumulate in the bone marrow and circulation.

Signs and symptoms occur because of the absence of mature cells normally produced by the bone marrow, including granulocytes (susceptibility to infection) and platelets (susceptibility to bleeding). In addition, if large numbers of immature malignant myeloblasts circulate, they may invade organs and rarely produce dysfunction. There are distinct morphologic subtypes (Table 66-1) that have largely overlapping clinical features. Of note is the propensity of pts with acute promyelocytic leukemia (APL) (FAB M3) to develop bleeding and disseminated intravascular coagulation, especially during induction chemotherapy, because of the release of procoagulants from their cytoplasmic granules.

Incidence and Etiology

In the United States about 19,520 cases occurred in 2018. AML accounts for about 80% of acute leukemias in adults. Etiology is unknown for the vast majority. As we age, mutations may occur in normal stem cells that convey a proliferative advantage and establish so-called clonal hematopoiesis. In the setting of clonal hematopoiesis, the relative risk for developing acute leukemia increases but the absolute risk is still very small. Three environmental exposures increase the risk: chronic benzene exposure, radiation exposure, and prior treatment with alkylating agents (especially in addition to radiation therapy) and topoisomerase II inhibitors (e.g., doxorubicin and etoposide). Chronic myeloid leukemia (CML), myelodysplasia, and myeloproliferative syndromes may all evolve into AML. Certain genetic abnormalities are associated with particular morphologic variants: t(15;17) with APL, inv(16) with eosinophilic leukemia; others occur in a number of types. Chromosome 11q23 abnormalities are often seen in leukemias developing after exposure to topoisomerase II inhibitors. Chromosome 5 or 7 deletions are seen in leukemias following radiation plus chemotherapy. The particular genetic abnormality has a strong influence on treatment outcome. Expression of MDR1 (multidrug resistance efflux pump) is common in older pts and adversely affects prognosis.

Clinical and Laboratory Features

Initial symptoms of acute leukemia have usually been present for <3 months; a preleukemic syndrome may be present in some 25% of pts with AML. Signs of anemia, pallor, fatigue, weakness, palpitations, and dyspnea on exertion are

TABLE 66-1 AML Classification Systems**World Health Organization classification^a****AML with recurrent genetic abnormalities**AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*^bAML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*^bAcute promyelocytic leukemia with t(15;17)(q22;q12); *PML-RARA*^bAML with t(9;11)(p22;q23); *MLLT3-MLL*AML with t(6;9)(p23;q34); *DEK-NUP214*AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1**Provisional entity: AML with mutated NPM1**Provisional entity: AML with mutated CEBPA***AML with myelodysplasia-related changes****Therapy-related myeloid neoplasms****AML not otherwise specified**

AML with minimal differentiation

AML without maturation

AML with maturation

Acute myelomonocytic leukemia

Acute monoblastic and monocytic leukemia

Acute erythroid leukemia

Acute megakaryoblastic leukemia

Acute basophilic leukemia

Acute panmyelosis with myelofibrosis

Myeloid sarcoma**Myeloid proliferations related to Down syndrome**

Transient abnormal myelopoiesis

Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm**Acute leukemia of ambiguous lineage**

Acute undifferentiated leukemia

Mixed phenotype acute leukemia with t(9;22)(q34;q11.20); *BCR-ABL1*Mixed phenotype acute leukemia with t(v;11q23); *MLL* rearranged

Mixed phenotype acute leukemia, B/myeloid, NOS

Mixed phenotype acute leukemia, T/myeloid, NOS

*Provisional entity: Natural killer (NK)-cell lymphoblastic leukemia/lymphoma***French-American-British (FAB) classification^c**

M0: Minimally differentiated leukemia

M1: Myeloblastic leukemia without maturation

M2: Myeloblastic leukemia with maturation

M3: Hypergranular promyelocytic leukemia

M4: Myelomonocytic leukemia

M4Eo: Variant: Increase in abnormal marrow eosinophils

M5: Monocytic leukemia

M6: Erythroleukemia (Di Guglielmo's disease)

M7: Megakaryoblastic leukemia

^aData from Swerdlow SH et al (eds): *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, 4th edition update, IARC Press, 2017.^bDiagnosis is AML regardless of blast count.^cData from Bennett JM et al: Proposed revised criteria for the classification of acute myeloid leukemia. *Ann Intern Med* 103:620, 1985.**Abbreviation:** AML, acute myeloid leukemia.

most common. White blood cell count (WBC) may be low, normal, or markedly elevated; circulating blast cells may or may not be present; with WBC $>100 \times 10^9$ blasts per liter, leukostasis in lungs and brain may occur. Minor pyogenic infections of the skin are common. Thrombocytopenia leads to spontaneous bleeding, epistaxis, petechiae, conjunctival hemorrhage, gingival bleeding, and bruising, especially with platelet count $<20,000/\mu\text{L}$. Anorexia and weight loss are common; fever may be present.

Bacterial and fungal infection are common; risk is heightened with total neutrophil count $<5000/\mu\text{L}$, and breakdown of mucosal and cutaneous barriers aggravates susceptibility; infections may be clinically occult in presence of severe leukopenia, and prompt recognition requires a high degree of clinical suspicion.

Hepatosplenomegaly occurs in about one-third of pts; leukemic meningitis may present with headache, nausea, seizures, papilledema, cranial nerve palsies.

Metabolic abnormalities may include hyponatremia, hypokalemia, elevated serum lactate dehydrogenase (LDH), hyperuricemia, and (rarely) lactic acidosis. With very high blast cell count in the blood, spurious hyperkalemia and hypoglycemia may occur (potassium released from and glucose consumed by tumor cells after the blood was drawn).

TREATMENT

Acute Myeloid Leukemia

Leukemic cell mass at time of presentation may be 10^{11} – 10^{12} cells; when total leukemic cell numbers fall below $\sim 10^9$, they are no longer detectable in blood or bone marrow and pt appears to be in complete remission (CR). Thus, aggressive therapy must continue past the point when initial cell bulk is reduced if leukemia is to be eradicated. Typical phases of chemotherapy include remission induction and postremission therapy, with treatment lasting about 1 year. [Figure 66-1](#) outlines a treatment algorithm.

Supportive care with transfusions of red cells and platelets (from cytomegalovirus [CMV]-seronegative donors, if pt is a candidate for bone marrow transplantation) is very important, as are aggressive prevention, diagnosis, and treatment of infections. Colony-stimulating factors offer little or no benefit; some recommend their use in older pts and those with active infections. Febrile neutropenia should be treated with broad-spectrum antibiotics (e.g., ceftazidime 1 g q8h); if febrile neutropenia persists beyond 7 days, a broad spectrum antifungal agent should be added.

About 60–80% of pts will achieve initial remission when treated with cytarabine 100–200 (mg/m²)/d by continuous infusion for 7 days, and daunorubicin (45 [mg/m²]/d) or idarubicin (12–13 [mg/m²]/d) for 3 days. Addition of etoposide may improve CR duration. Half of treated pts enter CR with the first cycle of therapy, and another 25% require two cycles. About 10–30% of pts achieve 5-year disease-free survival and probable cure. Pts achieving a CR who have low risk of relapse (cells contain t[8;21] or inv[16]) receive 3–4 cycles of cytarabine. Those at high risk of relapse may be considered for allogeneic bone marrow transplantation.

Response to treatment after relapse is short, and prognosis for pts who have relapsed is poor. In APL, arsenic trioxide plus *trans*-retinoic acid (tretinoin) induces differentiation of the leukemic cells and molecular CRs. A fraction of pts may develop pulmonary symptoms from the sludging of differentiated neoplastic granulocytes in the lung. Glucocorticoids may speed recovery from this syndrome.

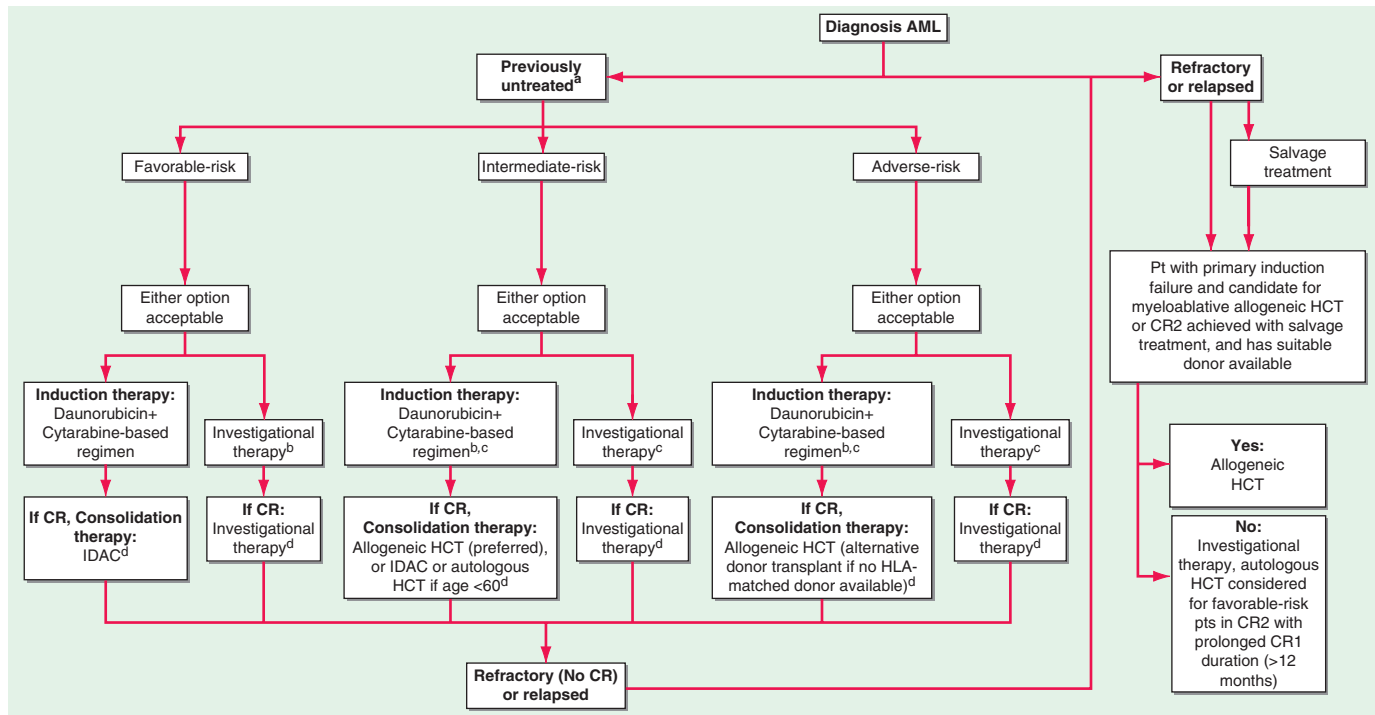


FIGURE 66-1 Flowchart for the therapy of newly diagnosed acute myeloid leukemia (AML). ^aRisk stratification according to the European LeukemiaNet. ^bYounger pts (<60–65 years) should routinely be offered investigational therapy on a backbone of standard chemotherapy for induction and consolidation. ^cOlder pts, especially those >65 years or with adverse-risk disease, or those who are unfit for intensive daunorubicin + cytarabine regimens, may be considered for investigational therapy alone or in combination with lower intensity chemotherapy regimens (azacitidine, decitabine). ^dInvestigational therapy as maintenance should be considered if available (after consolidation for younger pts and older pts with favorable-risk disease, and for all other older pts after induction).

For all forms of AML except acute promyelocytic leukemia (APL), standard induction therapy includes a regimen based on a 7-day continuous infusion of cytarabine (100–200 mg/m²/d) and a 3-day course of daunorubicin (60–90 mg/m²/d) with or without additional drugs. Idarubicin (12 mg/m²/d) could be used in place of daunorubicin (not shown). The value of postremission/consolidation therapy for older pts (>60 years) who do not have favorable-risk disease is uncertain. Pts who achieve complete remission (CR) undergo postremission consolidation therapy, including sequential courses of intermediate-risk cytarabine, allogeneic HCT, autologous HCT, or novel therapies, based on their predicted risk of relapse (i.e., risk-stratified therapy). Pts with APL (see text for treatment) usually receive tretinoin and arsenic trioxide–based regimens with or without anthracycline-based chemotherapy and possibly maintenance with tretinoin. HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; IDAC, intermediate dose cytarabine.

Bone marrow transplantation from identical twin or human leukocyte antigen (HLA)-identical sibling is effective treatment for AML. Typical protocol uses high-dose chemotherapy \pm total-body irradiation to ablate host marrow, followed by infusion of marrow from donor. Risks are substantial (unless marrow is from identical twin). Complications include graft-versus-host disease, interstitial pneumonitis, opportunistic infections (especially CMV). Comparison between transplantation and high-dose cytarabine as postremission therapy has not produced a clear advantage for either approach. Up to 30% of otherwise end-stage pts with refractory leukemia achieve probable cure from transplantation; results are better when transplant is performed during remission. Results are best for children and young adults.

Many new therapies are in development including agents that target kinases in important cellular pathways (e.g., FLT3, KIT, Aurora, and Polo-like kinases), epigenetic modulators (histone deacetylase, DNA methyltransferase, and isocitrate dehydrogenase inhibitors), chemotherapy agents (nucleosides), BCL2 inhibitors, and immunotherapies (CAR T cells, antibodies, immune checkpoint inhibitors).

CHRONIC MYELOID LEUKEMIA

CML is a clonal malignancy usually characterized by splenomegaly and production of increased numbers of granulocytes; course is initially indolent but eventually in leukemic phase (blast crisis) that has a poorer prognosis than de novo AML; rate of progression to blast crisis is variable; overall survival averages 4 years from diagnosis.

Incidence and Etiology

In the United States about 8430 cases have occurred in 2018. More than 90% of cases have a reciprocal translocation between chromosomes 9 and 22, creating the Philadelphia (Ph) chromosome and a fusion gene product called *BCR-ABL*. (BCR is from 9, ABL from 22.) The chromosome abnormality appears in all bone marrow-derived cells except T cells. The protein made by the chimeric gene is 210 kDa in chronic phase and 190 kDa in acute blast transformation. In some pts, the chronic phase is clinically silent and pts present with acute leukemia with the Ph chromosome.

Clinical and Laboratory Features

Symptoms develop gradually; easy fatigability, malaise, anorexia, abdominal discomfort and early satiety from the large spleen, excessive sweating. Occasional pts are found incidentally based on elevated leukocyte count. WBC is usually $>25,000/\mu\text{L}$ with the increase accounted for by granulocytes and their precursors back to the myelocyte stage; bands and mature forms predominate. Basophils may account for 10–15% of the cells in the blood. Platelet count is normal or increased. Anemia is often present. Neutrophil alkaline phosphatase score is low. Marrow is hypercellular with granulocytic hyperplasia. Marrow blast cell count is normal or slightly elevated. Serum levels of vitamin B_{12} , B_{12} -binding proteins, and LDH are elevated in proportion to the WBC. With high blood counts, spurious hyperkalemia and hypoglycemia may be seen.

Natural History

Chronic phase lasts for 2–4 years. Accelerated phase is marked by anemia disproportionate to the disease activity or treatment. Platelet counts fall. Additional cytogenetic abnormalities appear. Blast cell counts increase. Usually within 6–8 months, overt blast crisis develops in which maturation ceases and blasts predominate. The clinical picture is that of acute leukemia. Half of the cases become AML, one-third have morphologic features of acute lymphoid leukemia, 10% are erythroleukemia, and the rest are undifferentiated. Survival in blast crisis is often <4 months.

TREATMENT

Chronic Myeloid Leukemia

Criteria for response are provided in [Table 66-2](#). Allogeneic bone marrow transplantation has the potential to cure the disease in chronic phase. However, the first treatment is imatinib, a molecule that inhibits the chimeric gene product's tyrosine kinase activity. A daily oral dose of 400 mg produces complete hematologic remission of >90% and cytogenetic remission in 76%. If a matched donor is available, it is best to transplant pts in CR. Several mechanisms of resistance to imatinib have emerged, and it is unlikely that it leads to permanent remissions when used alone; however, follow-up is not sufficient to draw firm conclusions.

Pts who no longer respond to imatinib may respond to other tyrosine kinase inhibitors such as dasatinib (100 mg PO qd) or nilotinib (400 mg PO bid). The T315I mutation in the *BCR/ABL* gene conveys resistance to all three kinase inhibitors. Ponatinib (45 mg/d) is effective in pts with the T315I mutation, but concerns have been raised about vascular toxicity. Allopurinol, 300 mg/d, prevents urate nephropathy. The only curative therapy for the disease is HLA-matched allogeneic bone marrow transplantation. The optimal timing of transplantation is unclear, but transplantation in chronic phase is more effective than transplantation in accelerated phase or blast crisis. Transplantation appears most effective in pts treated within a year of diagnosis. Long-term disease-free survival may be obtained in 50–60% of transplanted pts. Infusion of donor lymphocytes can restore remission in relapsing pts. In pts without a matched donor, autologous transplantation may be helpful using peripheral blood stem cells. Treatment of pts in blast crisis with imatinib can obtain responses, but they are not durable.

MYELODYSPLASTIC SYNDROMES (MDS)

These are clonal abnormalities of marrow cells characterized by varying degrees of cytopenias affecting one or more cell lines. The World Health Organization (WHO) classification of MDS is shown in [Table 66-3](#). Other terms that have been

TABLE 66-2 Response Criteria in Chronic Myeloid Leukemia

Hematologic	
Complete response ^a	White blood cell count <10,000/μL, normal morphology Normal hemoglobin and platelet counts
Incomplete response	White blood cell count ≥10,000/μL
Cytogenetic	Percentage of bone marrow metaphases with t(9;22)
Complete response	0
Partial response	≤35
Minor response	36–85 ^b
No response	85–100
Molecular	Presence of <i>BCR/ABL</i> transcript by RT-PCR
Complete response	None (<0.1%)
Incomplete response	Any

^aComplete hematologic response requires the disappearance of splenomegaly.

^bUp to 15% normal metaphases are occasionally seen at diagnosis (when 30 metaphases are analyzed).

Abbreviation: RT-PCR, reverse transcriptase polymerase chain reaction.

TABLE 66-3 World Health Organization (WHO) Classification of Myelodysplastic Syndromes (MDS)/Neoplasms

NAME	RING SIDEROBLASTS	MYELOBLASTS	KARYOTYPE
MDS with single lineage dysplasia (MDS-SLD)	<15% (<5%) ^a	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	<15% (<5%) ^a	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)			
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	≥15% / ≥5% ^a	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	≥15% / ≥5% ^a	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except -7 or del(7q)
MDS with excess blasts (MDS-EB)			
MDS-EB-1	None or any	BM 5–9% or PB 2–4%, no Auer rods	Any
MDS-EB-2	None or any	BM 10–19% or PB 5–19% or Auer rods	Any
MDS, unclassifiable (MDS-U)			
• with 1% blood blasts	None or any	BM <5%, PB=1%, no Auer rods	Any
• with single lineage dysplasia and pancytopenia	None or any	BM <5%, PB=1%, no Auer rods	Any
• based on defining cytogenetic abnormality	15%	BM <5%, PB=1%, no Auer rods	MDS-defining abnormality

(Continued)

TABLE 66-3 World Health Organization (WHO) Classification of Myelodysplastic Syndromes (MDS)/Neoplasms (Continued)

NAME	RING SIDEROBLASTS	MYELOBLASTS	KARYOTYPE
MDS, unclassifiable (MDS-U)			
• with 1% blood blasts	None or any	BM <5%, PB=1%, no Auer rods	Any
• with single lineage dysplasia and pancytopenia	None or any	BM <5%, PB=1%, no Auer rods	Any
• based on defining cytogenetic abnormality	15%	BM <5%, PB=1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	None	BM <5%, PB <2%	Any

^aIf *SF3B1* mutation is present.

Abbreviations: BM, bone marrow; PB, peripheral blood.

used to describe one or more of the entities include *preleukemia* and *oligoblastic leukemia*.

Incidence and Etiology

About 3000 cases occur each year, mainly in persons >50 years old (median age, 68). As in AML, exposure to benzene, radiation, and chemotherapeutic agents may lead to MDS. Chromosome abnormalities occur in up to 80% of cases, including deletion of part or all of chromosomes 5, 7, and 9 (20 or 21 less commonly) and addition of part or all of chromosome 8. Mutations in genes involved in RNA splicing such as *SF3B1* have a more favorable outcome; mutations in genes often involved in AML such as *RUNX* and *ASXL1* have poorer prognosis.

Clinical and Laboratory Features

Symptoms depend on the affected lineages, 85% of pts are anemic, 50% have neutropenia, and about one-third have thrombocytopenia. The pathologic features of MDS are a cellular marrow with varying degrees of cytologic atypia including delayed nuclear maturation, abnormal cytoplasmic maturation, accumulation of ringed sideroblasts (iron-laden mitochondria surrounding the nucleus), uni- or bilobed megakaryocytes, micromegakaryocytes, and increased myeloblasts. Table 66-3 lists features used to identify distinct entities. Prognosis is defined by marrow blast %, karyotype, and lineages affected. The Revised International Prognostic Scoring System is shown in Table 66-4.

TREATMENT

Myelodysplastic Syndromes

Allogeneic bone marrow transplantation is the only curative therapy and may cure 60% of those so treated. However, the majority of pts with MDS are too old to receive transplantation. 5-Azacytidine (75 mg/m² daily × 7, q 4 weeks) can delay transformation to AML by 8–10 months. Decitabine (15 mg/m² by continuous IV infusion, q8h daily × 3, q 6 weeks) may induce responses lasting a median of 1 year in 20% of pts. Lenalidomide (10 mg/d), a thalidomide analogue with fewer central nervous system effects, causes a substantial fraction of pts with the

TABLE 66-4 Revised International Prognostic Scoring System (IPSS)

PROGNOSTIC VARIABLE	SCORE						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics ^a	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blast (percent)	≤2		>2 to <5		5 to 10	>10	
Hemoglobin (g/dL)	≥10		8 to <10	<8			
Platelets (cells/μL)	≥100	50 to 100	<50				
Absolute neutrophil count (cells/μL)	≥0.8	<0.8					
RISK GROUP	IPSS-R SCORE	MEDIAN OVERALL SURVIVAL (YEARS)		MEDIAN TIME TO 25 PERCENT AML EVOLUTION (YEARS)			
Very low	≤1.5	8.8		>14.5			
Low	>1.5 to 3.0	5.3		10.8			
Intermediate	>3 to 4.5	3.0		3.2			
High	>4.5 to 6	1.6		1.4			
Very high	>6	0.8		0.7			
The prognostic value of the IPSS-R was validated in an external cohort of 200 pts with MDS.							

^aCytogenetic definitions:

Very good: -Y, del(11q).

Good: Normal, del(5q), del(12p), del(20q), double including del(5q).

Intermediate: del(7q), +8, +19, i(17q), any other single, double not including del(5q) or -7/del(7q), or independent clones.

Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities.

Very poor: Complex: >3 abnormalities.

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndromes.

5q- syndrome to become transfusion-independent. Pts with low erythropoietin levels may respond to erythropoietin, and a minority of pts with neutropenia respond to granulocyte colony-stimulating factor. Supportive care is the cornerstone of treatment.

MYELOPROLIFERATIVE SYNDROMES

The three major myeloproliferative syndromes are polycythemia vera, idiopathic myelofibrosis, and essential thrombocytosis. All are clonal disorders of hematopoietic stem cells and all are associated with a mutation in the *JAK2* kinase (V617F) that results in activation of the kinase. The mutation is seen in 90% of pts with polycythemia vera and ~45% of pts with idiopathic myelofibrosis and essential thrombocytosis.

■ POLYCYTHEMIA VERA

The most common myeloproliferative syndrome, this is characterized by an increase in red blood cell (RBC) mass, massive splenomegaly, and clinical manifestations related to increased blood viscosity, including neurologic symptoms (vertigo, tinnitus, headache, visual disturbances) and thromboses (myocardial infarction, stroke, peripheral vascular disease; uncommonly, mesenteric and hepatic). It must be distinguished from other causes of increased RBC mass (Chap. 47). This is most readily done by assaying serum erythropoietin levels. Polycythemia vera is associated with very low erythropoietin levels; in other causes of erythrocytosis, erythropoietin levels are high. Assays for the *JAK2*(V617F) mutation are now widely available. Pts are effectively managed with phlebotomy. A daily aspirin and keeping the hematocrit <43% in women and <45% in men reduces the risk of thrombosis. Some pts require splenectomy to control symptoms, and those with severe pruritus may benefit from psoralens and UV light. Twenty percent develop myelofibrosis, <5% acute leukemia. An inhibitor of *JAK1* and *JAK2*, ruxolitinib, is being tested.

■ IDIOPATHIC MYELOFIBROSIS

This rare entity is characterized by marrow fibrosis, myeloid metaplasia with extramedullary hematopoiesis, and splenomegaly. Evaluation of a blood smear reveals teardrop-shaped RBC, nucleated RBC, and some early granulocytic forms, including promyelocytes. However, many entities may lead to marrow fibrosis and extramedullary hematopoiesis, and the diagnosis of primary idiopathic myelofibrosis is made only when the many other potential causes are ruled out. The following diseases are in the differential diagnosis: CML, polycythemia vera, Hodgkin's disease, cancer metastatic to the marrow (especially from breast and prostate), infection (particularly granulomatous infections), and hairy cell leukemia. Supportive therapy is generally used; novel inhibitors of *JAK2* and telomerase have shown activity in reducing splenomegaly and marrow fibrosis in some cases; however, no study has yet shown a particular drug therapy to improve survival. Cases that do not have *JAK2* mutations often have mutations in *CALR*.

■ ESSENTIAL THROMBOCYTOSIS

This is usually noted incidentally upon routine platelet count done in an asymptomatic person. Like myelofibrosis, many conditions can produce elevated platelet counts; thus, the diagnosis is one of exclusion. Platelet count must be >500,000/ μ L, and known causes of thrombocytosis must be ruled out including CML, iron deficiency, splenectomy, malignancy, infection, hemorrhage, polycythemia vera, myelodysplasia, and recovery from vitamin B₁₂ deficiency. Although

usually asymptomatic, pts should be treated if they develop migraine headache, transient ischemic attack, or other bleeding or thrombotic disease manifestations. Interferon α is effective therapy, as are anagrelide and hydroxyurea. Treatment should not be given just because the absolute platelet count is high in the absence of other symptoms. Usually platelet counts up to 1.5 million/ μL are not associated with bleeding or thrombosis, the two major risks. Bleeding can occur from platelet absorption of von Willebrand factor. *JAK2* and *CALR* mutations account for about 80% of cases; *MPL* mutations, about 10%.

67

Lymphoid Malignancies

**DEFINITION**

Neoplasms of lymphocytes usually represent malignant counterparts of cells at discrete stages of normal lymphocyte differentiation. When bone marrow and peripheral blood involvement dominate the clinical picture, the disease is classified as a *lymphoid leukemia*. When lymph nodes and/or other extranodal sites of disease are the dominant site(s) of involvement, the tumor is called a *lymphoma*. The distinction between lymphoma and leukemia is sometimes blurred; e.g., small lymphocytic lymphoma and chronic lymphoid leukemia are tumors of the same cell type and are distinguished arbitrarily on the basis of the absolute number of peripheral blood lymphocytes ($>5 \times 10^9/\text{L}$ defines leukemia).

CLASSIFICATION

Historically, lymphoid tumors have had separate pathologic classifications based on the clinical syndrome—lymphomas according to the Rappaport, Kiel, or Working Formulation systems; acute leukemias according to the French-American-British (FAB) system; Hodgkin's disease (HD) according to the Rye classification. Myelomas have generally not been subclassified by pathologic features of the neoplastic cells. The World Health Organization (WHO) has proposed a unifying classification system that brings together all lymphoid neoplasms into a single framework. Although the new system bases the definitions of disease entities on histology, genetic abnormalities, immunophenotype, and clinical features, its organization is based on cell of origin (B cell vs. T cell) and maturation stage (precursor vs. mature) of the tumor, features that are of limited value to the clinician. [Table 67-1](#) lists the disease entities according to a more clinically useful schema based on the clinical manifestations and natural history of the diseases.

INCIDENCE

Lymphoid tumors are increasing in incidence. Nearly 141,000 cases were diagnosed in 2018 in the United States ([Fig. 67-1](#)), including 74,680 cases of non-Hodgkin's lymphoma, 8500 cases of Hodgkin's lymphoma, 30,770 cases of myeloma, 20,940 cases of chronic lymphoid leukemia, and 5960 cases of acute lymphoid leukemia.

ETIOLOGY

The cause(s) for the vast majority of lymphoid neoplasms is unknown. The malignant cells are monoclonal and often contain numerous genetic abnormalities. Some genetic alterations are characteristic of particular histologic entities: t(8;14) in Burkitt's lymphoma, t(14;18) in follicular lymphoma, t(11;14) in mantle cell lymphoma, t(2;5) in anaplastic large cell lymphoma, translocations or

TABLE 67-1 Clinical Schema of Lymphoid Neoplasms**Chronic Lymphoid Leukemias/Lymphomas**

- Chronic lymphocytic leukemia/small lymphocytic lymphoma (99% B cell, 1% T cell)
- Prolymphocytic leukemia (90% B cell, 10% T cell)
- Large granular lymphocyte leukemia (80% NK cell, 20% T cell)
- Hairy cell leukemia (99–100% B cell)

Indolent Lymphoma

- Follicular center cell lymphoma, grades I and II (100% B cell)
- Lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia (100% B cell)
- Marginal zone lymphoma (100% B cell)
 - Extranodal (MALT lymphoma)
 - Nodal (monocytoid B cell lymphoma)
 - Splenic marginal zone lymphoma
- Cutaneous T cell lymphoma (mycosis fungoides) (100% T cell)

Aggressive Lymphoma

- Diffuse large cell lymphoma (85% B cell, 15% T cell) includes immunoblastic
- Follicular center cell lymphoma, grade III (100% B cell)
- Mantle cell lymphoma (100% B cell)
- Primary mediastinal (thymic) large B cell lymphoma (100% B cell)
- Burkitt-like lymphoma (100% B cell)
- Peripheral T cell lymphoma (100% T cell)
- Angioimmunoblastic lymphoma (100% T cell)
- Angiocentric lymphoma (80% T cell, 20% NK cell)
- Intestinal T cell lymphoma (100% T cell)
- Anaplastic large cell lymphoma (70% T cell, 30% null cell)

Acute Lymphoid Leukemias/Lymphomas

- Precursor lymphoblastic leukemia/lymphoma (80% T cell, 20% B cell)
- Burkitt's leukemia/lymphoma (100% B cell)
- Adult T cell leukemia/lymphoma (100% T cell)

Plasma Cell Disorders (100% B cell)

- Monoclonal gammopathy of uncertain significance
- Solitary plasmacytoma
- Extramedullary plasmacytoma
- Multiple myeloma
- Plasma cell leukemia

Hodgkin's Lymphoma (cell of origin mainly B cell)

- Lymphocyte predominant
- Nodular sclerosis
- Mixed cellularity
- Lymphocyte depleted

Abbreviations: MALT, mucosa-associated lymphatic tissue; NK, natural killer.

mutations involving *bcl-6* on 3q27 in diffuse large cell lymphoma, and others. In most cases, translocations involve insertion of a distant chromosome segment into the antigen receptor genes (either immunoglobulin or T cell receptor) during the rearrangement of the gene segments that form the receptors.

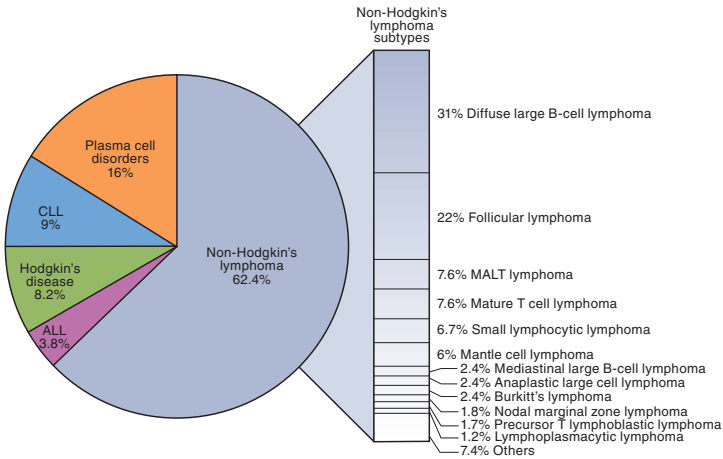


FIGURE 67-1 Relative frequency of lymphoid malignancies. ALL, acute lymphoid leukemia; CLL, chronic lymphoid leukemia; MALT, mucosa-associated lymphoid tissue.

Three viruses—Epstein-Barr virus (EBV), human herpesvirus 8 (HHV-8) (both herpes family viruses), and human T-lymphotropic virus type I (HTLV-I, a retrovirus)—may cause some lymphoid tumors. EBV has been strongly associated with African Burkitt's lymphoma and the lymphomas that complicate immunodeficiencies (disease-related or iatrogenic). EBV has an uncertain relationship to mixed cellularity HD and angiocentric lymphoma. HHV-8 causes a rare entity, body cavity lymphoma, mainly in pts with AIDS. HTLV-I is associated with adult T cell leukemia/lymphoma (ATL). Both the virus and the disease are endemic to southwestern Japan and the Caribbean.

Gastric *Helicobacter pylori* infection is associated with gastric mucosa-associated lymphoid tissue (MALT) lymphoma and perhaps gastric large-cell lymphoma. Eradication of the infection produces durable remissions in about half of pts with gastric MALT lymphoma. MALT lymphomas of other sites are associated with either infection (ocular adnexae, *Chlamydia psittaci*; small intestine, *Campylobacter jejuni*; skin, *Borrelia*) or autoimmunity (salivary gland, Sjögren's syndrome; thyroid gland, Hashimoto's thyroiditis).

Inherited or acquired immunodeficiencies and autoimmune disorders predispose individuals to lymphoma. Lymphoma is 17 times more common in HIV-infected than in HIV-noninfected people. Lymphoma occurs with increased incidence in farmers and meat workers; HD is increased in wood workers.

■ DIAGNOSIS AND STAGING

Excisional biopsy is the standard diagnostic procedure; adequate tissue must be obtained. Tissue undergoes three kinds of studies: (1) light microscopy to discern the pattern of growth and the morphologic features of the malignant cells, (2) flow cytometry for assessment of immunophenotype, and (3) genetic studies (cytogenetics, DNA sequencing). Needle aspirates of nodal or extranodal masses are not adequate diagnostic procedures. Leukemia diagnosis and lymphoma staging include generous bilateral iliac crest bone marrow biopsies. Differential diagnosis of adenopathy is reviewed in [Chap. 46](#).

Staging varies with the diagnosis. In acute leukemia, peripheral blood blast counts are most significant in assessing prognosis. In chronic leukemia, peripheral

blood red blood cell (RBC) and platelet counts are most significant in assessing prognosis. Non-Hodgkin's lymphomas have five clinical prognostic factors; indolent and aggressive lymphomas share three of these, advanced stage, high lactate dehydrogenase (LDH) levels, and age >60 years. In follicular lymphoma, the last two factors are Hb <120 g/L (<12 g/dL) and more than four nodal sites of involvement. In a newer scheme for follicular lymphoma, marrow involvement and β_2 -microglobulin levels replace LDH and stage. In aggressive lymphoma, more than one extranodal site and performance status predict outcome. In myeloma, serum levels of paraprotein, creatinine, and β_2 -microglobulin levels predict survival.

CHRONIC LYMPHOID LEUKEMIAS/LYMPHOMAS

Most of these entities have a natural history measured in years. (Prolymphocytic leukemia is very rare and can be very aggressive.) Chronic lymphocytic leukemia (CLL) is the most common entity in this group (~21,000 cases/year in the United States) and the most common leukemia in the Western world.

■ CHRONIC LYMPHOCYTIC LEUKEMIA

Usually presents as asymptomatic lymphocytosis in pts >60 years. The malignant cell is a CD5+ B cell that looks like a normal small lymphocyte. Trisomy 12 and deletions of 13q, 11q, and 17p are the most common genetic abnormalities. Prognosis is related to stage; stage is determined mainly by the degree to which the tumor cells crowd out normal hematopoietic elements from the marrow (Table 67-2). Cells may infiltrate nodes and spleen as well as marrow. Nodal involvement may be related to the expression of an adhesion molecule that allows the cells to remain in the node rather than recirculate. Pts often have hypogammaglobulinemia. Up to 20% have autoimmune antibodies that may produce autoimmune hemolytic anemia, thrombocytopenia, or red cell aplasia. Death is from infection, marrow failure, or intercurrent illnesses. In 5%, the disease evolves to aggressive lymphoma (Richter's syndrome) that is refractory to treatment.

Subsets of CLL may exist based on whether the immunoglobulin expressed by the tumor cell contains mutations (more indolent course, good prognosis) or retains the germ-line sequence (more aggressive course, poor response to therapy). Methods to distinguish the two subsets clinically are not well defined; CD38+ tumors may have poorer prognosis. The expression of ZAP-70, an intracellular tyrosine kinase normally present in T cells and aberrantly expressed in about 45% of CLL cases, may be a better way to define prognostic subsets.

TABLE 67-2 Staging of B-Cell CLL and Relation to Survival

STAGE	CLINICAL FEATURES	MEDIAN SURVIVAL, YEARS
RAI		
0	Lymphocytosis	12
I	Lymphocytosis + adenopathy	9
II	Lymphocytosis + splenomegaly	7
III	Anemia	1-2
IV	Thrombocytopenia	1-2
BINET		
A	No anemia/thrombocytopenia, <3 involved sites	>10
B	No anemia/thrombocytopenia, >3 involved sites	5
C	Anemia and/or thrombocytopenia	2

ZAP-70-positive cases usually need treatment within about 3–4 years from diagnosis; ZAP-70-negative cases usually don't require treatment for 8–11 years.

TREATMENT

Chronic Lymphocytic Leukemia

Supportive care is generally given until anemia or thrombocytopenia develops. At that time, tests are indicated to assess the cause of the anemia or thrombocytopenia. Decreased RBC and/or platelet counts related to peripheral destruction may be treated with splenectomy or glucocorticoids without cytotoxic therapy in many cases. If marrow replacement is the mechanism, therapy is indicated. Fludarabine, 25 (mg/m²)/d IV × 5 days every 4 weeks, induces responses in about 75% of pts, complete responses in half. Rituximab (375–500 mg/m² day 1), fludarabine (25 mg/m² days 2–4 on cycle 1 and 1–3 in subsequent cycles), plus cyclophosphamide (250 mg/m² with fludarabine) induce complete responses in nearly 70% of pts but the regimen is associated with significant myelotoxicity. Glucocorticoids increase the risk of infection without adding a substantial antitumor benefit. Ibrutinib, an inhibitor of Bruton's tyrosine kinase, is highly active in CLL and many use it as primary therapy. Alkylating agents such as bendamustine and chlorambucil are also active against the tumor. Venetoclax (an inhibitor of bcl-2) is also an effective agent. Monthly IV immunoglobulin (IVIg) significantly reduces risk of serious infection but is expensive and usually reserved for pts who have had a serious infection. Therapeutic intent is palliative in most pts. Young pts may be candidates for high-dose therapy and autologous or allogeneic hematopoietic cell transplantation; long-term disease-free survival has been noted. Minitransplant, in which the preparative regimen is immunosuppressive but not myeloablative, may be less toxic and as active or more active in disease treatment than high-dose therapy. Monoclonal antibodies alemtuzumab (anti-CD52) and rituximab, obinutuzumab, and ofatumumab (all anti-CD20s) also are active as single agents or combined with chlorambucil. Chimeric antigen receptor T cells directed at CD19 or CD22 are also used. The bcl-2 inhibitor venetoclax in combination with ibrutinib has a high level of activity.

INDOLENT LYMPHOMAS

These entities have a natural history measured in years. Median survival is about 14 years. Follicular lymphoma is the most common indolent lymphoma, accounting for about one-third of all lymphoid malignancies.

■ FOLLICULAR LYMPHOMA

Usually presents with painless peripheral lymphadenopathy, often involving several nodal regions. "B symptoms" (fever, sweats, weight loss) occur in 10%, less common than with Hodgkin's lymphoma. In about 25%, nodes wax and wane before the pt seeks medical attention. Median age is 55 years. Disease is widespread at diagnosis in 85%. Liver and bone marrow are commonly involved extranodal sites.

The tumor has a follicular or nodular growth pattern reflecting the follicular center origin of the malignant cell. The t(14;18) is present in 85% of cases, resulting in the overexpression of bcl-2, a protein involved in prevention of programmed cell death. The normal follicular center B cell is undergoing active mutation of the immunoglobulin variable regions in an effort to generate antibody of higher affinity for the selecting antigen. Follicular lymphoma cells also have a high rate of mutation that leads to the accumulation of genetic damage. Over time, follicular lymphomas acquire sufficient genetic damage (e.g., mutated p53) to

TABLE 67-3 Follicular Lymphoma International Prognostic Index-2 (FLIPI-2)

Five clinical risk factors:

- Age >60 years
- Serum β_2 -microglobulin increased
- Hemoglobin <12 gm/dL
- Bone marrow involvement
- Longest diameter of largest node >6 cm

0 factor = low risk:	5-year progression-free survival 76–80%
1–2 factors = intermediate risk:	5-year progression-free survival 49–51%
3–5 factors = high risk:	5-year progression-free survival 20–37%

accelerate their growth and evolve into diffuse large B-cell lymphomas that are often refractory to treatment. The majority of pts dying from follicular lymphoma have undergone histologic transformation. This transformation occurs at a rate of about 3% per year and is an attribute of the disease, not the treatment. The rate of histologic progression has decreased as treatment has improved. The international prognostic index for follicular lymphoma is shown in [Table 67-3](#).

TREATMENT

Follicular Lymphoma

Only 15% of pts have localized disease, but the majority of these pts are curable with radiation therapy. Although many forms of treatment induce tumor regression in advanced-stage pts, disease cure has been elusive. No therapy, single-agent alkylators, nucleoside analogues (fludarabine, cladribine), combination chemotherapy, radiation therapy, and biologic agents (interferon [IFN] α , monoclonal antibodies such as rituximab [anti-CD20]) are all considered appropriate. More than 90% of pts are responsive to treatment; complete responses are seen in about 50–75% of pts treated aggressively. The median duration of remission of pts treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) + rituximab exceeds 6 years. Bendamustine + rituximab is an active combination. Younger pts are being treated experimentally with high-dose therapy and autologous hematopoietic stem cells or minitransplant. It is not yet clear whether this is curative. Radioimmunotherapy with isotopes guided by anti-CD20 antibody (ibritumomab tiuxetan, In-111; tositumomab, I-131) may produce durable responses. Combination chemotherapy with or without monoclonal antibody maintenance may prolong survival and delay or prevent histologic progression, especially in pts with poor prognostic features. Remissions appear to last longer with chemotherapy plus rituximab or obinutuzumab; some data suggest that the longer remissions are leading to improved survival.

AGGRESSIVE LYMPHOMAS

A large number of pathologic entities share an aggressive natural history; median survival untreated is 6 months, and nearly all untreated pts are dead within 1 year. Pts may present with asymptomatic adenopathy or symptoms referable to involvement of practically any nodal or extranodal site: Mediastinal involvement may produce superior vena cava syndrome or pericardial tamponade; retroperitoneal nodes may obstruct ureters; abdominal masses may produce pain, ascites, or

GI obstruction or perforation; CNS involvement may produce confusion, cranial nerve signs, headache, seizures, and/or spinal cord compression; bone involvement may produce pain or pathologic fracture. About 45% of pts have B symptoms.

Diffuse large B-cell lymphoma is the most common histologic diagnosis among the aggressive lymphomas, accounting for 35–45% of all lymphomas. Aggressive lymphomas together account for ~60% of all lymphoid tumors. About 85% of aggressive lymphomas are of mature B-cell origin; 15% are derived from peripheral (postthymic) T cells.

APPROACH TO THE PATIENT

Aggressive Lymphoma

Early diagnostic biopsy is critical. Pt workup is directed by symptoms and known patterns of disease. Pts with Waldeyer's ring involvement should undergo careful evaluation of the GI tract. Pts with bone or bone marrow involvement should have a lumbar puncture to evaluate meningeal CNS involvement.

TREATMENT

Aggressive Lymphomas

Localized aggressive lymphomas are usually treated with four cycles of CHOP combination chemotherapy ± involved-field radiation therapy. About 85% of these pts are cured. CHOP + rituximab appears to be even more effective than CHOP + radiation therapy. The specific therapy used for pts with more advanced disease is controversial. Six cycles of CHOP + rituximab is the treatment of choice for advanced-stage disease. Outcome is influenced by tumor bulk (usually measured by LDH levels, stage, and number of extranodal sites) and physiologic reserve (usually measured by age and Karnofsky status) (Table 67-4). CHOP + rituximab cures

TABLE 67-4 International Prognostic Index for NHL

Five clinical risk factors:

- Age ≥60 years
- Serum lactate dehydrogenase levels elevated
- Performance status ≥2 (ECOG) or ≤70 (Karnofsky)
- Ann Arbor stage III or IV
- >1 site of extranodal involvement

Pts are assigned a number for each risk factor they have.

Pts are grouped differently based on the type of lymphoma.

For diffuse large B-cell lymphoma:

0, 1 factor = low risk:	35% of cases; 5-year survival, 73%
2 factors = low-intermediate risk:	27% of cases; 5-year survival, 51%
3 factors = high-intermediate risk:	22% of cases; 5-year survival, 43%
4, 5 factors = high risk:	16% of cases; 5-year survival, 26%

For diffuse large B-cell lymphoma treated with R-CHOP:

0 factor = very good:	10% of cases; 5-year survival, 94%
1, 2 factors = good:	45% of cases; 5-year survival, 79%
3, 4, 5 factors = poor:	45% of cases; 5-year survival, 55%

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NHL, non-Hodgkin's lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

about two-thirds of pts. Infusional chemotherapy regimens like dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) plus rituximab may be more effective in the more aggressive double-hit lymphomas that have mutations in *c-Myc* and *bcl-6*. The use of a sequential high-dose chemotherapy regimen in pts with high-intermediate and high-risk disease has yielded long-term survival in about 75% of pts in some institutions. Other studies fail to confirm a role for high-dose therapy.

About 30–45% of pts not cured with initial standard combination chemotherapy may be salvaged with high-dose therapy and autologous hematopoietic stem cell transplantation.

Specialized approaches are required for lymphomas involving certain sites (e.g., CNS, stomach) or under certain complicating clinical circumstances (e.g., concurrent illness, AIDS). Lymphomas occurring in iatrogenically immunosuppressed pts may regress when immunosuppressive medication is withheld. Lymphomas occurring post-allogeneic marrow transplant may regress with infusions of donor leukocytes.

Pts with rapidly growing bulky aggressive lymphoma may experience tumor lysis syndrome when treated ([Chap. 27](#)); prophylactic measures (hydration, urine alkalinization, allopurinol, rasburicase) may be lifesaving.

ACUTE LYMPHOID LEUKEMIAS/LYMPHOMAS

■ ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOBLASTIC LYMPHOMA

These are more common in children than adults (~6000 total cases/year). In children, most cases of acute leukemia are of B-cell origin. The majority of cases of acute leukemia in adults and all cases of lymphoblastic lymphoma have tumor cells that appear to be of thymic origin, and pts may have mediastinal masses. Pts usually present with recent onset of signs of marrow failure (pallor, fatigue, bleeding, fever, infection). Hepatosplenomegaly and adenopathy are common. Males may have testicular enlargement reflecting leukemic involvement. Meningeal involvement may be present at diagnosis or develop later. Elevated LDH, hyponatremia, and hypokalemia may be present, in addition to anemia, thrombocytopenia, and high peripheral blood blast counts. The leukemic cells are more often FAB type L2 in adults than in children, where L1 predominates. Leukemia diagnosis requires at least 20% lymphoblasts in the marrow. Prognosis is adversely affected by high presenting white count, age >35 years, and the presence of t(9;22), t(1;19), and t(4;11) translocations. HOX11 expression identifies a more favorable subset of T cell acute lymphoblastic leukemia.

TREATMENT

Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma

Successful treatment requires intensive induction phase, CNS prophylaxis, and maintenance chemotherapy that extend for about 2 years. Vincristine, L-asparaginase, cytarabine, daunorubicin, and prednisone are particularly effective agents. Intrathecal or high-dose systemic methotrexate is effective CNS prophylaxis. Long-term survival of 60–65% of pts may be achieved. The role and timing of bone marrow transplantation in primary therapy are debated, but up to 30% of relapsed pts may be cured with salvage transplantation.

■ BURKITT'S LYMPHOMA/LEUKEMIA

This is also more common in children. It is associated with translocations involving the *c-myc* gene on chromosome 8 rearranging with immunoglobulin heavy or light chain genes. Pts often have disseminated disease with large abdominal masses, hepatomegaly, and adenopathy. If a leukemic picture predominates, it is classified as FAB L3.

TREATMENT**Burkitt's Lymphoma/Leukemia**

Resection of large abdominal masses improves treatment outcome. Aggressive leukemia regimens that include vincristine, cyclophosphamide, 6-mercaptopurine, doxorubicin, and prednisone are active. CODOX-M and the BFM regimen are the most effective regimens. Cure may be achieved in 50–60%. The need for maintenance therapy is unclear. Prophylaxis against tumor lysis syndrome is important (Chap. 27).

■ ADULT T CELL LEUKEMIA/LYMPHOMA (ATL)

This is very rare; only a small fraction (~2%) of persons infected with HTLV-I go on to develop the disease. Some HTLV-I-infected pts develop spastic paraplegia from spinal cord involvement without developing cancer. The characteristic clinical syndrome of ATL includes high white count without severe anemia or thrombocytopenia, skin infiltration, hepatomegaly, pulmonary infiltrates, meningeal involvement, and opportunistic infections. The tumor cells are CD4+ T cells with cloven hoof- or flower-shaped nuclei. Hypercalcemia occurs in nearly all pts and is related to cytokines produced by the tumor cells.

TREATMENT**Adult T Cell Leukemia/Lymphoma**

Aggressive therapy is associated with serious toxicity related to the underlying immunodeficiency. Glucocorticoids relieve hypercalcemia. The tumor is responsive to therapy, but responses are generally short lived. Zidovudine and IFN may be palliative in some pts. Lenalidomide and the monoclonal anti-CCR4 receptor antibody, mogamulizumab have antitumor activity.

PLASMA CELL DISORDERS

The hallmark of plasma cell disorders is the production of immunoglobulin molecules or fragments from abnormal plasma cells. The intact immunoglobulin molecule, or the heavy chain or light chain produced by the abnormal plasma cell clone, is detectable in the serum and/or urine and is called the M (for monoclonal) component. The amount of the M component in any given pt reflects the tumor burden in that pt. In some, the presence of a clonal light chain in the urine (Bence Jones protein) is the only tumor product that is detectable. M components may be seen in pts with other lymphoid tumors, nonlymphoid cancers, and non-cancerous conditions such as cirrhosis, sarcoidosis, parasitic infestations, and autoimmune diseases.

■ MULTIPLE MYELOMA

A malignant proliferation of plasma cells in the bone marrow (notably not in lymph nodes). Nearly 31,000 new cases are diagnosed each year. Disease

manifestations result from tumor expansion, local and remote actions of tumor products, and the host response to the tumor. About 70% of pts have bone pain, usually involving the back and ribs, precipitated by movement. Bone lesions are multiple, lytic, and rarely accompanied by an osteoblastic response. Thus, bone scans are less useful than radiographs. The production of osteoclast-activating cytokines by tumor cells leads to substantial calcium mobilization, hypercalcemia, and symptoms related to it. Decreased synthesis and increased catabolism of normal immunoglobulins lead to hypogammaglobulinemia, and a poorly defined tumor product inhibits granulocyte migration. These changes create a susceptibility to bacterial infections, especially the pneumococcus, *Klebsiella pneumoniae*, and *Staphylococcus aureus* affecting the lung and *Escherichia coli* and other gram-negative pathogens affecting the urinary tract. Infections affect at least 75% of pts at some time in their course. Renal failure may affect 25% of pts; its pathogenesis is multifactorial—hypercalcemia, infection, toxic effects of light chains, urate nephropathy, and dehydration. Neurologic symptoms may result from hyperviscosity, cryoglobulins, and rarely amyloid deposition in nerves. Anemia occurs in 80% related to myelophthisis and inhibition of erythropoiesis by tumor products. Clotting abnormalities may produce bleeding.

Diagnosis

Marrow plasmacytosis >10%, lytic bone lesions, and a serum and/or urine M component are the classic triad. Monoclonal gammopathy of uncertain significance (MGUS) is much more common than myeloma, affecting about 6% of people aged >70 years; in general, MGUS is associated with a level of M component <20 g/L, low serum β_2 -microglobulin, <10% marrow plasma cells, and no bone lesions. Lifetime risk of progression of MGUS to myeloma is about 25%; risk of progression is increased if the paraprotein is IgM, the paraprotein level is >1.5 g/dL, or the free light chain ratio is <0.26 or >1.65.

Staging

Disease stage influences survival (Table 67-5).

TREATMENT

Multiple Myeloma

About 10% of pts have very slowly progressive disease (the so-called smoldering myeloma) and do not require treatment until the paraprotein levels rise above 50 g/L or progressive bone disease occurs. Pts with solitary plasmacytoma and extramedullary plasmacytoma are usually cured with localized radiation therapy. Supportive care includes early treatment of infections; control of hypercalcemia with glucocorticoids, hydration, and natriuresis; chronic administration of bisphosphonates to antagonize skeletal destruction; and prophylaxis against urate nephropathy and dehydration. Therapy aimed at the tumor is usually palliative. Initial therapy is usually one of several approaches, based on whether the pt is a candidate for high-dose therapy and autologous stem cell transplant. Transplant eligible (avoid alkylating agents): lenalidomide, 5–25 mg/d PO for 21 days every 28 days, plus dexamethasone, 40 mg/d on days 1–4 each month, with bortezomib 1.3 mg/m² IV or SC days 1, 8, and 15, produces responses in nearly 100% of pts and one-third of them are complete. Maintenance therapy with lenalidomide appears to improve survival. Thromboprophylaxis is used with lenalidomide. Transplant ineligible: the same regimens can be used but alkylating agents may also be palliative, e.g., melphalan, 8 mg/m² orally for 4–7 days every 4–6 weeks, plus prednisone. About 60% of pts have significant symptomatic improvement plus a 75% decline in the M component. Bortezomib also appears to improve response rates to melphalan. Experimental approaches

TABLE 67-5 Myeloma Staging Systems

Durie-Salmon staging system		
STAGE	CRITERIA	ESTIMATED TUMOR BURDEN $\times 10^{12}$ CELLS/m ²
I	All of the following: 1. Hemoglobin >100 g/L (>10 g/dL) 2. Serum calcium <3 mmol/L (<12 mg/dL) 3. Normal bone x-ray or solitary lesion 4. Low M-component production a. IgG level <50 g/L (<5 g/dL) b. IgA level <30 g/L (<3 g/dL) c. Urine light chain <4 g/24 h	<0.6 (low)
II	Fitting neither I nor III	0.6–1.20 (intermediate)
III	One or more of the following: 1. Hemoglobin <85 g/L (<8.5 g/dL) 2. Serum calcium >3 mmol/L (>12 mg/dL) 3. Advanced lytic bone lesions 4. High M-component production a. IgG level >70 g/L (>7 g/dL) b. IgA level >50 g/L (>5 g/dL) c. Urine light chains >12 g/24 h	>1.20 (high)
LEVEL	STAGE	MEDIAN SURVIVAL, MONTHS
Subclassification based on serum creatinine levels		
A <177 μ mol/L (<2 mg/dL)	IA	61
B >177 μ mol/L (>2 mg/dL)	IIA, B	55
	IIIA	30
	IIIB	15
International staging system		
β_2 M <3.5 , alb ≥ 3.5	I (28%)	62
β_2 M <3.5 , alb <3.5 or β_2 M = 3.5–5.5	II (39%)	44
β_2 M >5.5	III (33%)	29

Note: β_2 M, serum β_2 -microglobulin in mg/L; alb, serum albumin in g/dL; (#), % pts presenting at each stage.

using sequential high-dose pulses of melphalan plus two successive autologous stem cell transplants have produced complete responses in about 50% of pts <65 years. Long-term follow-up is required to see whether survival is enhanced. New proteasome inhibitors like carfilzomib and ixazomib, immune modulators like pomalidomide, monoclonal antibodies like daratumumab (anti-CD38) and

elotuzumab (anti-SLAMF7), and histone deacetylase inhibitors like panobinostat are being tested in various combinations. Entering pts on clinical trials will provide a basis for decision making. Palliatively treated pts generally follow a chronic course and median overall survival is now 8+ years.

■ HODGKIN'S LYMPHOMA

About 8500 new cases are diagnosed each year. HD is a tumor of Reed-Sternberg cells, aneuploid cells that usually express CD30 and CD15 but may also express other B or T cell markers. Most tumors are derived from B cells in that immunoglobulin genes are rearranged but not expressed. Most of the cells in an enlarged node are normal lymphoid, plasma cells, monocytes, and eosinophils. The etiology is unknown, but the incidence in both identical twins is 99-fold increased over the expected concordance, suggesting a genetic susceptibility. Distribution of histologic subtypes is 75% nodular sclerosis, 20% mixed cellularity, with lymphocyte predominant and lymphocyte depleted representing about 5%.

Clinical Manifestations

Usually presents with asymptomatic lymph node enlargement or with adenopathy associated with fever, night sweats, weight loss, and sometimes pruritus. Mediastinal adenopathy (common in nodular sclerosing HD) may produce cough. Spread of disease tends to be to contiguous lymph node groups. Superior vena cava obstruction or spinal cord compression may be presenting manifestation. Involvement of bone marrow and liver is rare.

Differential Diagnosis

- *Infection*: mononucleosis, viral syndromes, *Toxoplasma*, *Histoplasma*, primary tuberculosis
- *Other malignancies*: especially head and neck cancers
- *Sarcoidosis*: mediastinal and hilar adenopathy

Immunologic and Hematologic Abnormalities

- Defects in cell-mediated immunity (remains even after successful treatment of lymphoma), cutaneous anergy, diminished antibody production to capsular antigens of *Haemophilus* and pneumococcus
- Anemia; elevated erythrocyte sedimentation rate, leukemoid reaction, eosinophilia, lymphocytopenia, fibrosis, and granulomas in marrow

Staging

The Ann Arbor staging classification is shown in [Table 67-6](#). Disease is staged by performing physical examination, chest x-ray, thoracoabdominal CT, bone marrow biopsy, ultrasound examinations, and lymphangiogram. Staging laparotomy should only be used to evaluate the spleen only if radiation therapy alone is being contemplated as treatment. Pathologic staging is unnecessary if the pt is treated with systemic chemotherapy.

TREATMENT

Hodgkin's Disease

About 85% of pts are curable. Therapy should be performed by experienced clinicians in centers with appropriate facilities. Most pts are clinically staged and treated with chemotherapy alone or combined-modality therapy. Those with stage II disease often receive either two or four cycles of doxorubicin, bleomycin,

TABLE 67-6 The Ann Arbor Staging System for Hodgkin's Lymphoma

STAGE	DEFINITION
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes should be considered "lateralized" and, when involved on both sides, constitute stage II disease)
III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm
III ₁	Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes
III ₂	Subdiaphragmatic involvement includes paraortic, iliac, or mesenteric nodes plus structures in III ₁
IV	Involvement of extranodal site(s) beyond that designated as "E" More than one extranodal deposit at any location Any involvement of liver or bone marrow
A	No symptoms
B	Unexplained weight loss of >10% of the body weight during the 6 months before staging investigation Unexplained, persistent, or recurrent fever with temperatures >38°C (100.5°F) during the previous month Recurrent drenching night sweats during the previous month
E	Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow

vinblastine, dacarbazine (ABVD) with or without involved-field radiation therapy or Stanford V, a combined-modality program using lower doses of chemotherapy. Those with stage III or IV disease receive six cycles of combination chemotherapy, usually ABVD. Replacing bleomycin with the anti-CD30 immunotoxin, brentuximab vedotin, is equally effective or possibly slightly more effective than ABVD. Pts with any stage disease accompanied by a large mediastinal mass (greater than one-third the greatest chest diameter) should receive combined-modality therapy with mechlorethamine, vincristine, procarbazine, prednisone (MOPP)/ABVD or MOPP-ABV hybrid followed by mantle field radiation therapy. (Radiation plus ABVD is too toxic to the lung.) A persistently positive midtreatment (after two cycles) positron emission tomography scan is associated with a higher risk of relapse and need for additional therapy. About one-half of pts (or more) not cured by their initial chemotherapy regimen may be rescued by high-dose therapy and autologous stem cell transplant. The likelihood of the success of salvage therapy is related to the length of initial remission; pts with initial remissions lasting more than a year are more likely to achieve long-term disease control than those whose initial remission was shorter than a year. Brentuximab vedotin has activity in pts relapsing after transplant.

With long-term follow-up, it has become clear that more pts are dying of late fatal toxicities related to radiation therapy (myocardial infarction, stroke, second cancers) than from HD. Radiation therapy and its late toxicities can be avoided by using combination chemotherapy alone in early-stage disease as well as in advanced-stage disease.

68

Skin Cancer



■ MALIGNANT MELANOMA

Most dangerous cutaneous malignancy, high metastatic potential, poor prognosis with metastatic spread.

Incidence

Melanoma was diagnosed in 91,270 people in the United States in 2018 and caused 9320 deaths.

Predisposing Factors (Table 68-1)

Fair complexion, sun exposure, family history of melanoma, dysplastic nevus syndrome (autosomal dominant disorder with multiple nevi of distinctive appearance and cutaneous melanoma may be associated with 9p deletion), and presence of a giant congenital nevus. Blacks have a low incidence.

Prevention

Sun avoidance lowers risk. Sunscreens are not proven effective.

Types

1. *Superficial spreading melanoma*: Most common; begins with initial radial growth phase before invasion.
2. *Lentigo maligna melanoma*: Very long radial growth phase before invasion, lentigo maligna (Hutchinson's melanotic freckle) is precursor lesion, most common in elderly and in sun-exposed areas (esp. face).
3. *Acral lentiginous*: Most common form in darkly pigmented pts; occurs on palms and soles, mucosal surfaces, in nail beds and mucocutaneous junctions; similar to lentigo maligna melanoma but with more aggressive biologic behavior.
4. *Nodular*: Generally poor prognosis because of invasive growth from onset.

Biology

About half of melanomas carry an activating somatic mutation in the *BRAF* gene, often a valine to glutamate substitution at amino acid 600 (V600E). *N-ras* is mutated in about 20% and rare pts have activating mutations in *c-kit*. These mutations have been targeted by therapeutic agents that have antitumor activity.

Clinical Appearance

Generally pigmented (rarely amelanotic); color of lesions varies, but red, white, and/or blue are common, in addition to brown and/or black. Suspicion should be raised by a pigmented skin lesion that is >6 mm in diameter, asymmetric, has an irregular surface or border, or has variation in color.

TABLE 68-1 Factors Associated with Increased Risk of Melanoma

Total body nevi (higher number = higher risk)
Family or personal history
Dysplastic nevi
Light skin/hair/eye color
Poor tanning ability
Freckling
UV exposure/sunburns/tanning booths
<i>CDKN2A</i> mutation
<i>MC1R</i> variants

Prognosis

Best with thin lesions without evidence of metastatic spread; with increasing thickness, ulceration, or evidence of nodal spread, prognosis worsens. Stage I (primary tumor without spread) has 80–92% 15-year survival. Stage II (>1–4 mm) has a 51–62% 15-year survival. Stage III (regional nodes with tumor) has a 60% 15-year survival when 1–3 nodes are microscopically involved and 22–38% when 1–3 nodes are macroscopically involved or 4 or more are involved. Stage IV (disseminated disease) has <10% 15-year survival.

TREATMENT**Malignant Melanoma**

Early recognition and local excision for localized disease is best; 1- to 2-cm margins are as effective as 4- to 5-cm margins and do not usually require skin grafting. Elective lymph node dissection offers no advantage in overall survival compared with deferral of surgery until clinical recurrence. Pts with stage II disease may have risk of recurrence reduced with adjuvant therapy (immune checkpoint inhibitors or interferon-alpha) but this is controversial. More data support nivolumab or pembrolizumab in resected stage III disease, and perhaps targeted therapy in 50% of pts with *BRAF* mutations. Metastatic disease may be treated with chemotherapy or immunotherapy (Table 68-2). Vemurafenib 960 mg PO bid or dabrafenib 150 mg PO bid induces responses in about 50% of pts with *BRAF* mutations. Median survival is about 16 months. Some patients develop secondary keratoacanthomas or squamous cell cancers from activation of the MET pathway. Addition of a MET inhibitor (trametinib 2 mg/d) to a *BRAF* inhibitor improved response rate to 64% and median overall survival to >20 months and prevented secondary skin cancers. The anti-CTLA4 antibody ipilimumab prolongs survival by about 4 months. The combination of ipilimumab and the PD-1 blocker nivolumab induced responses in both *BRAF* mutant and *BRAF* wild-type tumors. Response rate 58% with responses lasting about 12 months. Dacarbazine (250 mg/m² IV daily × 5 q3w) plus tamoxifen (20 mg/m² PO daily) may induce partial responses in one-quarter of pts. IFN and interleukin 2 (IL-2) at maximum tolerated doses induce partial responses in 15% of pts.

TABLE 68-2 Treatment Options for Metastatic Melanoma

Surgery: metastasectomy for small number of lesions

Immunotherapy

Interleukin-2

Immune checkpoint blockade

- Anti-CTLA-4: ipilimumab
- Anti-PD-1: nivolumab, pembrolizumab
- Combined ipilimumab and nivolumab

Experimental

Anti-PD-L1

Molecular targeted therapy

BRAF inhibitor: vemurafenib, dabrafenib

MEK inhibitor: trametinib, cobimetinib

Oncolytic virus: talimogene laherpaepvec

Chemotherapy: dacarbazine, temozolomide, paclitaxel, albumin-bound paclitaxel, carboplatin

Rare long remissions occur with IL-2. Temozolomide is an oral agent that has some activity. It can enter the central nervous system (CNS) and is being evaluated with radiation therapy for CNS metastases. No therapy for metastatic disease is curative. Vaccines and adoptive cellular therapies are being tested.

■ BASAL CELL CARCINOMA (BCC)

Most common form of skin cancer; most frequently on sun-exposed skin, esp. face.

Predisposing Factors

Fair complexion, chronic UV exposure, exposure to inorganic arsenic (i.e., Fowler's solution or insecticides such as Paris green), or exposure to ionizing radiation.

Prevention

Avoidance of sun exposure and use of sunscreens lower risk.

Types

Five general types: noduloulcerative (most common), superficial (mimics eczema), pigmented (may be mistaken for melanoma), morpheaform (plaquelike lesion with telangiectasia—with keratotic is most aggressive), keratotic (basosquamous carcinoma).

Clinical Appearance

Classically a pearly, translucent, smooth papule with rolled edges and surface telangiectasia.

TREATMENT

Basal Cell Carcinoma

Local removal with electrodesiccation and curettage, excision, cryosurgery, or radiation therapy; metastases are rare but may spread locally. Exceedingly unusual for BCC to cause death. Locally advanced or metastatic disease may respond to vismodegib, an inhibitor of the hedgehog pathway often activated in this disease.

■ SQUAMOUS CELL CARCINOMA (SCC)

Less common than basal cell but more likely to metastasize.

Predisposing Factors

Fair complexion, chronic UV exposure, previous burn, or other scar (i.e., scar carcinoma), exposure to inorganic arsenic or ionizing radiation. Actinic keratosis is a premalignant lesion. Actinic keratoses can be treated with topic 5-fluorouracil.

Types

Most commonly occurs as an ulcerated nodule or a superficial erosion on the skin. *Variants include:*

- *Bowen's disease:* Erythematous patch or plaque, often with scale; noninvasive; involvement limited to epidermis and epidermal appendages (i.e., SCC in situ).
- *Scar carcinoma:* Suggested by sudden change in previously stable scar, esp. if ulceration or nodules appear.
- *Verrucous carcinoma:* Most commonly on plantar aspect of foot; low-grade malignancy but may be mistaken for a common wart.

Clinical Appearance

Hyperkeratotic papule or nodule or erosion; nodule may be ulcerated.

TREATMENT**Squamous Cell Carcinoma**

Local excision and Mohs micrographic surgery are most common; radiation therapy in selected cases. Metastatic disease may be treated with radiation therapy or with combination biologic therapy; 13-*cis*-retinoic acid 1 mg/d PO plus IFN 3 million units/d SC. Chemotherapy may be used palliatively.

Prognosis

Favorable if secondary to UV exposure; less favorable if in sun-protected areas or associated with ionizing radiation.

SKIN CANCER PREVENTION

Most skin cancer is related to sun exposure. Encourage pts to avoid the sun and use sunscreen.

69

Head and Neck Cancer

Epithelial cancers may arise from the mucosal surfaces of the head and neck including the sinuses, oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx. These tumors are usually squamous cell cancers. Thyroid cancer is discussed in [Chap. 173](#).

INCIDENCE AND EPIDEMIOLOGY

About 51,540 cases (about 3% of adult malignancies) are diagnosed each year and 10,000 people die from the disease. Oral cavity, oropharynx, and larynx are the most frequent sites of primary lesions in the United States; nasopharyngeal primaries are more common in the Far East and Mediterranean countries. Alcohol and tobacco (including smokeless) abuse are risk factors. Human papillomavirus (HPV; usually types 16 and 18) is associated with over half of oropharynx cancers in Western countries and HPV-related cancers have a better prognosis, particularly in nonsmokers.

PATHOLOGY

Nasopharyngeal cancer in the Far East has a distinct histology, nonkeratinizing undifferentiated carcinoma with infiltrating lymphocytes called *lymphoepithelioma*, and a distinct etiology, Epstein-Barr virus. Squamous cell head and neck cancer may develop from premalignant lesions (erythroplakia, leukoplakia), and the histologic grade affects prognosis. Pts who have survived head and neck cancer commonly develop a second cancer of the head and neck, lung, or esophagus, presumably reflecting the exposure of the upper aerodigestive mucosa to similar carcinogenic stimuli.

■ GENETIC ALTERATIONS

Chromosomal deletions and mutations have been found in chromosomes 3p, 9p, 17p, and 13q; mutations in p53 have been reported. Cyclin D1 may be overexpressed. Epidermal growth factor receptor is commonly overexpressed.

■ CLINICAL PRESENTATION

Most occur in persons >60 years. Symptoms vary with the primary site. Nasopharynx lesions do not usually cause symptoms until late in the course and then cause unilateral serous otitis media or nasal obstruction or epistaxis. Oral cavity cancers present as nonhealing ulcers, sometimes painful. Oropharyngeal lesions also present late with sore throat or otalgia. Hoarseness may be an early sign of laryngeal cancer. Rare pts present with painless, rock-hard cervical or supraclavicular lymph node enlargement. Staging is based on the size of primary tumor and involvement of lymph nodes. Distant metastases occur in <10% of pts.

TREATMENT

Head and Neck Cancer

Three categories of disease are common: localized, locally or regionally advanced, and recurrent or metastatic. *Localized disease* occurs in about one-third of pts and is treated with curative intent by surgery or radiation therapy. Radiation therapy is preferred for localized larynx cancer to preserve organ function; surgery is used more commonly for oral cavity lesions. Overall 5-year survival is 60–90%, and most recurrences occur within 2 years. *Locally advanced disease* is the most common presentation (>50%). Combined-modality therapy using induction chemotherapy, then surgery followed by concomitant chemotherapy and radiation therapy, is most effective. The use of three cycles of cisplatin (75 mg/m² IV day 1) and docetaxel (75 mg/m² IV day 1) plus 5-fluorouracil (5-FU) (750 [mg/m²]/d by 96- to 120-h continuous infusion) before or during radiation therapy is more effective than surgery plus radiation therapy, although mucositis is also more severe; 5-year survival is 34–50%. Cetuximab plus radiation therapy may be more effective than radiation therapy alone but does not improve outcomes when combined with chemoradiotherapy. Head and neck cancer pts are frequently malnourished and often have intercurrent illness. Those who obtain a remission often develop hypothyroidism. Pts with *recurrent* or *metastatic disease* (about 10% of pts) are treated palliatively with cisplatin plus 5FU or paclitaxel (200–250 mg/m² with granulocyte colony-stimulating factor support) or with single-agent chemotherapy (a taxane, methotrexate, cisplatin, or carboplatin). Response rates are usually 30–50% and median survival of about 3 months. Use of immune checkpoint inhibitors in salvage therapy has increased median survival to 7.5 months.

■ PREVENTION

The most important intervention is to get the pts to stop smoking. Long-term survival is significantly better in those who stop smoking. Chemopreventive therapy with *cis*-retinoic acid (3 months of 1.5 [mg/kg]/d followed by 9 months of 0.5 [mg/kg]/d PO) may cause regression of leukoplakia but has no consistent effect on development of cancer and may increase the risk in active smokers.

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Lung Cancer

**■ INCIDENCE**

Lung cancer was diagnosed in about 116,440 men and 110,710 women in the United States in 2019, and 86% of pts die within 5 years. Lung cancer, the leading cause of cancer death, accounts for 26% of all cancer deaths in men and 25% in women. Peak incidence occurs between ages 55 and 65 years. Incidence is decreasing in men and increasing in women.

■ HISTOLOGIC CLASSIFICATION

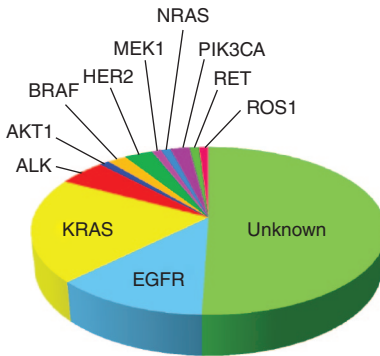
Four major types account for 88% of primary lung cancers: epidermoid (squamous), 29%; adenocarcinoma (including bronchioloalveolar), 35%; large cell, 9%; and small cell (or oat cell), 18%. Histology (small-cell versus non-small-cell types) is a major determinant of treatment approach. Small cell is usually widely disseminated at presentation, whereas non-small cell may be localized. Epidermoid and small cell typically present as central masses, whereas adenocarcinomas and large cell usually present as peripheral nodules or masses. Epidermoid and large cell cavitate in 20–30% of pts.

■ ETIOLOGY

The major cause of lung cancer is tobacco use, particularly cigarette smoking. Lung cancer cells may have ≥ 10 acquired genetic lesions, most commonly point mutations in *ras* oncogenes; amplification, rearrangement, or transcriptional activation of *myc* family oncogenes; overexpression of *bcl-2*, *Her2/neu*, and telomerase; and deletions involving chromosomes 1p, 1q, 3p12-13, 3p14 (FHIT gene region), 3p21, 3p24-25, 3q, 5q, 9p (p16 and p15 cyclin-dependent kinase inhibitors), 11p13, 11p15, 13q14 (*rb* gene), 16q, and 17p13 (*p53* gene). Loss of 3p and 9p is the earliest event, detectable even in hyperplastic bronchial epithelium; *p53* abnormalities and *ras* point mutations are usually found only in invasive cancers. A small but significant subset of pts with adenocarcinoma have activating mutations in the gene for the epidermal growth factor (EGF) receptor, or activating fusion events involving the *alk* or *ros* gene. Driver mutations in lung cancer are depicted in [Fig. 70-1](#).

■ CLINICAL MANIFESTATIONS

Only 5–15% are detected while asymptomatic. Central endobronchial tumors cause cough, hemoptysis, wheeze, stridor, dyspnea, pneumonitis. Peripheral lesions cause pain, cough, dyspnea, symptoms of lung abscess resulting from cavitation. Metastatic spread of primary lung cancer may cause tracheal obstruction, dysphagia, hoarseness, Horner's syndrome. Other problems of regional spread include superior vena cava syndrome, pleural effusion, respiratory failure. Extrathoracic metastatic disease affects 50% of pts with epidermoid cancer, 80% with adenocarcinoma and large cell, and $>95\%$ with small cell. Clinical problems result from brain metastases, pathologic fractures, liver invasion, and spinal cord compression. Paraneoplastic syndromes may be a presenting finding of lung cancer or first sign of recurrence ([Chap. 78](#)). Systemic symptoms occur in 30% and include weight loss, anorexia, fever. Endocrine syndromes occur in 12% and include hypercalcemia (epidermoid), syndrome of inappropriate antidiuretic hormone secretion (small cell), gynecomastia (large cell). Skeletal connective tissue syndromes include clubbing in 30% (most often non-small cell) and hypertrophic pulmonary osteoarthropathy in 1–10% (most often adenocarcinomas), with clubbing, pain, and swelling.



Frequency of driver mutations in NSCLC	
AKT1	1%
ALK	3–7%
BRAF	1–3%
EGFR	10–35%
HER2	2–4%
KRAS	15–25%
MEK1	1%
NRAS	1%
PIK3CA	1–3%
RET	1–2%
ROS1	1–2%

FIGURE 70-1 Driver mutations in adenocarcinomas.

■ STAGING (TABLES 70-1 AND 70-2)

Two parts to staging are: (1) determination of location (anatomic staging) and (2) assessment of pt's ability to withstand antitumor treatment (physiologic staging). Non-small-cell tumors are staged by the TNM/International Staging System (ISS). The T (tumor), N (regional node involvement), and M (presence or absence of distant metastasis) factors are taken together to define different stage groups. Small-cell tumors are staged by two-stage system: limited stage disease—confined to one hemithorax and regional lymph nodes; extensive

TABLE 70-1 Comparison of Seventh and Eighth Edition TNM Staging Systems for Non-Small-Cell Lung Cancer

	TNM STAGING SYSTEM FOR LUNG CANCER (7TH EDITION)	TNM STAGING SYSTEM FOR LUNG CANCER (8TH EDITION)
Primary tumor (T)		
T1	Tumor ≤ 3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus	T1 tumor ≤ 3 cm in diameter surrounds by lung or visceral pleural without evidence of main bronchus
T1a	Tumor ≤ 2 cm in diameter	Tumor < 1 cm
T1b	Tumor > 2 cm but ≤ 3 cm in diameter	Tumor ≥ 1 cm but ≤ 2 cm
T1c	N/A	Tumor > 2 cm but ≤ 3 cm
T2	Tumor > 3 cm but ≤ 7 cm, or tumor with any of the following features:	T2 tumor > 3 cm but ≤ 5 cm or tumor with any of the following features that does not involve the entire lung
	Involves main bronchus ≥ 2 cm distal to carina	Involves main bronchus ≥ 2 cm distal to carina
	Invades visceral pleura	Invades visceral pleura
	Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung	Associate with atelectasis or obstructive pneumonitis that extends to the hilar region
T2a	Tumor > 3 cm but ≤ 5 cm	Tumor > 3 cm but ≤ 4 cm
T2b	Tumor > 5 cm but ≤ 7 cm	Tumor > 4 cm but ≤ 5 cm

(Continued)

TABLE 70-1 Comparison of Seventh and Eighth Edition TNM Staging Systems for Non-Small-Cell Lung Cancer (Continued)

	TNM STAGING SYSTEM FOR LUNG CANCER (7TH EDITION)	TNM STAGING SYSTEM FOR LUNG CANCER (8TH EDITION)
T3	Tumor >7 cm or any of the following:	>5 cm but ≤7 cm or any of the following:
	Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina)	Directly invades any of the following chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina)
	Atelectasis or obstructive pneumonitis of the entire lung	Atelectasis or obstructive pneumonitis of the entire lung
	Separate tumor nodules in the same lobe	
T4	Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe	7 cm or any of the following invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe
Regional lymph nodes (N)		
N0	No regional lymph node metastases	N0 No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)	N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)	N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant metastasis (M)		
M0	No distant metastasis	M0 No distant metastasis
M1	Distant metastasis	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion	M1 a separate nodule(s) in a contralateral tumor with pleural nodules or malignant pleural or pericardial effusion
M1b	Distant metastasis (in extrathoracic organs)	Single metastasis in a single organ
M1c		multiple metastases in a single organ or in several organs

Abbreviation: TNM, tumor-node-metastasis.

Source: Reproduced with permission from Goldstraw P et al: The IASLC Lung Cancer Staging Project. *J Thorac Oncol* 2:706, 2007.

TABLE 70-2 Comparison of Seventh and Eighth Edition TNM Staging Systems for Non-Small-Cell Lung Cancer

STAGE GROUPINGS SEVENTH EDITION				STAGE GROUPINGS EIGHTH EDITION			
Stage IA	T1a-T1b	N0	M0	Stage IA1	T1a	N0	M0
				Stage IA2	T1b	N0	M0
				Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0	Stage IB	T2a	N0	M0
Stage IIA	T1a, T1b,T2a T2b	N1 N0	M0 M0	Stage IIA T2bN0M0	T2b	N0	M0
Stage IIB	T2b	N1	M0	Stage IIB	T1a- T2b	N1	M0
	T3	N0	M0		T3	N0	M0
Stage IIIA	T1a,T1b, T2a,T2b	N2	M0	Stage IIIA	T1-2b	N2	M0
	T3	N1,N2	M0		T3	N1	M0
	T4	N0,N1	M0		T4	N0/N1	M0
Stage IIIB	T4	N2	M0	Stage IIIB	T1-2b	N3	M0
	Any T	N3	M0		T3/T4	N0/N1	M0
Stage IIIC	N/A				T3/T4	N3	M0
Stage IV	Any T	Any N	M1a or M1b	Stage IVA	Any T	Any N	M1a/ M1b
				Stage IV B	Any T	Any N	M1c

disease—involvement beyond this. General staging procedures include careful ear, nose, and throat examination; chest x-ray (CXR); chest and abdominal CT scanning; and positron emission tomography scan. CT scans may suggest mediastinal lymph node involvement and pleural extension in non-small-cell lung cancer, but a definitive evaluation of mediastinal spread requires histologic examination. Routine radionuclide scans are not obtained in asymptomatic pts. If a mass lesion is on CXR and no obvious contraindications to curative surgical approach are noted, the mediastinum should be investigated. Major contraindications to curative surgery include extrathoracic metastases, superior vena cava syndrome, vocal cord and phrenic nerve paralysis, malignant pleural effusions, metastases to contralateral lung, and histologic diagnosis of small-cell cancer.

TREATMENT

Lung Cancer (Table 70-3)

1. Surgery in pts with localized disease and non-small-cell cancer; however, majority initially thought to have curative resection ultimately succumb to metastatic disease. Adjuvant chemotherapy (cisplatin, four cycles at 100 mg/m² plus a second active agent [etoposide, vinblastine, vinorelbine, vindesine, a taxane]) in pts with total resection of stage IIA and IIB diseases may extend survival.
2. Solitary pulmonary nodule: factors suggesting resection include cigarette smoking, age ≥35 years, relatively large (>2 cm) lesion, lack of calcification, chest symptoms, and growth of lesion compared with old CXR.
3. For unresectable stage II non-small-cell lung cancer, combined thoracic radiation therapy and cisplatin-based chemotherapy reduces mortality by about 25% at 1 year.

TABLE 70-3 Summary of Treatment Approach to Pts with Lung Cancer**Non-Small-Cell Lung Cancer**

Stages IA, IB, IIA, IIB, and some IIIA:

Surgical resection for stages IA, IB, IIA, and IIB

Surgical resection with complete-mediastinal lymph node dissection and consideration of neoadjuvant CRx for stage IIIA disease with “minimal N2 involvement” (discovered at thoracotomy or mediastinoscopy)

Consider postoperative RT for pts found to have N2 disease

Stage IB: Discussion of risk/benefits of adjuvant CRx; not routinely given

Stage II: Adjuvant CRx

Curative potential RT for “nonoperable” pts

Stage IIIA with selected types of stage T3 tumors:

Tumors with chest wall invasion (T3): en bloc resection of tumor with involved chest wall and consideration of postoperative RT

Superior sulcus (Pancoast’s) (T3) tumors: preoperative RT (30–45 Gy) and CRx followed by en bloc resection of involved lung and chest wall with postoperative RT

Proximal airway involvement (<2 cm from carina) without mediastinal nodes: sleeve resection if possible preserving distal normal lung or pneumonectomy

Stages IIIA “advanced, bulky, clinically evident N2 disease” (discovered preoperatively) and IIIB disease that can be included in a tolerable RT port:

Curative potential concurrent RT + CRx if performance status and general medical condition are reasonable; otherwise, sequential CRx followed by RT, or RT alone; CRx plus immune checkpoint inhibition for selected pts

Stage IIIB disease with carinal invasion (T4) but without N2 involvement:

Consider pneumonectomy with tracheal sleeve resection with direct reanastomosis to contralateral mainstem bronchus

Stage IV and more advanced IIIB disease:

RT to symptomatic local sites

CRx for ambulatory pts; consider CRx and bevacizumab or CRx plus immune checkpoint inhibition for selected pts

Chest tube drainage of large malignant pleural effusions

Consider resection of primary tumor and metastasis for isolated brain or adrenal metastases

Small-Cell Lung Cancer

Limited stage (good performance status): combination CRx + concurrent chest RT

Extensive stage (good performance status): combination CRx with or without immune checkpoint inhibition

Complete tumor responders (all stages): consider prophylactic cranial RT

Poor-performance-status pts (all stages)

Modified-dose combination CRx

Palliative RT

Bronchioloalveolar or Adenocarcinoma with EGF Receptor Mutations or ALK rearrangements

Gefitinib or erlotinib, inhibitors of EGF receptor kinase activity

Ceritinib or brigatinib, alk inhibitors

(Continued)

TABLE 70-3 Summary of Treatment Approach to Pts with Lung Cancer (Continued)**All Pts**

RT for brain metastases, spinal cord compression, weight-bearing lytic bony lesions, symptomatic local lesions (nerve paralyses, obstructed airway, hemoptysis, intrathoracic large venous obstruction, in non-small-cell lung cancer and in small-cell cancer not responding to CRx)

Appropriate diagnosis and treatment of other medical problems and supportive care during CRx

Encouragement to stop smoking

Entrance into clinical trial, if eligible

Abbreviations: CRx, chemotherapy; EGF, epidermal growth factor; RT, radiotherapy.

4. For unresectable non-small-cell cancer, metastatic disease, or refusal of surgery, consider for radiation therapy; addition of cisplatin/taxane-based chemotherapy may reduce death risk by 13% at 2 years and improve quality of life. Pemetrexed has activity in pts with progressive disease.
5. Small-cell cancer: combination chemotherapy is standard mode of therapy; response after 6–12 weeks predicts median- and long-term survival.
6. Addition of radiation therapy to chemotherapy in limited-stage small-cell lung cancer can increase 5-year survival from about 11% to 20%.
7. Prophylactic cranial irradiation improves survival of limited-stage small-cell lung cancer by another 5%.
8. Laser obliteration of tumor through bronchoscopy in presence of bronchial obstruction.
9. Radiation therapy for brain metastases, spinal cord compression, symptomatic masses, bone lesions.
10. Encourage cessation of smoking.
11. Pts with adenocarcinoma carcinoma (3% of all pts with lung cancer): 7% of these have activating mutations in the EGF receptor. These pts often respond to gefitinib or erlotinib, EGF receptor inhibitors. About 5% of these have activating rearrangements of the *alk* gene and may respond to ceritinib or brigatinib.
12. Immune checkpoint inhibitors are being tested in nearly every clinical setting in pts with lung cancer. Anti-PD1 and anti-PD-L1 antibodies appear to be effective alone or added to chemotherapy. Predicting response remains imprecise; some studies suggest higher tumor mutation burden is a key predictor of response. The relationship of PD-L1 expression on the tumor to response is unclear. Response rates are about 40–50% and progression-free survival is increased.

■ PROGNOSIS

At the time of diagnosis, only 20% of pts have localized disease. Overall 5-year survival is 30% for males and 50% for females with localized disease and 5% for pts with advanced disease. Survival as a function of stage is listed in [Table 70-4](#).

■ SCREENING

The National Cancer Institute study of lung cancer screening of high-risk pts (age 55–74 years with 30+ pack-year smoking history) with low-dose helical CT scan reduced lung cancer mortality by 20% but had only a small effect on overall mortality.

TABLE 70-4 Five-Year Survival by Stage and TNM Classification of Non-Small-Cell Lung Cancer

STAGE	TNM SEVENTH EDITION	5-YEAR SURVIVAL, %
IA	T1a-T1bN0M0	83
IB	T2aN0M0	68
IIA	T1a-T2aN1M0 T2bN0M0	60
IIB	T2bN1M0 T3N0M0	53
IIIA	T1a-T3N2M0 T3N1M0 T4N0-1M0	36
IIIB	T4N2M0 T1a-T4N3M0	26
IV	Any T Any N plus M1a or M1b	13

Abbreviation: TNM, tumor-node-metastasis.

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Breast Cancer



INCIDENCE AND EPIDEMIOLOGY

The most common tumor in women; 266,120 women in the United States were diagnosed in 2019 and 40,920 died with breast cancer. Men also get breast cancer; F:M is 150:1. Breast cancer is hormone-dependent. Women with late menarche, early menopause, and first full-term pregnancy by age 18 years have a significantly reduced risk. The average American woman has about a one in nine lifetime risk of developing breast cancer. Dietary fat is a controversial risk factor. Oral contraceptives have little, if any, effect on risk and lower the risk of endometrial and ovarian cancer. Voluntary interruption of pregnancy does not increase risk. Estrogen replacement therapy may slightly increase the risk, but the beneficial effects of estrogen on quality of life, bone mineral density, and decreased risk of colorectal cancer appear to be somewhat outnumbered by increases in cardiovascular and thrombotic diseases. Women who received therapeutic radiation before age 30 years are at increased risk. Breast cancer risk is increased when a sister and mother also had the disease.

GENETICS

Perhaps 8–10% of breast cancer is familial. *BRCA-1* mutations account for about 5%. *BRCA-1* maps to chromosome 17q21 and appears to be involved in transcription-coupled DNA repair. Ashkenazi Jewish women have a 1% chance of having a common mutation (deletion of adenine and guanine at position 185). The *BRCA-1* syndrome includes an increased risk of ovarian cancer in women and prostate cancer in men. *BRCA-2* on chromosome 11 may account for 2–3% of breast cancer. Mutations are associated with an increased risk of breast cancer in men and women. Germ-line mutations in p53 (Li-Fraumeni syndrome) are very rare, but breast cancer, sarcomas, and other malignancies occur in such families.

Germ-line mutations in *PALB2*, *hCHK2*, and *PTEN* may account for some familial breast cancer. Sporadic breast cancers show many genetic alterations, including overexpression of *HER2/neu* in 25% of cases, p53 mutations in 40%, and loss of heterozygosity at other loci.

Genetic analysis has defined distinct subsets of breast cancers (see below). Tests for expression of panels of genes have been developed that can predict clinical behavior and be used to determine type and duration of therapy.

■ DIAGNOSIS

Breast cancer is usually diagnosed by biopsy of a nodule detected by mammogram or by palpation. Women should be strongly encouraged to examine their breasts monthly. In premenopausal women, questionable or nonsuspicious (small) masses should be reexamined in 2–4 weeks. A mass in a premenopausal woman that persists throughout her cycle and any mass in a postmenopausal woman should be aspirated. If the mass is a cyst filled with nonbloody fluid that goes away with aspiration, the pt is returned to routine screening. If the cyst aspiration leaves a residual mass or reveals bloody fluid, the pt should have a mammogram and excisional biopsy. If the mass is solid, the pt should undergo a mammogram and excisional biopsy. Screening mammograms performed every other year beginning at age 50 years have been shown to save lives. The controversy regarding screening mammograms beginning at age 40 years relates to the following facts: (1) the disease is much less common in the 40- to 49-year age group, and screening is generally less successful for less common problems; (2) workup of mammographic abnormalities in the 40- to 49-year age group less commonly diagnoses cancer; and (3) about 50% of women who are screened annually during their forties have an abnormality at some point that requires a diagnostic procedure (usually a biopsy), yet very few evaluations reveal cancer. However, many believe in the value of screening mammography beginning at age 40 years. After 13–15 years of follow-up, women who start screening at age 40 years have a small survival benefit. Women with familial breast cancer more often have false-negative mammograms. MRI is a better screening tool in these women. Women with dense breasts (>50% fibroglandular tissue) are said to be at increased risk (1.2- to 2-fold), but it is not clear that they require increased surveillance.

■ CLINICAL AND MOLECULAR STAGING

Therapy and prognosis are dictated by stage of disease (Table 71-1). Unless the breast mass is large or fixed to the chest wall, staging of the ipsilateral axilla is performed at the time of lumpectomy (see below). Within pts of a given stage, individual characteristics of the tumor may influence prognosis: expression of estrogen receptor improves prognosis, while overexpression of *HER2/neu*, mutations in p53, high growth fraction, and aneuploidy worsen the prognosis. Molecular profiling has identified genetically distinct subsets including luminal A and B (estrogen receptor positive), normal breast-like, *HER2*-amplified, and basal (or triple-negative based on no expression of hormone receptors or overexpression of *HER2*). These subsets differ in prognosis. Breast cancer can spread almost anywhere but commonly goes to bone, lungs, liver, soft tissue, and brain.

TREATMENT

Breast Cancer

Five-year survival rate by stage is shown in Table 71-2. Treatment varies with stage of disease and expression of hormone receptors and *HER2*.

TABLE 71-1 Staging of Breast Cancer

Primary Tumor (T)			
T0	No evidence of primary tumor		
TIS	Carcinoma in situ		
T1	Tumor ≤ 2 cm		
T1a	Tumor >0.1 cm but ≤ 0.5 cm		
T1b	Tumor >0.5 but ≤ 1 cm		
T1c	Tumor >1 cm but ≤ 2 cm		
T2	Tumor >2 cm but ≤ 5 cm		
T3	Tumor >5 cm		
T4	Extension to chest wall, inflammation, satellite lesions, ulcerations		
Regional Lymph Nodes (N)			
PNO(i-)	No regional lymph node metastasis histologically, negative IHC		
PNO(i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster >0.2 mm		
PNO(mol-)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)		
PNO(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)		
PN1	Metastasis in one to three axillary lymph nodes, or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent		
PN1mi	Micrometastasis (>0.2 mm, none >2 mm)		
PN1a	Metastasis in one to three axillary lymph nodes		
PN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent ^a		
PN1c	Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent. ^a (If associated with greater than three positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.)		
pN2	Metastasis in four to nine axillary lymph nodes, or in clinically apparent internal mammary lymph nodes in the absence of axillary lymph node metastasis		
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent ^a ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral subcarinal lymph nodes		
Distant Metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis (includes spread to ipsilateral supraclavicular nodes)		
Stage Grouping			
Stage 0	TIS	N0	M0
Stage I	T1	N0	M0

(Continued)

TABLE 71-1 Staging of Breast Cancer (Continued)

Stage IIA	T0	N1	M0
	T1	N1	M0
Stage IIB	T2	N0	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
Stage IIIB	T3	N1, N2	M0
	T4	Any N	M0
Stage IIIC	Any T	N3	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

^aClinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

Abbreviations: IHC, immunohistochemistry; RT-PCR, reverse transcriptase/polymerase chain reaction.

Source: Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, 7th ed. New York, Springer, 2010; www.springeronline.com.

Ductal carcinoma in situ is noninvasive tumor present in the breast ducts. Treatment of choice is wide excision with breast radiation therapy. In one study, adjuvant tamoxifen further reduced the risk of recurrence.

Invasive breast cancer can be classified as operable, locally advanced, and metastatic. In operable breast cancer, the outcome of primary therapy is the same with modified radical mastectomy or lumpectomy followed by breast radiation therapy. Axillary dissection may be replaced with sentinel node biopsy to evaluate node involvement. The sentinel node is identified by injecting a dye in the tumor site at surgery; the first node in which dye appears is the sentinel node. Women with tumors <1 cm and negative axillary nodes require no additional therapy beyond their primary lumpectomy and breast radiation. Adjuvant combination chemotherapy for 6 months appears to benefit premenopausal women with positive lymph nodes, pre- and postmenopausal women with negative lymph nodes but with large tumors or poor prognostic features, and postmenopausal women with positive lymph nodes whose tumors do not express estrogen receptors. Estrogen receptor–positive tumors >1 cm with or without involvement of lymph nodes are treated with aromatase inhibitors. Women who

TABLE 71-2 A 5-Year Survival Rate for Breast Cancer by Stage

STAGE	5-YEAR SURVIVAL (PERCENTAGE OF PTS)
0	99
I	92
IIA	82
IIB	65
IIIA	47
IIIB	44
IV	14

Source: Modified from data of the National Cancer Institute—Surveillance, Epidemiology, and End Results (SEER). National Institutes of Health (NIH).

began treatment with tamoxifen before aromatase inhibitors were approved should switch to an aromatase inhibitor after 5 years of tamoxifen and continue for another 5 years.

Adjuvant chemotherapy is added to hormonal therapy in estrogen receptor-positive, node-positive women and is used without hormonal therapy in estrogen receptor-negative node-positive women, whether they are pre- or postmenopausal. Various regimens have been used. The most effective regimen appears to be four cycles of doxorubicin, 60 mg/m², plus cyclophosphamide, 600 mg/m², IV on day 1 of each 3-week cycle followed by four cycles of paclitaxel, 175 mg/m², by 3-h infusion on day 1 of each 3-week cycle. In women with HER2+ tumors, trastuzumab augments the ability of chemotherapy to prevent recurrence. The activity of other combinations is being explored. In premenopausal women, ovarian ablation (e.g., with the luteinizing hormone-releasing hormone [LHRH] inhibitor goserelin) may be as effective as adjuvant chemotherapy.

Tamoxifen adjuvant therapy (20 mg/d for 5 years) or an aromatase inhibitor (anastrozole, letrozole, exemestane) is used for postmenopausal women with tumors expressing estrogen receptors whose nodes are positive or whose nodes are negative but with large tumors or poor prognostic features. Breast cancer will recur in about half of pts with localized disease. High-dose adjuvant therapy with marrow support does not appear to benefit even women with high risk of recurrence. In pts with tumors expressing *Her2*, use of adjuvant trastuzumab with chemotherapy reduces risk of recurrence by at least 50%.

Pts with locally advanced breast cancer benefit from neoadjuvant combination chemotherapy (e.g., CAF: cyclophosphamide 500 mg/m², doxorubicin 50 mg/m², and 5-fluorouracil 500 mg/m² all given IV on days 1 and 8 of a monthly cycle for 6 cycles) followed by surgery plus breast radiation therapy.

Treatment for metastatic disease depends on estrogen receptor status and treatment philosophy. No therapy is known to cure pts with metastatic disease. Randomized trials do not show that the use of high-dose therapy with hematopoietic stem cell support improves survival. Median survival is about 22 months with conventional treatment: aromatase inhibitors for estrogen receptor-positive tumors and combination chemotherapy for receptor-negative tumors. Pts whose tumors express *HER2/neu* have higher response rates by adding trastuzumab (anti-HER2/neu) to chemotherapy. Trastuzumab emtansine is a drug conjugate that targets HER2-expressing cells and has antitumor activity. Some advocate sequential use of active single agents in the setting of metastatic disease. Active agents in anthracycline- and taxane-resistant disease include capecitabine, vinorelbine, gemcitabine, irinotecan, and platinum agents. Pts progressing on adjuvant tamoxifen may benefit from an aromatase inhibitor such as letrozole or anastrozole. Half of pts who respond to one endocrine therapy will respond to another. Bisphosphonates reduce skeletal complications and may promote antitumor effects of other therapy. Radiation therapy is useful for palliation of symptoms.

■ PREVENTION

Women with breast cancer have a 0.5% per year risk of developing a second breast cancer. Women at increased risk of breast cancer can reduce their risk by 49% by taking tamoxifen or an aromatase inhibitor for 5 years. Women with *BRCA-1* mutations can reduce the risk by 90% with simple mastectomy.

72

Tumors of the Gastrointestinal Tract

**ESOPHAGEAL CARCINOMA**

In 2019 in the United States, 17,060 cases and 16,080 deaths; less frequent in women than men. Highest incidence in focal regions of China, Iran, Afghanistan, Siberia, and Mongolia. In the United States, blacks more frequently affected than whites; usually presents sixth decade or later; 5-year survival <10% because most pts present with advanced disease.

■ PATHOLOGY

Twenty percent squamous cell carcinoma, most commonly in upper two-thirds; 75% adenocarcinoma, usually in distal third, arising in region of columnar metaplasia (Barrett's esophagus), glandular tissue, or as direct extension of proximal gastric adenocarcinoma; lymphoma and melanoma rare. Five percent of all esophageal cancers occur in the upper third, 20% in the middle third, and 75% in the lower third. Fifteen percent of tumors express *HER2/neu*.

■ RISK FACTORS

Major risk factors for squamous cell carcinoma: ethanol abuse, smoking (combination is synergistic); other risks: lye ingestion and esophageal stricture, radiation exposure, head and neck cancer, achalasia, smoked opiates, Plummer-Vinson syndrome, tylosis, chronic ingestion of extremely hot tea, deficiency of vitamin A, zinc, molybdenum, selenium. Barrett's esophagus, chronic gastroesophageal reflux, obesity, and smoking are risk factors for adenocarcinoma.

■ CLINICAL FEATURES

Progressive dysphagia (first with solids, then liquids), rapid weight loss common, chest pain (from mediastinal spread), odynophagia, pulmonary aspiration (obstruction, tracheoesophageal fistula), hoarseness (laryngeal nerve palsy), hypercalcemia (parathyroid hormone-related peptide hypersecretion by squamous carcinomas); bleeding infrequent, occasionally severe; examination often unremarkable.

■ DIAGNOSIS

Double-contrast barium swallow useful as initial test in dysphagia; flexible esophagogastrosopy most sensitive and specific test; pathologic confirmation by combining endoscopic biopsy and cytologic examination of mucosal brushings (neither alone sufficiently sensitive); CT and endoscopic ultrasonography valuable to assess local and nodal spread. PET scanning can also assess mediastinal nodes and distant sites.

TREATMENT**Esophageal Carcinoma**

Surgical resection feasible in only 40% of pts; associated with high complication rate (fistula, abscess, aspiration). *Squamous cell carcinoma*: Surgical resection after chemotherapy [5-fluorouracil (5FU), cisplatin] plus radiation therapy prolongs survival and may provide improved cure rate. *Adenocarcinoma*: Curative resection rarely possible; <20% of pts with resectable tumors survive 5 years. Palliative measures include laser ablation, mechanical dilatation, radiotherapy,

and a luminal prosthesis to bypass the tumor. Gastrostomy or jejunostomy are frequently required for nutritional support. Preoperative chemotherapy with concurrent radiation therapy is somewhat more effective but more toxic therapy. Addition of bevacizumab provides minimal benefit.

GASTRIC CARCINOMA

Highest incidence in Japan, China, Chile, Ireland; incidence decreasing worldwide, eightfold in the United States over past 60 years; in 2019, 27,510 new cases and 11,140 deaths. Male:female = 2:1; peak incidence sixth and seventh decades; overall 5-year survival <15%.

■ RISK FACTORS

Decreasing incidence in the United States over past 80 years. Increased incidence in lower socioeconomic groups; environmental component is suggested by studies of migrants and their offspring. Several dietary factors correlated with increased incidence: nitrates, smoked foods, heavily salted foods; genetic component suggested by increased incidence in first-degree relatives of affected pts; other risk factors: atrophic gastritis, *Helicobacter pylori* infection, Billroth II gastrectomy, gastrojejunostomy, adenomatous gastric polyps, pernicious anemia, hyperplastic gastric polyps (latter two associated with atrophic gastritis), Ménétrier's disease, slight increased risk with blood group A.

■ PATHOLOGY

Adenocarcinoma in 85%; usually focal (polypoid, ulcerative), two-thirds arising in antrum or lesser curvature, frequently ulcerative ("intestinal type"); less commonly diffuse infiltrative (linitis plastica) or superficial spreading (diffuse lesions more prevalent in younger pts; exhibit less geographic variation; have extremely poor prognosis); spreads primarily to local nodes, liver, peritoneum; systemic spread uncommon; lymphoma accounts for 15% (most frequent extranodal site in immunocompetent pts), either low-grade tumor of mucosa-associated lymphoid tissue (MALT) or aggressive diffuse large B cell lymphoma; leiomyosarcoma or gastrointestinal stromal tumor (GIST) is rare.

■ CLINICAL FEATURES

Most commonly presents with progressive upper abdominal discomfort, frequently with weight loss, anorexia, nausea; acute or chronic GI bleeding (mucosal ulceration) common; dysphagia (location in cardia); vomiting (pyloric and widespread disease); early satiety; examination often unrevealing early in course; later, abdominal tenderness, pallor, and cachexia most common signs; palpable mass uncommon; metastatic spread may be manifest by hepatomegaly, ascites, left supraclavicular or scalene adenopathy, periumbilical, ovarian, or prerectal mass (Blumer's shelf), low-grade fever, skin abnormalities (nodules, dermatomyositis, acanthosis nigricans, or multiple seborrheic keratoses). Laboratory findings: iron-deficiency anemia in two-thirds of pts; fecal occult blood in 80%; rarely associated with pancytopenia and microangiopathic hemolytic anemia (from marrow infiltration), leukemoid reaction, migratory thrombophlebitis, or acanthosis nigricans.

■ DIAGNOSIS

Double-contrast barium swallow useful but has been supplanted by the more sensitive and specific esophagogastrosocopy and CT for staging and assessing resectability; pathologic confirmation by biopsy and cytologic examination of mucosal brushings; superficial biopsies less sensitive for lymphomas (frequently submucosal); important to differentiate benign from malignant gastric ulcers with multiple biopsies and follow-up examinations to demonstrate ulcer healing.

TREATMENT

Gastric Carcinoma

Adenocarcinoma: Gastrectomy offers only chance of cure (only possible in less than one-third); the rare tumors limited to mucosa are resectable for cure in 80%; deeper invasion, nodal metastases decrease 5-year survival to 20% of pts with resectable tumors in absence of obvious metastatic spread (Table 72-1). Subtotal gastrectomy has similar efficacy to total gastrectomy for distal stomach lesions, but with less morbidity; no clear benefit for resection of spleen and a portion of the pancreas, or for radical lymph node removal. Adjuvant chemotherapy (5FU/leucovorin) plus radiation therapy following primary surgery leads to a 7-month increase in median survival. Neoadjuvant chemotherapy with epirubicin or docetaxel with cisplatin, and 5FU or capecitabine may downstage tumors and increase the efficacy of surgery. Use of chemotherapy before and after surgery may be more effective. Immune checkpoint inhibitors appear to have activity in some pts. Palliative therapy for pain, obstruction, and bleeding includes surgery,

TABLE 72-1 Staging System for Gastric Carcinoma

STAGE	TNM	FEATURES	DATA FROM ACS	
			NO. OF CASES, %	5-YEAR SURVIVAL, %
0	T _{is} N0M0	Node negative; limited to mucosa	1	90
IA	T1N0M0	Node negative; invasion of lamina propria or submucosa	7	59
IB	T2N0M0 T1N1M0	Node negative; invasion of muscularis propria	10	44
II	T1N2M0 T2N1M0 T3N0M0	Node positive; invasion beyond mucosa but within wall Or Node negative; extension through wall	17	29
IIIA	T2N2M0 T3N1-2M0	Node positive; invasion of muscularis propria or through wall	21	15
IIIB	T4N0-1M0	Node negative; adherence to surrounding tissue	14	9
IIIC	T4N2-3M0 T3N3M0	>3 nodes positive; invasion of serosa or adjacent structures 7 or more positive nodes; penetrates wall without invading serosa or adjacent structures		
IV	T4N2M0 T1-4N0-2-M1	Node positive; adherence to surrounding tissue Or Distant metastases	30	3

Abbreviations: ACS, American Cancer Society; TNM, tumor-node-metastasis.

endoscopic dilatation, radiation therapy, chemotherapy, and ramucirumab, an antiangiogenic antibody.

Lymphoma: Low-grade MALT lymphoma is caused by *H. pylori* infection, and eradication of the infection causes complete remissions in 50% of pts; rest are responsive to combination chemotherapy including cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) plus rituximab. Diffuse large B cell lymphoma may be treated with either CHOP plus rituximab or subtotal gastrectomy followed by chemotherapy; 50–60% 5-year survival.

Leiomyosarcoma: Surgical resection curative in most pts. Tumors expressing the *c-kit* tyrosine kinase (CD117)—GIST—respond to imatinib mesylate in a substantial fraction of cases.

BENIGN GASTRIC TUMORS

Much less common than malignant gastric tumors; hyperplastic polyps most common, with adenomas, hamartomas, and leiomyomas rare; 30% of adenomas and occasional hyperplastic polyps are associated with gastric malignancy; polyposis syndromes include Peutz-Jeghers and familial polyposis (hamartomas and adenomas), Gardner's (adenomas), and Cronkhite-Canada (cystic polyps). See "Colonic Polyps," next.

■ CLINICAL FEATURES

Usually asymptomatic; occasionally present with bleeding or vague epigastric discomfort.

TREATMENT

Benign Gastric Tumors

Endoscopic or surgical excision.

SMALL-BOWEL TUMORS

■ CLINICAL FEATURES

Uncommon tumors (~5% of all GI neoplasms); usually present with bleeding, abdominal pain, weight loss, fever, or intestinal obstruction (intermittent or fixed); increased incidence of lymphomas in pts with gluten-sensitive enteropathy, Crohn's disease involving small bowel, AIDS, prior organ transplantation, autoimmune disorders.

■ PATHOLOGY

Usually benign; most common are adenomas (usually duodenal), leiomyomas (intramural), and lipomas (usually ileal); 50% of malignant tumors are adenocarcinoma, usually in duodenum (at or near ampulla of Vater) or proximal jejunum, commonly coexisting with benign adenomas; primary intestinal lymphomas (non-Hodgkin's) account for 25% and occur as focal mass (Western type), which is usually a T cell lymphoma associated with prior celiac disease, or diffuse infiltration (Mediterranean type), which is usually immunoproliferative small-intestinal disease (IPSID; α -heavy chain disease), a B cell MALT lymphoma associated with *Campylobacter jejuni* infection, which can present as intestinal malabsorption; carcinoid tumors (usually asymptomatic) occasionally produce bleeding or intussusception (see next).

■ DIAGNOSIS

Endoscopy and biopsy most useful for tumors of duodenum and proximal jejunum; otherwise barium x-ray examination best diagnostic test; direct small-bowel instillation of contrast (enteroclysis) occasionally reveals tumors not seen

with routine small-bowel radiography; angiography (to detect plexus of tumor vessels) or laparotomy often required for diagnosis; CT useful to evaluate extent of tumor (esp. lymphomas).

TREATMENT

Small-Bowel Tumors

Surgical excision; adjuvant chemotherapy appears helpful for focal lymphoma; IPSID appears to be curable with combination chemotherapy used in aggressive lymphoma plus oral antibiotics (e.g., tetracycline); no proven role for chemotherapy or radiation therapy for other small-bowel tumors.

COLONIC POLYPS

■ TUBULAR ADENOMAS

Present in ~30% of adults; pedunculated or sessile; usually asymptomatic; ~5% cause occult blood in stool; may cause obstruction; overall risk of malignant degeneration correlates with size (<2% if <1.5 cm in diameter; >10% if >2.5 cm in diameter) and is higher in sessile polyps; 65% found in rectosigmoid colon; diagnosis by barium enema, sigmoidoscopy, or colonoscopy. *Treatment:* Full colonoscopy to detect synchronous lesions (present in 30%); endoscopic resection (surgery if polyp large or inaccessible by colonoscopy); follow-up surveillance by colonoscopy every 2–3 years.

■ VILLOUS ADENOMAS

Generally larger than tubular adenomas at diagnosis; often sessile; high risk of malignancy (up to 30% when >2 cm); more prevalent in left colon; occasionally associated with potassium-rich secretory diarrhea. *Treatment:* As for tubular adenomas.

■ HYPERPLASTIC POLYPS

Asymptomatic; usually incidental finding at colonoscopy; rarely >5 mm; no malignant potential. No treatment required.

■ HEREDITARY POLYPOSIS SYNDROMES

See [Table 72-2](#).

1. *Familial polyposis coli (FPC):* Diffuse pancolonc adenomatous polyposis (up to several thousand polyps); autosomal dominant inheritance associated with deletion in adenomatous polyposis coli (*APC*) gene on chromosome 5; colon carcinoma from malignant degeneration of polyp in 100% by age 40. *Treatment:* Prophylactic total colectomy or subtotal colectomy with ileoproctostomy before age 30; subtotal resection avoids ileostomy but necessitates frequent proctoscopic surveillance; periodic colonoscopic or annual radiologic screening of siblings and offspring of pts with FPC until age 35; sulindac and other nonsteroidal anti-inflammatory drugs (NSAIDs) cause regression of polyps and inhibit their development.
2. *Gardner's syndrome:* Variant of FPC with associated soft tissue tumors (epidermoid cysts, osteomas, lipomas, fibromas, desmoids); higher incidence of gastroduodenal polyps, ampullary adenocarcinoma. *Treatment:* As for FPC; surveillance for small-bowel disease with fecal occult blood testing after colectomy.

TABLE 72-2 Hereditary (Autosomal Dominant) Gastrointestinal Polyposis Syndromes

SYNDROME	DISTRIBUTION OF POLYPS	HISTOLOGIC TYPE	MALIGNANT POTENTIAL	ASSOCIATED LESIONS
Familial adenomatous polyposis	Large intestine	Adenoma	Common	None
Gardner's syndrome	Large and small intestines	Adenoma	Common	Osteomas, fibromas, lipomas, epidermoid cysts, ampullary cancers, congenital hypertrophy of retinal pigment epithelium
Turcot's syndrome	Large intestine	Adenoma	Common	Brain tumors
MYH-associated polyposis	Large intestine	Adenoma	Common	None
Nonpolyposis syndrome (Lynch's syndrome)	Large intestine (often proximal)	Adenoma	Common	Endometrial and ovarian tumors (most frequently) gastric, genitourinary, pancreatic, biliary cancers (less frequently)
Peutz-Jeghers syndrome	Small and large intestines, stomach	Hamartoma	Rare	Mucocutaneous pigmentation; tumors of the ovary, breast, pancreas, endometrium
Juvenile polyposis	Large and small intestines, stomach	Hamartoma, rarely progressing to adenoma	Rare	Various congenital abnormalities

- MYH-associated polyposis*: Rare autosomal recessive syndrome due to biallelic mutation of *MUT4H*. *Treatment*: Biennial surveillance colonoscopy starting at age 25–30.
- Turcot's syndrome*: Rare variant of FPC with associated malignant brain tumors. *Treatment*: As for FPC.
- Nonpolyposis syndrome*: Familial syndrome with up to 50% risk of colon carcinoma; peak incidence in fifth decade; associated with multiple primary cancers (esp. endometrial); autosomal dominant; due to defective DNA mismatch repair.
- Juvenile polyposis*: Multiple benign colonic and small-bowel hamartomas; intestinal bleeding common. *Other symptoms*: abdominal pain, diarrhea; occasional intussusception. Rarely recur after excision; low risk of colon cancer from malignant degeneration of interspersed adenomatous polyps. Prophylactic colectomy controversial.

7. *Peutz-Jeghers syndrome*: Numerous hamartomatous polyps of entire GI tract, though denser in small bowel than colon; GI bleeding common; somewhat increased risk for the development of cancer at GI and non-GI sites. Prophylactic surgery not recommended.

COLORECTAL CANCER

Second most common internal cancer in humans; accounts for 10% of cancer-related deaths in the United States; incidence increases dramatically above age 50, nearly equal in men and women. In 2019, 145,600 new cases, 51,020 deaths.

■ ETIOLOGY AND RISK FACTORS

Most colon cancers arise from adenomatous polyps. Genetic steps from polyp to dysplasia to carcinoma in situ to invasive cancer have been defined, including point mutation in *K-ras* proto-oncogene, hypomethylation of DNA leading to enhanced gene expression, allelic loss at the *APC* gene (a tumor suppressor), allelic loss at the *DCC* (deleted in colon cancer) gene on chromosome 18, and loss and mutation of *p53* on chromosome 17. Hereditary nonpolyposis colon cancer arises from mutations in the DNA mismatch repair genes, *hMSH2* gene on chromosome 2 and *hMLH1* gene on chromosome 3. Mutations lead to colon and other cancers. Diagnosis requires three or more relatives with colon cancer, one of whom is a first-degree relative; one or more cases diagnosed before age 50; and involvement of at least two generations. Environmental factors also play a role including exposure to therapeutic radiation; smoking; increased prevalence in developed countries, urban areas, advantaged socioeconomic groups; increased risk in pts with hypercholesterolemia, coronary artery disease; correlation of risk with low-fiber, high-animal-fat diets, although direct effect of diet remains unproven; decreased risk with long-term dietary calcium supplementation and, possibly, daily aspirin ingestion. Risk increased in first-degree relatives of pts; families with increased prevalence of cancer; and pts with history of breast or gynecologic cancer, familial polyposis syndromes, >10-year history of ulcerative colitis or Crohn's colitis, >15-year history of ureterosigmoidostomy. Tumors in pts with strong family history of malignancy are frequently located in right colon and commonly present before age 50; high prevalence in pts with *Streptococcus bovis* bacteremia.

■ PATHOLOGY

Nearly always adenocarcinoma; 75% located distal to the splenic flexure (except in association with polyposis or hereditary cancer syndromes); may be polypoid, sessile, fungating, or constricting; subtype and degree of differentiation do not correlate with course. Degree of invasiveness at surgery (Dukes' classification) is single best predictor of prognosis (Fig. 72-1). Rectosigmoid tumors may spread to lungs early because of systemic paravertebral venous drainage of this area. *Other predictors of poor prognosis*: preoperative serum carcinoembryonic antigen (CEA) >5 ng/mL (>5 µg/L), poorly differentiated histology, bowel perforation, venous invasion, adherence to adjacent organs, aneuploidy, specific deletions in chromosomes 5, 17, 18, and mutation of *ras* proto-oncogene. Fifteen percent have defects in DNA repair.

■ CLINICAL FEATURES

Left-sided colon cancers present most commonly with rectal bleeding, altered bowel habits (narrowing, constipation, intermittent diarrhea, tenesmus), and abdominal or back pain; cecal and ascending colon cancers more frequently present with symptoms of anemia, occult blood in stool, or weight loss; *other complications*: perforation, fistula, volvulus, inguinal hernia; *laboratory findings*: anemia in 50% of right-sided lesions.

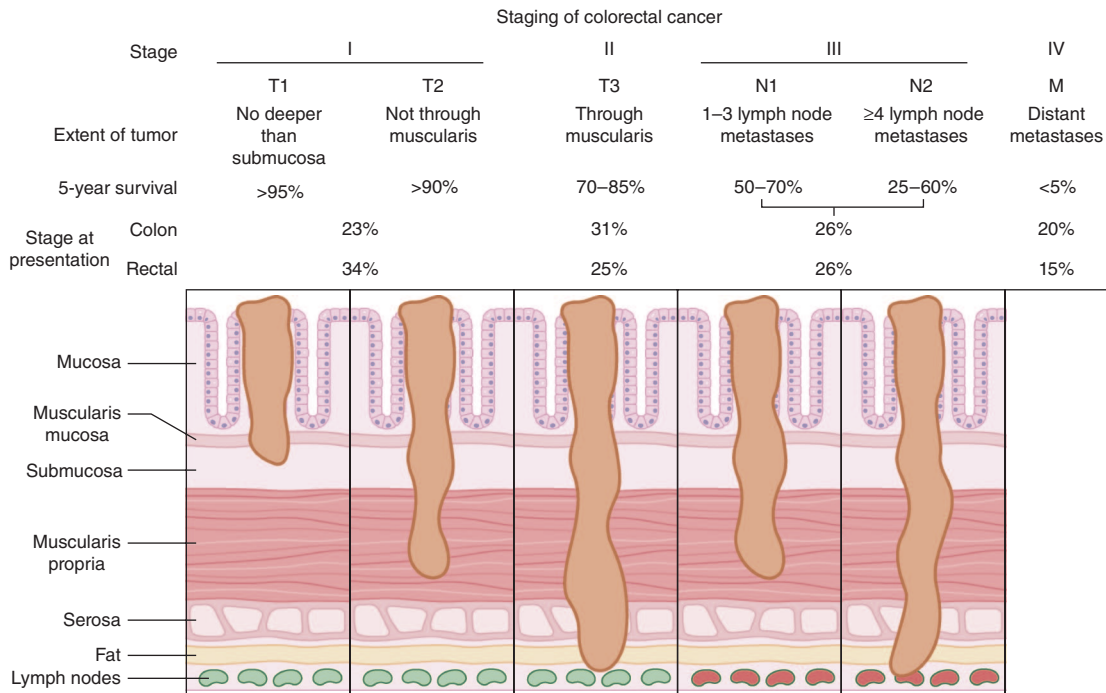


FIGURE 72-1 Staging and prognosis for pts with colorectal cancer.

■ DIAGNOSIS

Early diagnosis aided by screening asymptomatic persons with fecal occult blood testing (see next); >50% of all colon cancers are within reach of a 60-cm flexible sigmoidoscope; air-contrast barium enema will diagnose ~85% of colon cancers not within reach of sigmoidoscope; colonoscopy most sensitive and specific, permits tumor biopsy and removal of synchronous polyps (thus preventing neoplastic conversion), but is more expensive. Radiographic or virtual colonoscopy has not been shown to be a better diagnostic method than colonoscopy.

TREATMENT

Colorectal Cancer

Local disease: Surgical resection of colonic segment containing tumor; preoperative evaluation to assess prognosis and surgical approach includes full colonoscopy, chest films, biochemical liver tests, plasma CEA level, and possible abdominal CT. Resection of isolated hepatic metastases possible in selected cases. Adjuvant radiation therapy to pelvis with concomitant 5FU chemotherapy decreases local recurrence rate of rectal carcinoma (no apparent effect on survival); radiation therapy without benefit on colon tumors; preoperative radiation therapy may improve resectability and local control in pts with rectal cancer. Total mesorectal excision is more effective than conventional anteroposterior resection in rectal cancer. Adjuvant chemotherapy (5FU/leucovorin plus oxaliplatin, or FOLFOX plus bevacizumab, or 5FU/leucovorin plus irinotecan, or FOLFIRI) decreases recurrence rate and improves survival of stage C (III); survival benefit from adjuvant therapy is not so clear in stage B (II) tumors; periodic determination of serum CEA level useful to follow therapy and assess recurrence. *Follow-up after curative resection:* Yearly liver tests, complete blood count, follow-up radiologic or colonoscopic evaluation at 1 year—if normal, repeat every 3 years, with routine screening interim (see below); if polyps detected, repeat 1 year after resection. *Advanced tumor (locally unresectable or metastatic):* Systemic chemotherapy (5FU/leucovorin plus oxaliplatin plus bevacizumab), irinotecan usually used in second treatment; antibodies to the epidermal growth factor (EGF) receptor (cetuximab, panitumumab) appear to enhance the effect of chemotherapy but are ineffective in tumors with *ras* mutations; intraarterial chemotherapy (floxuridine [FUDR]) and/or radiation therapy may palliate symptoms from hepatic metastases. Solitary hepatic metastases may be resected by partial hepatectomy with 25% 5-year survival. The subset of pts with mismatch repair deficiency appear more sensitive to chemotherapy and to immune checkpoint inhibitors.

■ PREVENTION

Early detection of colon carcinoma may be facilitated by routine screening of stool for occult blood (Hemoccult II, ColonCare, Hemosure); however, sensitivity only ~50% for carcinoma; specificity for tumor or polyp ~25–40%. Newer tests (e.g., Cologard) incorporating detection of blood and mutated genes are more sensitive and specific. *False positives for occult blood:* ingestion of red meat, iron, aspirin; upper GI bleeding. *False negatives:* vitamin C ingestion, intermittent bleeding. Genetic testing is unaffected by these factors. Annual digital rectal examination and fecal occult blood testing recommended for pts over age 40, screening by flexible sigmoidoscopy every 3 years after age 50, earlier in pts at increased risk (see above); careful evaluation of all pts with positive fecal occult blood tests (flexible sigmoidoscopy and air-contrast barium enema or colonoscopy alone) reveals polyps in 20–40% and carcinoma in ~5%; screening of asymptomatic persons allows earlier detection of colon cancer (i.e., earlier Dukes' stage) and achieves greater

resectability rate; decreased overall mortality from colon carcinoma seen only after 13 years of follow-up. More intensive evaluation of first-degree relatives of pts with colon carcinoma frequently includes screening air-contrast barium enema or colonoscopy after age 40. NSAIDs and cyclooxygenase 2 inhibitors appear to prevent polyp development and induce regression in high-risk groups, but have not been recommended for average-risk pts at this time.

ANAL CANCER

Accounts for 1–2% of large-bowel cancer, 8300 cases and 1290 deaths in 2019; associated with chronic irritation, e.g., from condyloma acuminata, perianal fissures/fistulas, chronic hemorrhoids, leukoplakia, trauma from anal intercourse. Women are more commonly affected than men. Homosexual men are at increased risk. Human papillomavirus is etiologic. Presents with bleeding, pain, and perianal mass. Radiation therapy plus chemotherapy (5FU and mitomycin) leads to complete response in 80% when the primary lesion is <3 cm. Abdominoperineal resection with permanent colostomy is reserved for those with large lesions or whose disease recurs after chemoradiotherapy.

BENIGN LIVER TUMORS

Hepatocellular adenomas occur most commonly in women in the third or fourth decades who take birth control pills. Most are found incidentally but may cause pain; intratumoral hemorrhage may cause circulatory collapse. Ten percent may become malignant. Women with these adenomas should stop taking birth control pills. Large tumors near the liver surface may be resected. Focal nodular hyperplasia is also more common in women but seems not to be caused by birth control pills. Lesions are vascular on angiography and have septae and are usually asymptomatic.

HEPATOCELLULAR CARCINOMA

About 42,030 cases in the United States in 2019, but worldwide this may be the most common tumor; 31,780 deaths in 2019 in the United States. Male:female = 4:1; tumor usually develops in cirrhotic liver in persons in fifth or sixth decade. High incidence (and increasing) in Asia and Africa is related to etiologic relationship between this cancer and hepatitis B and C infections. Effective vaccines for hepatitis B prevention and successful chemotherapy of hepatitis C should reduce the incidence. Aflatoxin exposure contributes to etiology and leaves a molecular signature, a mutation in codon 249 of the gene for p53. Mutations in *TERT* (telomerase reverse transcriptase) promoter and *CTNNB1* (beta-catenin gene) are common.

■ MODES OF PRESENTATION

A pt with known liver disease develops an abnormality on ultrasound or rising α fetoprotein (AFP) or des-gamma-carboxy prothrombin (DCP) due to absence of vitamin K; abnormal liver function tests; cachexia, abdominal pain, fever.

■ PHYSICAL FINDINGS

Jaundice, asthenia, itching, tremors, disorientation, hepatomegaly, splenomegaly, ascites, peripheral edema.

TREATMENT

Hepatocellular Carcinoma

Surgical resection or liver transplantation is therapeutic option but rarely successful. Radiofrequency ablation, transcatheter arterial embolization (TACE),

and ^{90}Y trium can cause regression of small tumors. Sorafenib or lenvatinib may produce partial responses lasting a few months.

■ SCREENING AND PREVENTION

Screening populations at risk has given conflicting results. Hepatitis B vaccine prevents the disease. Interferon α (IFN- α) may prevent liver cancer in persons with chronic active hepatitis C disease and possibly in those with hepatitis B. Combination therapy with a viral protease inhibitor (e.g., ledipasvir) and a viral polymerase inhibitor (e.g., sofosbuvir) for 12–24 weeks cures most pts with chronic hepatitis C.

PANCREATIC CANCER

In 2019 in the United States, about 56,770 new cases and 45,750 deaths. The incidence is decreasing somewhat, but nearly all diagnosed cases are fatal. The tumors are ductal adenocarcinomas and are not usually detected until the disease has spread. About 70% of tumors are in the pancreatic head, 20% in the body, and 10% in the tail. Mutations in *K-ras* have been found in 85% of tumors, and the p16 cyclin-dependent kinase inhibitor on chromosome 9 may also be implicated. Long-standing diabetes, chronic pancreatitis, and smoking increase the risk; coffee-drinking, alcoholism, and cholelithiasis do not. Pts present with pain and weight loss, the pain often relieved by bending forward. Jaundice commonly complicates tumors of the head, due to biliary obstruction. CA-19-9 can serve as a tumor marker in serum in some pts. Curative surgical resections are feasible in about 10%. Adjuvant chemotherapy (5FU) may benefit some pts after resection. Gemcitabine plus erlotinib or capecitabine may palliate symptoms in pts with advanced disease. Fit pts may obtain some benefit from the combination regimen, FOLFIRINOX, that includes 5FU, irinotecan, and oxaliplatin. FOLFIRINOX prolongs disease-free survival after complete resection.

ENDOCRINE TUMORS OF THE GI TRACT AND PANCREAS

■ CARCINOID TUMOR

Carcinoid tumor accounts for 75% of GI endocrine tumors; incidence is about 15 cases per million population. Ninety percent originate in Kulchitsky cells of the GI tract, most commonly the appendix, ileum, and rectum. Carcinoid tumors of the small bowel and bronchus have a more malignant course than tumors of other sites. About 5% of pts with carcinoid tumors develop symptoms of the carcinoid syndrome, the classic triad being cutaneous flushing, diarrhea, and valvular heart disease. For tumors of GI tract origin, symptoms imply metastases to liver.

Diagnosis can be made by detecting the site of tumor or documenting production of >15 mg/d of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the urine. Octreotide scintigraphy identifies sites of primary and metastatic tumor in about two-thirds of cases.

TREATMENT

Carcinoid Tumor

Surgical resection where feasible. Symptoms may be controlled with histamine blockers, serotonin receptor antagonists, and octreotide, 150–1500 mg/d in three doses or the sustained release formulation octreotide-LAN 10–30 mg IM monthly. Hepatic artery embolization and chemotherapy (5FU plus streptozocin or doxorubicin) have been used for metastatic disease. IFN- α at 3–10 million units SC

three times a week may relieve symptoms. Everolimus, an mTOR inhibitor, and sunitinib, a kinase inhibitor, have antitumor effects. Radiolabeled octreotide congeners are also effective. Prognosis ranges from 95% 5-year survival for localized disease to 20% 5-year survival for those with liver metastases. Median survival of pts with carcinoid syndrome is 2.5 years from the first episode of flushing.

■ PANCREATIC ISLET-CELL TUMORS

Gastrinoma, insulinoma, VIPoma, glucagonoma, and somatostatinoma account for the vast majority of pancreatic islet-cell tumors; their characteristics are shown in [Table 72-3](#). The tumors are named for the dominant hormone they produce. They are generally slow-growing and produce symptoms related to hormone production. *Gastrinomas* and *peptic ulcer disease* constitute the Zollinger-Ellison syndrome. Gastrinomas are rare (4 cases per 10 million population), and in 25–50%, the tumor is a component of a multiple endocrine neoplasia type 1 (MEN 1) syndrome.

Insulinoma may present with Whipple's triad: fasting hypoglycemia, symptoms of hypoglycemia, and relief after IV glucose. Normal or elevated serum insulin levels in the presence of fasting hypoglycemia are diagnostic. Insulinomas may also be associated with MEN 1.

TABLE 72-3 Gastrointestinal Endocrine Tumor Syndromes

SYNDROME	CELL TYPE	CLINICAL FEATURES	PERCENTAGE MALIGNANT	MAJOR PRODUCTS
Carcinoid syndrome	Enterochromaffin, enterochromaffin-like	Flushing, diarrhea, wheezing, hypotension	~100	Serotonin, histamine, miscellaneous peptides
Zollinger-Ellison, gastrinoma	Non- β islet cell, duodenal G cell	Peptic ulcers, diarrhea	~70	Gastrin
Insulinoma	Islet β cell	Hypoglycemia	~10	Insulin
VIPoma (Verner-Morrison, WDHA)	Islet D_1 cell	Diarrhea, hypokalemia, hypochlorhydria	~60	Vasoactive intestinal peptide
Glucagonoma	Islet A cell	Mild diabetes mellitus, erythema necrolytica migrans, glossitis	>75	Glucagon
Somatostatinoma	Islet D cell	Diabetes mellitus, diarrhea, steatorrhea, gallstones	~70	Somatostatin

Abbreviation: WDHA, watery diarrhea, hypokalemia, achlorhydria.

Verner and Morrison described a syndrome of watery diarrhea, hypokalemia, achlorhydria, and renal failure associated with pancreatic islet tumors that produce vasoactive intestinal polypeptide (VIP). *VIPomas* are rare (1 case per 10 million) but often grow to a large size before producing symptoms.

Glucagonoma is associated with diabetes mellitus and necrolytic migratory erythema, a characteristic red, raised, scaly rash usually located on the face, abdomen, perineum, and distal extremities. Glucagon levels >1000 ng/L not suppressed by glucose are diagnostic.

The classic triad of *somatostatinoma* is diabetes mellitus, steatorrhea, and cholelithiasis.

Provocative tests may facilitate diagnosis of functional endocrine tumors: tolbutamide enhances somatostatin secretion by somatostatinomas; pentagastrin enhances calcitonin secretion from medullary thyroid (C cell) tumors; secretin enhances gastrin secretion from gastrinomas. If imaging techniques fail to detect tumor masses, angiography or selective venous sampling for hormone determination may reveal the site of tumor. Metastases to nodes and liver should be sought by CT or MRI.

TREATMENT

Pancreatic Islet-Cell Tumors

Tumor is surgically removed, if possible. Everolimus 10 mg PO qd or sunitinib 37.5 mg PO qd may produce meaningful delay (~12 months) in progressive disease and prolong survival in pts with metastatic disease. Octreotide inhibits hormone secretion in the majority of cases. Radiolabeled octreotide agents have antitumor effects and can induce long-term stable disease. IFN- α may reduce symptoms. Streptozotocin plus doxorubicin combination chemotherapy may produce responses in 60–90% of cases. Embolization or chemoembolization of hepatic metastases may be palliative.

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Genitourinary Tract Cancer



BLADDER CANCER

■ INCIDENCE AND EPIDEMIOLOGY

Annual incidence in the United States is about 80,470 cases with 17,670 deaths. Median age is 65 years. Smoking accounts for 50% of the risk. Exposure to polycyclic aromatic hydrocarbons increases the risk, especially in slow acetylators. Risk is increased in chimney sweeps, dry cleaners, and those involved in aluminum manufacturing. Chronic cyclophosphamide exposure increases risk ninefold. *Schistosoma haematobium* infection also increases risk, especially of squamous histology.

■ ETIOLOGY

Lesions involving chromosome 9q are an early event. Deletions in 17p (p53), 18q (the DCC locus), 13q (RB), 3p, and 5q are characteristic of invasive lesions.

Overexpression of epidermal growth factor receptors and *HER2/neu* receptors is common.

■ PATHOLOGY

Over 90% of tumors are derived from transitional epithelium; 3% are squamous, 2% are adenocarcinomas, and <1% are neuroendocrine small cell tumors. Field effects are seen that place all sites lined by transitional epithelium at risk, including the renal pelvis, ureter, bladder, and proximal two-thirds of the urethra; 90% of tumors are in the bladder, 8% in the renal pelvis, and 2% in the ureter or urethra. Histologic grade influences survival. Lesion recurrence is influenced by size, number, and growth pattern of the primary tumor.

■ CLINICAL PRESENTATION

Hematuria is the initial sign in 80–90%; however, cystitis is a more common cause of hematuria (22% of all hematuria) than is bladder cancer (15%). Pts are initially staged and treated by endoscopy. Superficial tumors are removed at endoscopy; muscle invasion requires more extensive surgery.

TREATMENT

Bladder Cancer

Management is based on extent of disease: superficial, invasive, or metastatic. Frequency of presentation is 75% superficial, 20% invasive, and 5% metastatic. Superficial lesions are resected at endoscopy. Although complete resection is possible in 80%, 30–80% of cases recur; grade and stage progression occur in 30%. Intravesical instillation of bacille Calmette-Guérin (BCG) reduces the risk of recurrence by 40–45%. Recurrence is monitored every 3 months.

The standard management of muscle-invasive disease is radical cystectomy (see [Table 73-1](#)). Five-year survival is 70% for those without invasion of perivesicular fat or lymph nodes, 50% for those with invasion of fat but not lymph nodes, 35% for those with one node involved, and 10% for those with six or more

TABLE 73-1 Treatment Approaches to MIBC Pts

TREATMENT	PT SELECTION	CLINICAL OUTCOMES
Bladder-sparing chemoradiation	No CIS, no hydronephrosis, maximal TURBT required	65% cure, 55% bladder intact, highly dependent on pt selection
Bladder-sparing partial cystectomy	Solitary tumors in dome of bladder are ideal	Variable, highly dependent on pt selection
Cystectomy	Any MIBC pt	50% cure with surgery alone, highly dependent on pathologic stage
Neoadjuvant cisplatin-based chemotherapy	Cisplatin-eligible MIBC pts	5–10% improvement in overall survival compared to cystectomy alone
Adjuvant cisplatin-based chemotherapy	Cisplatin-eligible high-risk postcystectomy MIBC pts (pT3-4, N+)	Similar improvement as neoadjuvant treatment, data less robust, many pts not suitable for adjuvant treatment

Abbreviations: CIS, carcinoma in situ; MIBC, muscle-invasive bladder cancer; TURBT, transurethral resection of bladder tumor.

involved nodes. Pts who cannot withstand radical surgery may have 30–35% 5-year survival with 5000- to 7000-cGy external beam radiation therapy. Bladder sparing may be possible in up to 45% of pts with two cycles of chemotherapy with CMV (methotrexate, 30 mg/m² days 1 and 8, vinblastine, 4 mg/m² days 1 and 8, cisplatin, 100 mg/m² day 2, q21d) followed by 4000-cGy radiation therapy given concurrently with cisplatin.

Metastatic disease is treated with combination chemotherapy. Useful regimens include CMV (see earlier), M-VAC (methotrexate, 30 mg/m² days 1, 15, 22; vinblastine, 3 mg/m² days 2, 15, 22; doxorubicin, 30 mg/m² day 2; cisplatin, 70 mg/m² day 2; q28d) or cisplatin (70 mg/m² day 2) plus gemcitabine (1000 mg/m² days 1, 8, 15 of a 28-day cycle) or carboplatin plus paclitaxel. Immune checkpoint blockers, anti-PD1 and anti-PD-L1 antibodies, have activity as single agents and are being incorporated into combination regimens. About 70% of pts respond to treatment, and 20% have a complete response; 10–15% have long-term disease-free survival.

RENAL CANCER

■ INCIDENCE AND EPIDEMIOLOGY

Annual incidence in the United States is about 73,820 cases with 14,770 deaths. Cigarette smoking accounts for 20–30% of cases. Risk is increased in acquired renal cystic disease. *There are two familial forms:* a rare autosomal dominant syndrome and von Hippel–Lindau disease. About 35% of pts with von Hippel–Lindau disease develop renal cancer. Incidence is also increased in those with tuberous sclerosis and polycystic kidney disease.

■ ETIOLOGY

Most cases are sporadic; however, the most frequent chromosomal abnormality (occurs in 60%) is deletion or rearrangement of 3p21-26. The von Hippel–Lindau gene has been mapped to that region and appears to have ubiquitin ligase activities that influence regulation of speed of transcription and turnover of damaged proteins. It is unclear how lesions in the gene lead to cancer.

■ PATHOLOGY

Five variants are recognized: clear cell tumors (75%), papillary tumors (15%), chromophobic tumors (5%), oncocytic tumors (3%), and collecting duct tumors (2%). Clear cell tumors arise from cells of the proximal convoluted tubules. Papillary tumors tend to be bilateral and multifocal and often show trisomy 7 and/or trisomy 17. Chromophobic and eosinophilic tumors less frequently have chromosomal aberrations and follow a more indolent course.

■ CLINICAL PRESENTATION

The classic triad of hematuria, flank pain, and flank mass is seen in only 10–20% of pts; hematuria (40%), flank pain (40%), palpable mass (33%), and weight loss (33%) are the most common individual symptoms. Paraneoplastic syndromes of erythrocytosis (3%), hypercalcemia (5%), and nonmetastatic hepatic dysfunction (Stauffer's syndrome) (15%) may also occur. Workup should include IV pyelography, renal ultrasonography, CT of abdomen and pelvis, chest x-ray (CXR), urinalysis, and urine cytology. Stage I is disease restricted to the kidney, stage II is disease contained within Gerota's fascia, stage III is locally invasive disease involving nodes and/or inferior vena cava, stage IV is invasion of adjacent organs or metastatic sites. *Prognosis is related to stage:* 66% 5-year survival for I, 64% for II, 42% for III, and 11% for IV.

TREATMENT**Renal Cancer**

Radical nephrectomy is standard for stages I, II, and most stage III pts. Surgery may also be indicated in the setting of metastatic disease for intractable local symptoms (bleeding, pain). Response rates of 40–48% have been noted with a range of different single agents, sunitinib (50 mg/d 4 weeks out of 6), sorafenib (400 mg bid), and temsirolimus (25 mg IV weekly) and the related drug, everolimus (10 mg PO daily), the PD1 inhibitor, nivolumab and cabozantinib (60 mg PO daily), an inhibitor of MET, AXL, and the vascular endothelial growth factor receptor. Sunitinib and sorafenib are thought to be antiangiogenic through inhibition of kinases in tumor cells. Temsirolimus is an inhibitor of mTOR. Nivolumab allows activation of T cells that kill the tumor cells. Combinations of PD1 or PD-L1-directed checkpoint blockers plus axitinib, a VEGF inhibitor, appear both more frequent and durable than those obtained with sunitinib alone. About 10–15% of pts with advanced-stage disease may benefit from interleukin 2 and/or interferon α (IFN- α). Addition of bevacizumab to IFN- α improves the response rate. Some remissions are durable. Chemotherapy is of little or no benefit.

TESTICULAR CANCER**■ INCIDENCE AND EPIDEMIOLOGY**

Annual incidence is about 9560 cases with 410 deaths. Peak age incidence is 20–40. Occurs 4–5 times more frequently in white than black men. Cryptorchid testes are at increased risk. Early orchiopexy may protect against testis cancer. Risk is also increased in testicular feminization syndromes, and Klinefelter syndrome is associated with mediastinal germ cell tumor.

■ ETIOLOGY

The cause is unknown. Disease is associated with a characteristic cytogenetic defect, isochromosome 12p.

■ PATHOLOGY

Two main subtypes are noted: seminoma and nonseminoma. Each accounts for ~50% of cases. Seminoma has a more indolent natural history and is highly sensitive to radiation therapy. Four subtypes of nonseminoma are defined as embryonal carcinoma, teratoma, choriocarcinoma, and endodermal sinus (yolk sac) tumor.

■ CLINICAL PRESENTATION

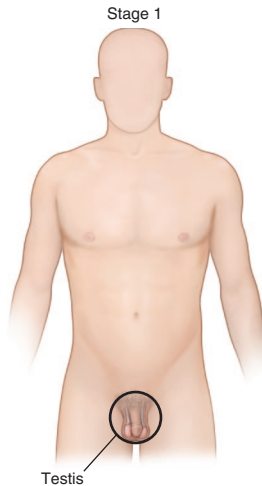
Painless testicular mass is the classic initial sign. In the presence of pain, differential diagnosis includes epididymitis or orchitis; a brief trial of antibiotics may be undertaken. Staging evaluation includes measurement of serum tumor markers α fetoprotein (AFP) and β -human chorionic gonadotropin (hCG), CXR, and CT scan of abdomen and pelvis. Lymph nodes are staged at resection of the primary tumor through an inguinal approach. Stage I disease is limited to the testis, epididymis, or spermatic cord; stage II involves retroperitoneal nodes; and stage III is disease outside the retroperitoneum. Among seminoma pts, 70% are stage I, 20% are stage II, and 10% are stage III. Among nonseminoma germ cell tumor pts, 33% are found in each stage. hCG may be elevated in either seminoma or nonseminoma, but AFP is elevated only in nonseminoma. Ninety-five percent

of pts are cured if treated appropriately. Primary nonseminoma in the mediastinum is associated with acute leukemia or other hematologic disorders and has a poorer prognosis than testicular primaries (~33%).

TREATMENT

Testicular Cancer (Figure 73-1)

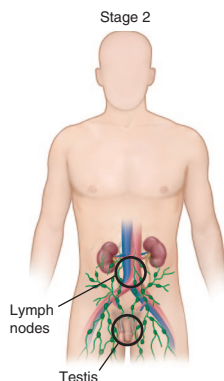
For stages I and II seminoma, inguinal orchiectomy followed by retroperitoneal radiation therapy to 2500–3000 cGy is effective. For stages I and II nonseminoma germ cell tumors, inguinal orchiectomy followed by retroperitoneal lymph node dissection is effective. For pts of either histology with bulky nodes or stage III disease, chemotherapy is given. Cisplatin (20 mg/m² days 1–5), etoposide (100 mg/m² days 1–5), and bleomycin (30 U days 2, 9, 16) given every 21 days for four cycles is the standard therapy. If tumor markers return to zero, residual masses are resected. Most are necrotic debris or teratomas. Salvage therapy rescues about 25% of those not cured with primary therapy.



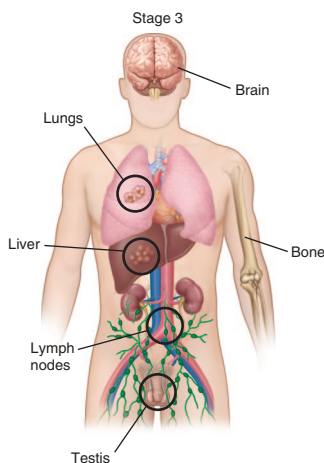
	Seminoma	NSGCT
Stage IA pT1: Testis only, no vascular/lymphatic invasion	Active surveillance; or, Adjuvant carboplatin x 1 cycle; or, Adjuvant para-aortic RT	Active surveillance; or, Nerve sparing RPLND
Stage IB pT2: Testis only, with vascular/lymphatic invasion or extension through tunica albuginea into tunica vaginalis	Active surveillance; or, Adjuvant carboplatin x 1 cycle; or, Adjuvant para-aortic RT	Adjuvant BEP x 1 cycle; or, Active surveillance; or, Nerve sparing RPLND
Stage IS Elevated serum tumor markers postorchiectomy	BEP x 3 cycles; or, EP x 4 cycles	BEP x 3 cycles; or, EP x 4 cycles

A

FIGURE 73-1 Stage-based treatment of testicular germ cell tumor.



	Seminoma	NSGCT
Stage IIA N1: nodes \leq 2 cm	Para-aortic and ipsilateral iliac RT; or, BEP x 3 cycles or EP x 4 cycles	Nerve-sparing RPLND; or, BEP x 3 cycles or EP x 4 cycles
Stage IIB N2: nodes > 2 to 5 cm	BEP x 3 cycles or EP x 4 cycles; or, Para-aortic and ipsilateral iliac RT	BEP x 3 cycles or EP x 4 cycles +/- post-chemotherapy RPLND
Stage IIC N3: nodes > 5 cm	BEP x 3 cycles or EP x 4 cycles	BEP x 3 cycles or EP x 4 cycles +/- post-chemotherapy RPLND

B

	Seminoma	NSGCT
Stage IIIA (good-risk)	BEP x 3 cycles; or, EP x 4 cycles	BEP x 3 cycles; or, EP x 4 cycles; +/- Post-chemotherapy surgery
Stage IIIB (intermediate-risk)	BEP x 4 cycles; or, VIP x 4 cycles	BEP x 4 cycles; or, VIP x 4 cycles +/- Post-chemotherapy surgery
Stage IIIC (poor-risk)	N/A	BEP x 4 cycles; or, VIP x 4 cycles +/- Post-chemotherapy surgery

Abbreviations: BEP, bleomycin, etoposide, cisplatin; EP, etoposide, cisplatin; NSGCT, non-seminomatous germ cell tumor; RPLND, retroperitoneal lymph node dissection; RT, radiation therapy; VIP, etoposide, ifosfamide, cisplatin.

C**FIGURE 73-1** (Continued)

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Gynecologic Cancer

**OVARIAN CANCER****INCIDENCE AND EPIDEMIOLOGY**

Annually in the United States, about 22,530 new cases are found and 13,980 women die of ovarian cancer. Incidence begins to rise in the fifth decade, peaking in the eighth decade. Risk is increased in nulliparous women and reduced by pregnancy (risk decreased about 10% per pregnancy) and oral contraceptives. About 5% of cases are familial.

GENETICS

Mutations in *BRCA-1* and *BRCA-2* predispose women to both breast and ovarian cancer. Cytogenetic analysis of epithelial ovarian cancers that are not familial often reveals complex karyotypic abnormalities, including structural lesions on chromosomes 1 and 11 and loss of heterozygosity for loci on chromosomes 3q, 6q, 11q, 13q, and 17. *C-myc*, *H-ras*, *K-ras*, and *HER2/neu* are often mutated or overexpressed. Unlike in colon cancer, a stepwise pathway to ovarian carcinoma is not apparent. Ovarian cancers may also occur in the setting of Lynch syndrome, inherited nonpolyposis colorectal cancer, due to mutations in the genes that repair DNA mismatches. The subset of women with endometrioid histology often have a mutation in *ARID1A*, a DNA repair complex component.

SCREENING

No benefit has been seen from screening women of average risk. Hereditary ovarian cancer accounts for 10% of all cases. Women with *BRCA-1* or *-2* mutations should consider prophylactic bilateral salpingo-oophorectomy by age 40.

CLINICAL PRESENTATION

Most pts present with abdominal pain, bloating, urinary symptoms, and weight gain indicative of disease spread beyond the true pelvis. Localized ovarian cancer is usually asymptomatic and detected on routine pelvic examination as a palpable nontender adnexal mass. Most ovarian masses detected incidentally in ovulating women are ovarian cysts that resolve over one to three menstrual cycles. Adnexal masses in postmenopausal women are more often pathologic and should be surgically removed. CA-125 serum levels are ≥ 35 U/mL in 80–85% of women with ovarian cancer, but other conditions may also cause elevations.

PATHOLOGY

Half of ovarian tumors are benign, one-third are malignant, and the rest are tumors of low malignant potential. These borderline lesions have cytologic features of malignancy but do not invade. Malignant epithelial tumors may be of five different types: serous (50%), mucinous (25%), endometrioid (15%), clear cell (5%), and Brenner tumors (1%, derived from urothelial or transitional epithelium). The remaining 4% of ovarian tumors are stromal or germ cell tumors, which are managed like testicular cancer in men ([Chap. 73](#)). Histologic grade is an important prognostic factor for the epithelial varieties.

STAGING

Extent of disease is ascertained by a surgical procedure that permits visual and manual inspection of all peritoneal surfaces and the diaphragm. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy, pelvic and paraaortic lymph node sampling, and peritoneal washings should be performed.

The staging system and its influence on survival are shown in [Table 74-1](#). About 23% of pts are stage I, 13% are stage II, 47% are stage III, and 16% are stage IV.

TREATMENT

Ovarian Cancer

Pts with stage I disease, no residual tumor after surgery, and well- or moderately differentiated tumors need no further treatment after surgery and have a 5-year survival of >95%. For stage II pts totally resected and stage I pts with poor histologic grade, adjuvant therapy with single-agent cisplatin or cisplatin plus paclitaxel produces 5-year survival of 80%. In the setting of bulky disease, maximal surgical cytoreduction is attempted. Those in whom no gross residual disease is left have a median survival of 39 months; those left with visible tumor, 17 months. Giving chemotherapy before definitive surgery (neoadjuvant) may increase the fraction of pts whose gross disease is resectable. Advanced-stage pts should receive paclitaxel, 175 mg/m² by 3-h infusion, followed by carboplatin dosed to an area under the curve (AUC) of 6 every 3 or 4 weeks. Carboplatin dose is calculated by the Calvert formula: dose = target AUC × (glomerular filtration rate + 25). Some data support intraperitoneal delivery of the chemotherapy and some data support the use of heated chemotherapy. The complete response rate is about 55%, and median survival is 38 months.

ENDOMETRIAL CANCER

■ INCIDENCE AND EPIDEMIOLOGY

The most common gynecologic cancer—61,180 cases are diagnosed in the United States and 12,160 pts die annually. It is primarily a disease of postmenopausal women. Obesity, altered menstrual cycles, infertility, late menopause, and postmenopausal bleeding are commonly encountered in women with endometrial cancer. Women taking tamoxifen to prevent breast cancer recurrence and those taking estrogen replacement therapy are at a modestly increased risk. Peak incidence is in the sixth and seventh decades.

■ CLINICAL PRESENTATION

Abnormal vaginal discharge (90%), abnormal vaginal bleeding (80%), and leukorrhea (10%) are the most common symptoms.

■ PATHOLOGY

Endometrial cancers are adenocarcinomas in 75–80% of cases. The remaining cases include mucinous carcinoma; papillary serous carcinoma; and secretory, ciliate, and clear cell varieties. Prognosis depends on stage, histologic grade, and degree of myometrial invasion.

■ STAGING

Total abdominal hysterectomy and bilateral salpingo-oophorectomy constitute both the staging procedure and the treatment of choice. The staging scheme and its influence on prognosis are shown in [Table 74-1](#). About 75% of pts are stage I, 13% are stage II, 9% are stage III, and 3% are stage IV.

TREATMENT

Endometrial Cancer

In women with poor histologic grade, deep myometrial invasion, or extensive involvement of the lower uterine segment or cervix, intracavitary or

TABLE 74-1 Staging and Survival in Gynecologic Malignancies

STAGE	OVARIAN	5-YEAR SURVIVAL, %	ENDOMETRIAL	5-YEAR SURVIVAL, %	CERVICAL	5-YEAR SURVIVAL, %
0	—		—		Carcinoma in situ	100
I	Confined to ovary	88–95	Confined to corpus	>90	Confined to uterus	85
II	Confined to pelvis	70–80	Involves corpus and cervix	~75	Invades beyond uterus but not pelvic wall	65
III	Intraabdominal spread	25–40	Extends outside the uterus but not outside the true pelvis	45–60	Extends to pelvic wall and/or lower third of vagina, or hydronephrosis	35
IV	Spread outside abdomen	17	Extends outside the true pelvis or involves the bladder or rectum	~20	Invades mucosa of bladder or rectum or extends beyond the true pelvis	7

external-beam radiation therapy is given. If cervical invasion is deep, preoperative radiation therapy may improve the resectability of the tumor. Stage III disease is managed with surgery and radiation therapy. Stage IV disease is usually treated palliatively. Progestational agents such as hydroxyprogesterone or megestrol and the antiestrogen tamoxifen may produce responses in 20% of pts. Doxorubicin, 60 mg/m² IV day 1, and cisplatin, 50 mg/m² IV day 1, every 3 weeks for 8 cycles produces a 45% response rate.

CERVICAL CANCER

■ INCIDENCE AND EPIDEMIOLOGY

In the United States, about 13,170 cases of invasive cervical cancer are diagnosed each year and 50,000 cases of carcinoma in situ are detected by Pap smear. Cervical cancer kills 4250 women a year, 85% of whom never had a Pap smear. It is a major cause of disease in underdeveloped countries and is more common in lower socioeconomic groups, in women with early sexual activity and/or multiple sexual partners, and in smokers. Human papilloma virus (HPV) types 16 and 18 are the major types associated with cervical cancer. The virus attacks the G₁ checkpoint of the cell cycle; its E7 protein binds and inactivates Rb protein, and E6 induces the degradation of p53. Risk factors include a large number of sexual partners, early age at first intercourse, a history of venereal disease, HIV infection, and heavy smoking.

■ SCREENING

Women should begin screening when they begin sexual activity or at age 20. After two consecutive negative annual Pap smears, the test should be repeated every 3 years. Abnormal smears dictate the need for a cervical biopsy, usually under colposcopy, with the cervix painted with 3% acetic acid, which shows abnormal areas as white patches. If there is evidence of carcinoma in situ, a cone biopsy is performed, which is therapeutic.

■ PREVENTION

Women, men, and children age 9–26 should obtain vaccination with Gardasil to prevent infection with two serotypes of virus (16 and 18) that cause 70% of the cervical cancer in the United States.

■ CLINICAL PRESENTATION

Pts present with abnormal bleeding or postcoital spotting or menometrorrhagia or intermenstrual bleeding. Vaginal discharge, low back pain, and urinary symptoms also may be present.

■ STAGING

Staging is clinical and consists of a pelvic examination under anesthesia with cystoscopy and proctoscopy. Chest x-ray, IV pyelography, and abdominal CT are used to search for metastases. The staging system and its influence on prognosis are shown in Table 74-1. At presentation, 47% of pts are stage I, 28% are stage II, 21% are stage III, and 4% are stage IV.

TREATMENT

Cervical Cancer

Carcinoma in situ is cured with cone biopsy. Stage I disease may be treated with radical hysterectomy or radiation therapy. Stages II–IV disease are usually treated with radiation therapy, often with both brachytherapy and teletherapy,

or combined-modality therapy. Pelvic exenteration is used uncommonly to control the disease, especially in the setting of centrally recurrent or persistent disease. Women with locally advanced (stage IIB–IVA) disease usually receive concurrent chemotherapy and radiation therapy. The chemotherapy acts as a radiosensitizer. Hydroxyurea, 5-fluorouracil (5FU), and cisplatin have all shown promising results given concurrently with radiation therapy. Cisplatin, 75 mg/m² IV over 4 h on day 1, and 5FU, 4 g given by 96-h infusion on days 1–5 of radiation therapy, is a common regimen. Relapse rates are reduced 30–50% by such therapy. Advanced-stage disease is treated palliatively with single agents (cisplatin, irinotecan, ifosfamide). Bevacizumab may improve the antitumor effects of chemotherapy. Potentially active agents include mTOR inhibitors (temsirolimus) and immune checkpoint inhibitors, especially in the subset of pts with tumors defective in DNA repair.

RARE GYNECOLOGIC TUMORS

Leiomyosarcomas may rarely occur within benign fibroid tumors. Chemotherapy with docetaxel/gemcitabine, ifosfamide/doxorubin, and trabectedin can have palliative effects. Gestational trophoblastic malignancy is curable with single agent (if localized; methotrexate or actinomycin D) or combination chemotherapy (if widely metastatic; EMA-CO, etoposide, methotrexate, and actinomycin D alternating with cyclophosphamide and vincristine).

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Tumors of the Nervous System



APPROACH TO THE PATIENT

Tumors of the Nervous System

Clinical Presentation Brain tumors can present with general and/or focal symptoms and signs. Nonspecific symptoms include headache with or without nausea and vomiting, cognitive difficulties, personality change, and gait disorder. The classic brain tumor headache predominates in the morning and improves during the day, but this pattern is seen only in a minority of pts. Papilledema may suggest elevated intracranial pressure. Focal symptoms and signs include hemiparesis, aphasia, or visual field deficit; these are typically subacute and progressive. Seizures are common, occurring in ~25% of pts with brain metastases or malignant glioma, and are the presenting symptom in up to 90% of pts with low-grade glioma.

Evaluation Primary brain tumors, unlike metastases, have no serologic features of malignancy such as an elevated ESR or tumor-specific antigens. Cranial MRI with contrast is the preferred diagnostic test for any pt suspected of having a brain tumor; CT should be reserved for pts unable to undergo MRI. Malignant brain tumors typically enhance with contrast and may have central areas of necrosis; they are characteristically surrounded by edema of the neighboring white matter. Low-grade gliomas typically do not enhance. Meningiomas have a typical appearance on MRI because they

are dural-based enhancing tumors with a dural tail that compress but do not invade the brain. Additional testing such as cerebral angiogram, EEG, or lumbar puncture is rarely indicated or helpful.

TREATMENT

Tumors of the Nervous System

SYMPTOMATIC TREATMENT

- Glucocorticoids (dexamethasone 8–16 mg/d PO or IV) to temporarily reduce edema
- Anticonvulsants (levetiracetam, topiramate, lamotrigine, valproic acid, or lacosamide) for pts who present with seizures ([Chap. 184](#)); there is no role for prophylactic anticonvulsant drugs
- Low-dose SC heparin for immobile pts

DEFINITIVE TREATMENT

- Based on the specific tumor types and includes surgery, radiotherapy (RT), and chemotherapy

■ PRIMARY INTRACRANIAL TUMORS

Astrocytomas Including Glioblastomas

Infiltrative tumors with a presumptive glial cell of origin. Most common primary intracranial neoplasm. Only known risk factors are ionizing radiation, uncommon hereditary syndromes (neurofibromatosis, tuberous sclerosis), and immunosuppression (primary CNS lymphoma). Infiltration along white matter pathways often prevents total resection. Imaging studies ([Fig. 75-1](#)) fail to indicate full tumor extent. Grade I tumors (pilocytic astrocytomas) are the most common tumor of childhood, typically in the cerebellum; can be cured if completely resected. Grade II astrocytomas usually present with seizures in young adults; if feasible should be surgically resected. In pts at higher risk for recurrence (subtotal resection or above the age of 40 years), radiation therapy (RT) followed by PCV (procarbazine, cyclohexylchloroethylnitrosourea [CCNU]), and vincristine) chemotherapy may possibly be of benefit. The tumor transforms to a malignant astrocytoma in most pts, leading to variable survival with a median of about 5–10 years. Grade III (anaplastic astrocytoma) and grade IV (glioblastoma) astrocytomas are treated similarly with maximal safe surgical resection followed by RT with concomitant temozolomide, followed by 6–12 months of adjuvant temozolomide. With this regimen, median survival is increased to 14.6–18 months compared to only 12 months with RT alone, and 5-year survival is approximately 10%. Despite optimal therapy, glioblastomas invariably recur. Treatment options for recurrent disease may include reoperation, carmustine wafers, and alternate chemotherapeutic regimens. Reirradiation is rarely helpful. Bevacizumab, a humanized vascular endothelial growth factor (VEGF) monoclonal antibody, increases progression-free survival but not overall survival.

Oligodendrogliomas

Generally more responsive to therapy and have a better prognosis than pure astrocytic tumors. Usually nonenhancing; often partially calcified. Treated with surgery and, in pts with residual disease or above the age of 40 years, RT and chemotherapy. Median survival in excess of 10 years.

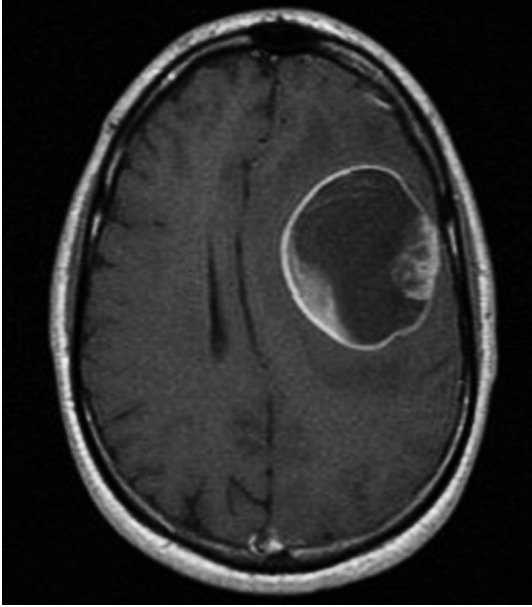


FIGURE 75-1 Postgadolinium T1 MRI of a large cystic left frontal glioblastoma.

Ependymomas

Derived from ependymal cells; highly cellular. Location—spinal canal more than intracranial in adults. If total excision possible, may be curable. Partially resected tumors will recur and require irradiation.

Primary CNS Lymphomas

B-cell malignancy; many occur in immunosuppressed pts (organ transplantation, HIV) and Epstein-Barr virus (EBV) plays an important role in this population. Incidence is increasing, particularly in immunocompetent, older individuals. May present as a single mass lesion (more common in immunocompetent pts) or as multiple mass lesions or meningeal disease. Ocular and leptomeningeal involvement each occur in 15–20% of pts. Dramatic, transient responses occur with glucocorticoids; therefore, whenever possible, glucocorticoids should be withheld until after biopsy obtained. Pts should be tested for HIV and extent of disease assessed by positron emission tomography (PET) or CT of the body, MRI of spine, CSF analysis, and slit-lamp examination of the eye. In immunocompetent pts, high-dose methotrexate produces median survival up to 50 months. Addition of cytarabine increases the response rate, and the anti-CD20 monoclonal antibody rituximab is often incorporated into the regimen. Whole-brain RT prolongs progression-free survival but not overall survival. In immunocompromised pts, prognosis is worse and treatment is with high-dose methotrexate-based regimens and, in HIV, antiretroviral therapy; whole-brain RT is reserved for pts who can't tolerate systemic chemotherapy.

Medulloblastomas

Most common malignant brain tumor of childhood. Half in posterior fossa; highly cellular; derived from neural precursor cells. Treatment with surgery, RT, and chemotherapy. Approximately 70% of pts have long-term survival, but usually at the cost of significant neurocognitive impairment.

Meningiomas

The most common primary brain tumor. Extra-axial mass attached to dura; dense and uniform contrast enhancement is diagnostic (Fig. 75-2). Total surgical resection of large, symptomatic benign meningiomas is curative. With subtotal resection, local RT reduces recurrence. Small, asymptomatic meningiomas may be followed radiologically without surgery. Treat rare aggressive meningiomas with excision and RT or stereotactic radiosurgery (SRS).

Schwannomas

Vestibular schwannomas present as progressive, unexplained unilateral hearing loss. MRI reveals dense, uniformly enhancing tumor at the cerebellopontine angle. Surgical excision may preserve hearing.

■ TUMORS METASTATIC TO THE NERVOUS SYSTEM

Hematogenous spread most common. Skull metastases rarely invade CNS; may compress adjacent brain or cranial nerves or obstruct intracranial venous sinuses. Primary tumors that commonly metastasize to the nervous system are listed in Table 75-1. Brain metastases are well demarcated by MRI and enhance in a ring pattern or diffusely. The radiographic appearance is nonspecific; similar-appearing lesions can occur with infection including brain abscesses, demyelinating lesions, sarcoidosis, radiation necrosis, or a primary brain tumor that is a second malignancy in a pt with systemic cancer. Biopsy rarely necessary for diagnosis because imaging alone in the appropriate clinical situation usually suffices. However, in approximately 10% of pts, a systemic cancer may present with brain metastases; in this situation biopsy of primary tumor or accessible brain metastasis is needed to plan treatment. Brain metastases are single in approximately

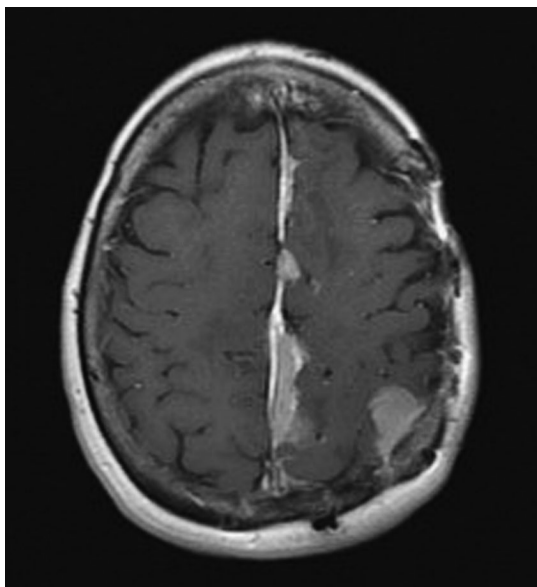


FIGURE 75-2 Postgadolinium T1 MRI demonstrating multiple meningiomas along the falx and left parietal cortex.

TABLE 75-1 Frequency of Nervous System Metastases by Common Primary Tumors

	BRAIN %	LM %	ESCC %
Lung	41	17	15
Breast	19	57	22
Melanoma	10	12	4
Prostate	1	1	10
GIT	7	—	5
Renal	3	2	7
Lymphoma	<1	10	10
Sarcoma	7	1	9
Other	11	—	18

Abbreviations: ESCC, epidural spinal cord compression; GIT, gastrointestinal tract; LM, leptomeningeal metastases.

one-half of pts and multiple in the other half. Treatment is with glucocorticoids, RT, or surgery. Standard treatment has previously been whole-brain RT; approximately 80% of pts improve with glucocorticoids and RT, but it is not curative, is associated with neurocognitive toxicity, and produces median survival of only 4–6 months. If feasible, SRS (gamma knife, linear accelerator, proton beam, or CyberKnife) has become the primary radiation oncology approach to brain metastases. It can sterilize visible lesions and produce local disease control in 80–90% of pts. SRS can effectively treat up to 10 lesions; it is, however, confined to lesions of ≤ 3 cm and is most effective in metastases of ≤ 1 cm.

Surgical excision of a single metastasis, or sometimes two lesions, followed by whole-brain RT is another option. Systemic chemotherapy may produce dramatic responses in highly chemosensitive tumor types such as germ cell tumors or small-cell lung cancer harboring specific epidermal growth factor receptor (EGFR) mutations that sensitize them to EGFR inhibitors. Immunotherapy can also be effective against primary tumors that are sensitive to this approach, such as melanoma.

Leptomeningeal Metastases

Also described as carcinomatous meningitis, meningeal carcinomatosis, or in the case of specific tumors, leukemic or lymphomatous meningitis. Presents as headache, encephalopathy, cranial nerve, or polyradicular symptoms. Diagnosis by CSF cytology, MRI (nodular meningeal tumor deposits or diffuse meningeal enhancement), or meningeal biopsy. Associated with hydrocephalus due to CSF pathway obstruction. Treatment is palliative, often with RT to the symptomatically involved areas, or chemotherapy (systemic or intrathecal).

Spinal Cord Compression from Metastases

(See [Chap. 22](#)). Expansion of vertebral body metastasis posteriorly into epidural space compresses spinal cord or cauda equina. Most common primary tumors are breast, lung, prostate, kidney, lymphoma, and myeloma. Back pain (>90%) precedes development of weakness, sensory level, or incontinence. Medical emergency; early recognition of impending spinal cord compression essential to avoid devastating sequelae. Diagnosis is by MRI; imaging of the entire spine important to identify additional clinically silent lesions. Demonstration of tumor cells in the CSF is definitive; however, CSF cytology is positive in only 50% of pts on the first lumbar puncture and still misses 10% after three CSF samples. New technologies, such as rare cell capture, enhance identification of tumor cells

in the CSF. Treatment is by surgical resection followed by RT. If surgery is not feasible, RT or SRS is the best option.

Complications of Radiation Therapy

Three patterns of radiation injury after CNS RT:

1. *Acute*: headache, sleepiness, nausea and vomiting, worse neurologic deficits during or immediately after RT. Rarely seen with current protocols. Can be both prevented and treated with glucocorticoids.
2. *Early delayed*: worsening or reappearance of a pre-existing neurologic deficit; within weeks to months of RT. Increased T2 signal and sometimes enhancement on MRI that can mimic tumor recurrence (“pseudoprogression”). Self-limited and improves with glucocorticoids; if very symptomatic may require resection. With spinal cord RT, Lhermitte sign with paraesthesias can occur; usually self-limited and benign.
3. *Late delayed*: dementia or other progressive neurologic deficits; typically months to years after RT. White matter abnormalities on MRI (leukoencephalopathy) or ring-enhancing mass (radiation necrosis). PET can distinguish delayed necrosis from tumor recurrence as can MR perfusion sequences. Progressive radiation necrosis is best treated palliatively with surgical resection unless it can be managed with glucocorticoids. Radiation injury of large arteries accelerates the development of atherosclerosis, increasing the risk of stroke years after RT. Endocrine dysfunction due to hypothalamus or pituitary gland injury can be due to delayed effects of RT. Development of a second neoplasm after RT also is a risk many years after exposure.

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Prostate Hyperplasia and Carcinoma



PROSTATE HYPERPLASIA

Enlargement of the prostate is nearly universal in aging men. Hyperplasia usually begins by age 45 years, occurs in the area of the prostate gland surrounding the urethra, and produces urinary outflow obstruction. Symptoms develop on average by age 65 in whites and 60 in blacks. Symptoms develop late because hypertrophy of the bladder detrusor compensates for ureteral compression. As obstruction progresses, urinary stream caliber and force diminish, hesitancy in stream initiation develops, and postvoid dribbling occurs. Dysuria and urgency are signs of bladder irritation (perhaps due to inflammation or tumor) and are usually not seen in prostate hyperplasia. As the postvoid residual increases, nocturia and overflow incontinence may develop. Common medications such as tranquilizing drugs and decongestants, infections, or alcohol may precipitate urinary retention. Because of the prevalence of hyperplasia, the relationship to neoplasia is unclear.

On digital rectal examination (DRE), a hyperplastic prostate is smooth, firm, and rubbery in consistency; the median groove may be lost. Prostate-specific antigen (PSA) levels may be elevated but are ≤ 10 ng/mL unless cancer is also present (see below). Cancer may also be present at lower levels of PSA.

TREATMENT**Prostate Hyperplasia**

Asymptomatic pts do not require treatment, and those with complications of urethral obstruction such as inability to urinate, renal failure, recurrent urinary tract infection, hematuria, or bladder stones clearly require surgical extirpation of the prostate, usually by transurethral resection (TURP). However, the approach to the remaining pts should be based on the degree of incapacity or discomfort from the disease and the likely side effects of any intervention. If the pt has only mild symptoms, watchful waiting is not harmful and permits an assessment of the rate of symptom progression. If therapy is desired by the pt, two medical approaches may be helpful: terazosin, an α_1 -adrenergic blocker (1 mg at bedtime, titrated to symptoms up to 20 mg/d), relaxes the smooth muscle of the bladder neck and increases urine flow; finasteride (5 mg/d) or dutasteride (2.5 mg/d), inhibitors of 5 α -reductase, block the conversion of testosterone to dihydrotestosterone and cause an average decrease in prostate size of ~24%. TURP has the greatest success rate but also the greatest risk of complications. Transurethral microwave thermotherapy (TUMT) may be comparably effective to TURP. Direct comparison has not been made between medical and surgical management.

PROSTATE CARCINOMA

In 2019, prostate cancer was diagnosed in 174,650 men in the United States—an incidence that is about 60% as high as breast cancer incidence. A decline in routine PSA testing has led to fewer cases. About 31,620 men died of prostate cancer in 2018. The early diagnosis of cancers in mildly symptomatic men found on screening to have elevated serum levels of PSA has complicated management. Like most other cancers, incidence is age-related. The disease is more common in blacks than whites. Symptoms are generally similar to and indistinguishable from those of prostate hyperplasia, but those with cancer more often have dysuria and back or hip pain. On histology, 95% are adenocarcinomas. Biologic behavior is affected by histologic grade (Gleason score).

In contrast to hyperplasia, prostate cancer generally originates in the periphery of the gland and may be detectable on DRE as one or more nodules on the posterior surface of the gland, hard in consistency and irregular in shape. Those with a negative DRE and PSA ≤ 4 ng/mL may be followed annually. Those with an abnormal DRE or a PSA >10 ng/mL should undergo transrectal ultrasound (TRUS)-guided biopsy or MRI-directed biopsy. Those with normal DRE and PSA of 4.1–10 ng/mL may be handled differently in different centers. Some would perform TRUS and biopsy any abnormality or follow if no abnormality were found. Some would repeat the PSA in a year and biopsy if the increase over that period were >0.75 ng/mL. Other methods of using PSA to distinguish early cancer from hyperplasia include quantitating bound and free PSA and relating the PSA to the size of the prostate (PSA density). Perhaps one-quarter of persons with prostate cancer do not have PSA elevations.

Lymphatic spread is assessed surgically; it is present in only 10% of those with Gleason grade 5 or lower and in 70% of those with grade 9 or 10. PSA level also correlates with spread; only 10% of those with PSA <10 ng/mL have lymphatic spread. Bone is the most common site of distant metastasis. Whitmore-Jewett staging includes A: tumor not palpable but detected at TURP; B: palpable tumor in one (B1) or both (B2) lobes; C: palpable tumor outside capsule; and D: metastatic disease.

TREATMENT**Prostate Carcinoma**

For pts with stages A through C disease, surgery (radical retropubic prostatectomy) and radiation therapy (conformal three-dimensional fields) are said to have similar outcomes; however, most pts are treated surgically. Both modalities are associated with impotence. Surgery is more likely to lead to incontinence. Radiation therapy is more likely to produce proctitis, perhaps with bleeding or stricture. Addition of hormonal therapy (goserelin) to radiation therapy of pts with localized disease appears to improve results. Pts usually must have a 5-year life expectancy to undergo radical prostatectomy. Stage A pts have survival identical to age-matched controls without cancer. Stage B and C pts have a 10-year survival of 82% and 42%, respectively.

Pts treated surgically for localized disease who develop rising PSA may undergo ProstaScint scanning (antibody to a prostate-specific membrane antigen). If no uptake is seen, the pt is observed. If uptake is seen in the prostate bed, local recurrence is implied and external beam radiation therapy is delivered to the site. (If the pt was initially treated with radiation therapy, this local recurrence may be treated with surgery.) However, in most cases, a rising PSA after local therapy indicates systemic disease. It is not clear when to intervene in such pts. Treatment is often initiated if the PSA doubling time is <10 months.

For pts with clinically apparent metastatic disease or rapidly rising PSA, androgen deprivation is the treatment of choice. Surgical castration is effective, but most pts prefer to take leuprolide, 7.5 mg depot form IM monthly (to inhibit pituitary gonadotropin production), plus flutamide, 250 mg PO tid (an androgen receptor blocker). The value of added flutamide is debated. Alternative approaches include adrenalectomy, hypophysectomy, estrogen administration, and medical adrenalectomy with aminoglutethimide. The median survival of stage D pts is 33 months. Pts occasionally respond to withdrawal of hormonal therapy with tumor shrinkage. Not all pts who develop disease progression on hormonal therapy are resistant to androgen deprivation. Second hormonal manipulations act by blocking androgen production in the tumor; abiraterone, a CYP17 inhibitor that blocks androgen synthesis and enzalutamide and apalutamide, structurally related antiandrogens, improve overall survival. Many pts who progress on hormonal therapy have androgen-independent tumors, often associated with genetic changes in the androgen receptor and new expression of *bcl-2*, which may contribute to chemotherapy resistance. Chemotherapy is used for palliation in prostate cancer. Mitoxantrone, estramustine, and taxanes, particularly docetaxel and cabazitaxel, appear to be active single agents, and combinations of drugs are being tested. Chemotherapy-treated pts are more likely to have pain relief than those receiving supportive care alone. Sipuleucel-T, an active specific immunotherapy, improves survival by about 4 months in hormone-refractory disease without producing any measurable change in the tumor. Bone pain from metastases may be palliated with strontium-89 or samarium-153. Bisphosphonates decrease the incidence of skeletal events.

■ PROSTATE CANCER PREVENTION

Finasteride and dutasteride have been shown to reduce the incidence of prostate cancer by 25%, but no effect on overall survival has been seen. In addition, the cancers that do occur appear to be shifted to higher Gleason grades, but the clinical course of disease does not seem to be altered.

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Cancer of Unknown Primary Site



Cancer of unknown primary site (CUPS) is defined as follows: biopsy-proven malignancy; primary site unapparent after history, physical examination, chest x-ray, abdominal and pelvic CT, complete blood count, chemistry survey, mammography (women), β -human chorionic gonadotropin (hCG) levels (men), α -fetoprotein (AFP) levels (men), and prostate-specific antigen (PSA) levels (men); and histologic evaluation not consistent with a primary tumor at the biopsy site. About 90% of CUPS tumors are adenocarcinomas (60% well or moderately-well differentiated; 30% poorly differentiated), 5% squamous cell, 2% neuroendocrine, and 3% undifferentiated malignancy. CUPS incidence is declining, probably because of better pathology diagnostic criteria; it accounts for about 3% of all cancers today, down from 10–15% 15 years ago. Most pts are age >60. The tumors are often aneuploid. Cell lines derived from such tumors frequently have abnormalities in chromosome 1.

■ CLINICAL PRESENTATION

Pts may present with fatigue, weight loss, pain, bleeding, abdominal swelling, subcutaneous masses, and lymphadenopathy. Once metastatic malignancy is confirmed, diagnostic efforts should be confined to evaluating the presence of potentially curable tumors, such as lymphoma, Hodgkin's disease, germ cell tumor, ovarian cancer, head and neck cancer, and primitive neuroectodermal tumor, or tumors for which therapy may be of significant palliative value such as breast cancer or prostate cancer. In general, efforts to evaluate the presence of these tumor types depend more on the pathologist than on expensive clinical diagnostic testing. Localizing symptoms, a history of carcinogen exposure, or a history of fulguration of skin lesion may direct some clinical testing; however, the careful light microscopic, ultrastructural, immunologic, karyotypic, and molecular biologic examination of adequate volumes of tumor tissue is the most important feature of the diagnostic workup in the absence of suspicious findings on history and physical examination. Immunohistochemical stains can be useful (Table 77-1).

Expression of cytokeratin subtypes may narrow the range of possible diagnoses (Fig. 77-1).

■ DIAGNOSIS

An approach to assessing unknown primary cancers with adenocarcinoma histology is shown in Fig. 77-2.

■ PROGNOSIS

Pts with squamous cell carcinoma have a median survival of 9 months; those with adenocarcinoma or unclassifiable tumors have a median survival of 4–6 months. Pts in whom a primary site is identified usually have a better prognosis. Limited sites of involvement and neuroendocrine histology are favorable prognostic factors. Pts without a primary diagnosis should be treated palliatively with radiation therapy to symptomatic lesions. All-purpose chemotherapy regimens rarely produce responses but always produce toxicity. Certain clinical features may permit individualized therapy.

SYNDROME OF UNRECOGNIZED EXTRAGONADAL GERM CELL CANCER

In pts <50 years with tumor involving midline structures, lung parenchyma, or lymph nodes and evidence of rapid tumor growth, germ cell tumor is a possible diagnosis. Serum tumor markers may or may not be elevated. Cisplatin, etoposide,

TABLE 77-1 Select Immunohistochemical Stains Useful in the Diagnosis of CUPS

LIKELY PRIMARY PROFILE	COMMONLY CONSIDERED IHC TO ASSIST IN DIFFERENTIAL DIAGNOSIS OF CUPS ^a
Breast	ER, GCDFP-15, mammaglobin, Her-2/neu, GATA3
Ovarian/mullerian	ER, WT1 gene, CK7, PAX8, PAX2
Lung adenocarcinoma	TTF-1; nuclear staining, napsin A, SP-A1
Germ cell	β-HCG, AFP, OCT3/4, CKIT, CD30 (embryonal), SALL4
Prostate	PSA, α-methylacyl CoA racemase/P504S (AMACR/P504S), P501S (prostein), and PSMA, NKX3-1
Intestinal	CK7, CK20, CDX-2, CEA
Neuroendocrine	Chromogranin, synaptophysin, CD56
Sarcoma	Desmin (desmoid tumors), factor VIII (angiosarcomas), CD31, smooth muscle actin (leiomyosarcoma), MyoD1 (rhabdomyosarcoma)
Renal	RCC, CD10, PAX8, CD10
Hepatocellular carcinoma	Hep Par-1, Arg-1, glypican-3
Melanoma	S100, SOX-10, vimentin, HMB-45, tyrosinase and melan-A
Urothelial	CK7, CK20, thrombomodulin, uroplakin III
Mesothelioma	Calretinin, WT1, D2-40, mesothelin
Lymphoma	LCA, CD3, CD4, CD5, CD20, CD45
SCC	p63, p40 (lung SCC), CK5/6

^aPatterns emerging from coexpression of stains are better than individual stains to suggest putative primary site. Even with optimization, no IHC panel is 100% sensitive or specific (e.g., ovarian mucinous carcinoma can exhibit positivity with intestinal markers).

Abbreviations: AFP, α fetoprotein; Arg-1, arginase-1; β-hCG, β-human chorionic gonadotropin; CEA, carcinoembryonic antigen; CUPS, cancer of unknown primary site; ER, estrogen receptor; GCDFP-15, gross cystic disease fibrous protein-15; IHC, immunohistochemistry; LCA, leukocyte common antigen; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SCC, squamous cell carcinoma; SP-A1, surfactant protein A precursor; TTF, thyroid transcription factor; WT, Wilms' tumor.

and bleomycin (**Chap. 73**) chemotherapy may induce complete responses in ≥25%, and ~15% may be cured. A trial of such therapy should probably also be undertaken in pts whose tumors have abnormalities in chromosome 12.

PERITONEAL CARCINOMATOSIS IN WOMEN

Women who present with pelvic mass or pain and an adenocarcinoma diffusely throughout the peritoneal cavity, but without a clear site of origin, have primary peritoneal papillary serous carcinoma. The presence of psammoma bodies in the tumor or elevated CA-125 levels may favor ovarian origin. Such pts should undergo debulking surgery followed by paclitaxel plus cisplatin or carboplatin combination chemotherapy (**Chap. 74**). About 20% of pts will respond, and 10% will survive at least 2 years.

CARCINOMA IN AN AXILLARY LYMPH NODE IN WOMEN

Such women should receive adjuvant breast cancer therapy appropriate for their menopausal status even in the absence of a breast mass on physical examination or mammography and undetermined or negative estrogen and progesterone receptors on the tumor (**Chap. 71**). Unless the ipsilateral breast is radiated, up to 50% of

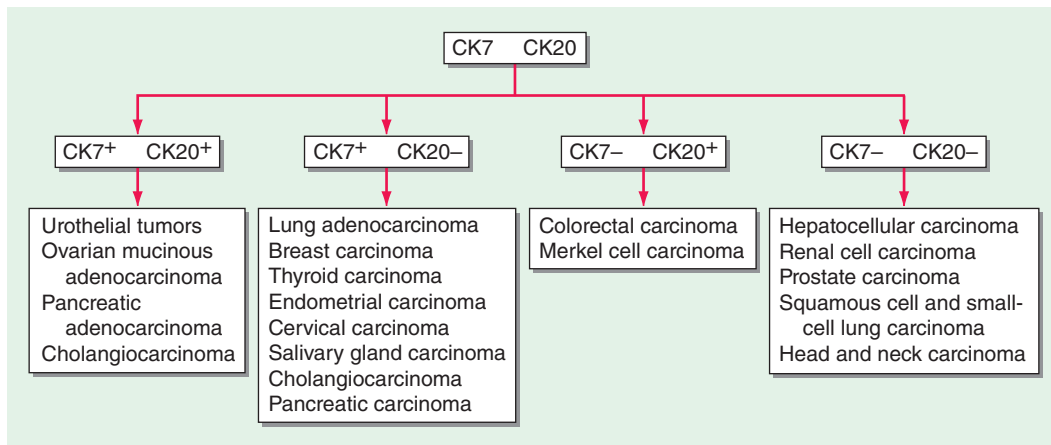


FIGURE 77-1 Approach to cytokeratin (CK7 and CK20) markers used in CUPS.

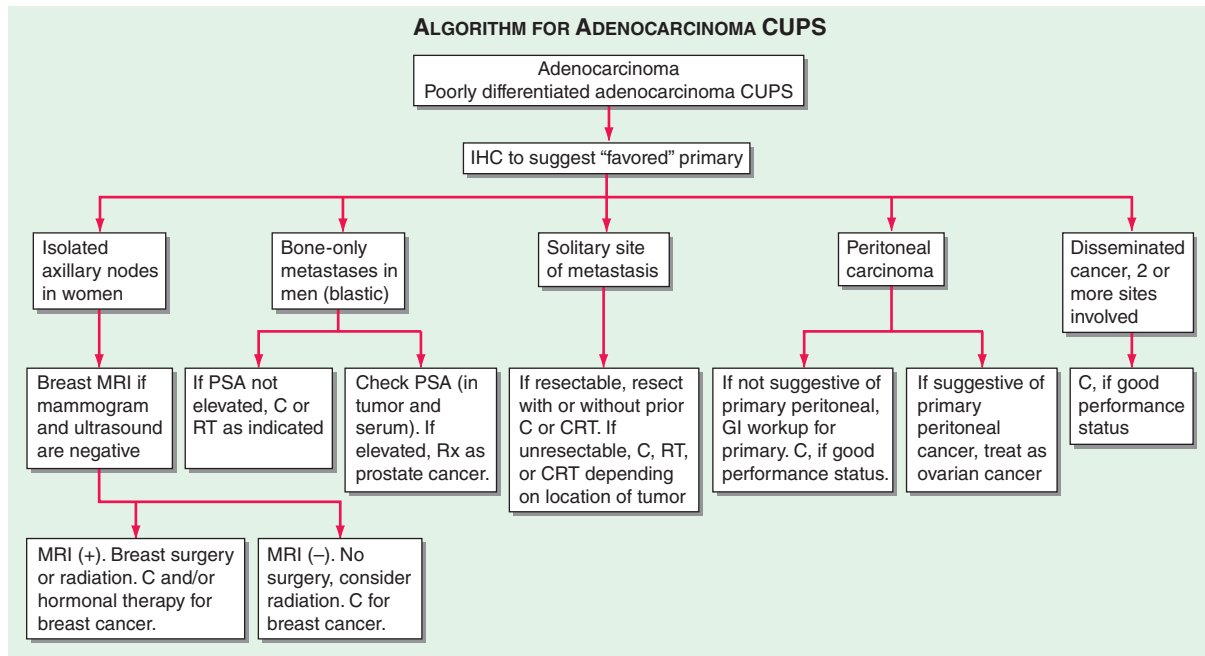


FIGURE 77-2 Algorithm for adenocarcinoma CUPS assessment. C, chemotherapy; CT, computed tomography; CUPS, cancer of unknown primary site; PET, positron emission tomography; RT, radiation therapy.

these pts will later develop a breast mass. Although this is a rare clinical situation, long-term survival similar to women with stage II breast cancer is possible.

OSTEOBLASTIC BONE METASTASES IN MEN

The probability of prostate cancer is high; a trial of empirical hormonal therapy (leuprolide and flutamide) is warranted ([Chap. 76](#)).

CERVICAL LYMPH NODE METASTASES

Even if panendoscopy fails to reveal a head and neck primary, treatment of such pts with cisplatin and 5-fluorouracil chemotherapy may produce a response; some responses are long-lived ([Chap. 69](#)).

78

Paraneoplastic Endocrine Syndromes



Both benign and malignant tumors of nonendocrine tissue can secrete a variety of hormones, principally peptide hormones, and many tumors produce more than one hormone ([Table 78-1](#)). At the clinical level, ectopic hormone production is important for two reasons.

First, endocrine syndromes that result may either be the presenting manifestations of the neoplasm or occur late in the course. The endocrine manifestations in some instances are of greater significance than the tumor itself, as in pts with benign or slowly growing malignancies that secrete corticotropin-releasing hormone and cause fulminant Cushing's syndrome. The frequency with which ectopic hormone production is recognized varies with the criteria used for diagnosis. The most common syndromes of clinical import are those of adrenocorticotrophic hormone (ACTH) hypersecretion, hypercalcemia, and hypoglycemia. Indeed, ectopic ACTH secretion is responsible for 15–20% of pts with Cushing's syndrome, and ~50% of pts with persistent hypercalcemia have a malignancy rather than hyperparathyroidism. Because of the rapidity of development of hormone secretion in some rapidly growing tumors, diagnosis may require a high index of suspicion, and hormone levels may be elevated out of proportion to the manifestations.

Second, ectopic hormones serve as valuable peripheral markers for neoplasia. Because of the broad spectrum of ectopic hormone secretion, screening measurements of plasma hormone levels for diagnostic purposes are not cost effective. However, in pts with malignancies that are known to secrete hormones, serial measurements of circulating hormone levels can serve as markers for completeness of tumor excision and for effectiveness of treatment. Likewise, tumor recurrence may be heralded by reappearance of elevated plasma hormone levels before mass effects of the tumor are evident. However, some tumors at recurrence do not secrete hormones, so hormone measurements cannot be relied on as the sole evidence of tumor activity.

TREATMENT

Paraneoplastic Endocrine Syndromes

Therapy of ectopic hormone-secreting tumors should be directed when possible toward removal of the tumor. When the tumor cannot be removed or is

TABLE 78-1 Paraneoplastic Syndromes Caused by Ectopic Hormone Production

PARANEOPLASTIC SYNDROME	ECTOPIC HORMONE	TYPICAL TUMOR TYPES ^a
Common		
Hypercalcemia of malignancy	PTHrP	Squamous cell (head and neck, lung, skin), breast, genitourinary, gastrointestinal
	1,25 dihydroxyvitamin D	Lymphomas
	PTH (rare)	Lung, ovary
	PGE ₂ (rare)	Renal, lung
SIADH	Vasopressin	Lung (squamous, small cell), gastrointestinal, genitourinary, ovary
Cushing's syndrome	ACTH	Lung (small cell, bronchial carcinoid, adenocarcinoma, squamous), thymus, pancreatic islet, medullary thyroid carcinoma
	CRH (rare)	Pancreatic islet, carcinoid, lung, prostate
	Ectopic expression of GIP, LH/hCG, other G protein-coupled receptors (rare)	Macronodular adrenal hyperplasia
Less Common		
Nonislet cell hypoglycemia	IGF-II	Mesenchymal tumors, sarcomas, adrenal, hepatic, gastrointestinal, kidney, prostate
	Insulin (rare)	Cervix (small cell carcinoma)
Male feminization	hCG ^b	Testis (embryonal, seminomas), germinomas, choriocarcinoma, lung, hepatic, pancreatic islet
Diarrhea or intestinal hypermotility	Calcitonin ^c	Lung, colon, breast, medullary thyroid carcinoma
	VIP	Pancreas, pheochromocytoma, esophagus
Rare		
Oncogenic osteomalacia	Phosphatonin (FGF23)	Hemangiopericytomas, osteoblastomas, fibromas, sarcomas, giant cell tumors, prostate, lung
Acromegaly	GHRH	Pancreatic islet, bronchial and other carcinoids
	GH	Lung, pancreatic islet
Hyperthyroidism	TSH	Hydatidiform mole, embryonal tumors, struma ovarii
Hypertension	Renin	Juxtaglomerular tumors, kidney, lung, pancreas, ovary

(Continued)

TABLE 78-1 Paraneoplastic Syndromes Caused by Ectopic Hormone Production (Continued)

PARANEOPLASTIC SYNDROME	ECTOPIC HORMONE	TYPICAL TUMOR TYPES ^a
Consumptive hypothyroidism	Type 3 deiodinase	Hepatic hemangiomas

^aOnly the most common tumor types are listed. For most ectopic hormone syndromes, an extensive list of tumors has been reported to produce one or more hormones.

^bhCG is produced eutopically by trophoblastic tumors. Certain tumors produce disproportionate amounts of the hCG α or hCG β subunit. High levels of hCG rarely cause hyperthyroidism because of weak binding to the TSH receptor.

^cCalcitonin is produced eutopically by medullary thyroid carcinoma and is used as a tumor marker.

Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; FGF23, fibroblast growth factor 23; GH, growth hormone; GHRH, growth hormone-releasing hormone; GIP, gastric inhibitory peptide; hCG, human chorionic gonadotropin; IGF, insulin-like growth factor; LH, luteinizing hormone; PGE₂, prostaglandin E₂; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TSH, thyroid-stimulating hormone; VIP, vasoactive intestinal peptide.

incurable, specific therapy can be directed toward inhibiting hormone secretion (octreotide for ectopic acromegaly or mitotane to inhibit adrenal steroidogenesis in the ectopic ACTH syndrome) or blocking the action of the hormone at the tissue level (demeclocycline for inappropriate vasopressin secretion).

■ HYPERCALCEMIA

The most common paraneoplastic syndrome, hypercalcemia of malignancy, accounts for 40% of all hypercalcemia. Of cancer pts with hypercalcemia, 80% have humoral hypercalcemia mediated by parathyroid hormone-related peptide; 20% have local osteolytic hypercalcemia mediated by cytokines such as interleukin 1 and tumor necrosis factor. Many tumor types may produce hypercalcemia (Table 78-1). Pts may have malaise, fatigue, confusion, anorexia, bone pain, polyuria, weakness, constipation, nausea, and vomiting. At high calcium levels, confusion, lethargy, coma, and death may ensue. Median survival of hypercalcemic cancer pts is 1–3 months. Treatment with saline hydration, furosemide diuresis, and pamidronate (60–90 mg IV) or zoledronate (4–8 mg IV) controls calcium levels within 2 days and suppresses calcium release for several weeks. Calcitonin (2–8 U/kg) may be useful if rapid action is needed. Oral bisphosphonates can be used for chronic treatment. In the setting of hematologic malignancies, hypercalcemia may respond to glucocorticoids.

■ HYPONATREMIA

Most commonly discovered in asymptomatic individuals as a result of serum electrolyte measurements, hyponatremia is usually due to tumor secretion of arginine vasopressin, a condition called *syndrome of inappropriate antidiuretic hormone secretion* (SIADH). Atrial natriuretic hormone also may produce hyponatremia. SIADH occurs most commonly in small cell lung cancer (15%) and head and neck cancer (3%). A number of drugs may produce the syndrome. Symptoms of fatigue, poor attention span, nausea, weakness, anorexia, and headache may be controlled by restricting fluid intake to 500 mL/d or blocking the effects of the hormone with 150- to 300-mg demeclocycline 3–4 times a day. Conivaptan, a vasopressin receptor blocker, is effective PO (20–120 mg bid) or IV (10–40 mg),

especially in combination with fluid restriction. Tolvaptan (15 mg/d) is also effective. With severe hyponatremia (<115 meq/L) or in the setting of mental status changes, normal saline infusion plus furosemide may be required; rate of correction should be <1 meq/L per hour to prevent complications like central pontine myelinolysis.

■ ECTOPIC ACTH SYNDROME

When pro-opiomelanocortin mRNA in the tumor is processed into ACTH, excessive secretion of glucocorticoids and mineralocorticoids may ensue. Pts develop Cushing's syndrome with hypokalemic alkalosis, weakness, hypertension, and hyperglycemia. About half the cases occur in small cell lung cancer. ACTH production adversely affects prognosis. Ketoconazole (300–600 mg bid) or metyrapone (250–500 mg qid) may be used to inhibit adrenal steroid synthesis.

79

Neurologic Paraneoplastic Syndromes



Paraneoplastic neurologic disorders (PNDs) are cancer-related syndromes that can affect any part of the nervous system; caused by mechanisms other than metastasis or by complications of cancer such as coagulopathy, stroke, metabolic and nutritional conditions, infections, and side effects of cancer therapy. In 60% of pts the neurologic symptoms precede cancer diagnosis. PNDs occur in 0.5–1% of all cancer pts, but they occur in 2–3% of pts with neuroblastoma or small cell lung cancer (SCLC), and in 30–50% of pts with thymoma or sclerotic myeloma.

■ CLINICAL FEATURES

Recognition of a distinctive paraneoplastic syndrome ([Table 79-1](#)) should prompt a search for cancer, because treatment of tumor may improve the course of PNDs; many of these disorders also occur without cancer. Diagnosis is based on the clinical pattern, exclusion of other cancer-related disorders, confirmatory serum or CSF antibodies, or occasionally electrodiagnostic testing. Most PNDs are mediated by immune responses triggered by neuronal proteins expressed by tumors. PNDs associated with immune responses against intracellular antigens often respond poorly to treatment ([Table 79-2](#)), whereas those associated with antibodies to synaptic or neuronal cell surface proteins are more responsive to immunotherapy ([Table 79-3](#)). For any type of PND, if antibody testing is negative, the diagnosis rests on the demonstration of cancer and the exclusion of other cancer-related or independent disorders. Combined whole-body CT and PET scans often uncover tumors undetected by other tests.

MRI and CSF studies are important to rule out neurologic complications due to direct spread of cancer. In most PNDs the MRI findings are nonspecific. CSF findings typically consist of mild to moderate pleocytosis (<200 mononuclear cells, predominantly lymphocytes), an increase in the protein concentration, and a variable presence of oligoclonal bands.

■ PARANEOPLASTIC ENCEPHALOMYELITIS AND FOCAL ENCEPHALITIS WITH ANTIBODIES AGAINST INTRACELLULAR NEURONAL PROTEINS (TABLE 79-2)

Encephalomyelitis describes an inflammatory process with multifocal involvement of the nervous system. Clinical manifestations depend on area involved, and syndromes may occur alone or in combination.

TABLE 79-1 Paraneoplastic Syndromes of the Nervous System

CLASSIC SYNDROMES: USUALLY OCCUR WITH CANCER ASSOCIATION	NONCLASSIC SYNDROMES: MAY OCCUR WITH AND WITHOUT CANCER ASSOCIATION
Encephalomyelitis Limbic encephalitis Cerebellar degeneration (adults) Opsoclonus-myoclonus Subacute sensory neuronopathy Gastrointestinal paresis or pseudo-obstruction Dermatomyositis (adults) Lambert-Eaton myasthenic syndrome Cancer- or melanoma-associated retinopathy	Brainstem encephalitis Stiff-person syndrome Progressive encephalomyelitis with rigidity and myoclonus Necrotizing myelopathy Motor neuron disease Guillain-Barré syndrome Subacute and chronic mixed sensory-motor neuropathies Neuropathy associated with plasma cell dyscrasias and lymphoma Vasculitis of nerve Pure autonomic neuropathy Acute necrotizing myopathy Polymyositis Optic neuropathy BDUMP Peripheral nerve hyperexcitability (neuromyotonia) Myasthenia gravis

Abbreviation: BDUMP, bilateral diffuse uveal melanocytic proliferation.

- *Cortical encephalitis*, which may present as “epilepsia partialis continua.”
- *Limbic encephalitis*, characterized by confusion, depression, agitation, anxiety, severe deficits in forming new memories, partial complex seizures, and sometimes dementia (the MRI usually shows unilateral or bilateral medial temporal lobe abnormalities).
- *Brainstem encephalitis* presents with eye movement disorders (nystagmus, opsoclonus, supranuclear or nuclear paresis), cranial nerve paresis, dysarthria, dysphagia, and central autonomic dysfunction.
- *Opsoclonus-myoclonus syndrome* consists of involuntary, chaotic eye movements in all directions of gaze plus myoclonus; it is frequently associated with ataxia.
- *Paraneoplastic cerebellar ataxia* begins as dizziness, oscillopsia, blurry or double vision, nausea, and vomiting; a few days or weeks later, dysarthria, gait and limb ataxia, and variable dysphagia can appear.
- *Myelitis*, which may cause lower or upper motor neuron symptoms, myoclonus, muscle rigidity, and spasms.
- *Autonomic dysfunction* occurs as a result of involvement of the neuraxis at multiple levels, including hypothalamus, brainstem, and autonomic nerves. Cardiac arrhythmias, postural hypotension, and central hypoventilation are frequent causes of death.
- *Cancer-associated retinopathies* involve cone and rod dysfunction with photosensitivity, progressive loss of vision and color perception, central or ring scotomas, night blindness, and attenuation of photopic and scotopic responses in the electroretinogram (ERG).

TABLE 79-2 Antibodies to Intracellular Antigens, Syndromes, and Associated Cancers

ANTIBODY	ASSOCIATED NEUROLOGIC SYNDROME(S)	TUMORS
Anti-Hu (ANNA1)	Encephalomyelitis, subacute sensory neuropathy	SCLC
Anti-Yo (PCA1)	Cerebellar degeneration	Ovary, breast
Anti-Ri (ANNA2)	Cerebellar degeneration, opsoclonus, brainstem encephalitis	Breast, gynecologic, SCLC
Anti-CRMP5 (CV2)	Encephalomyelitis, chorea, optic neuritis, uveitis, peripheral neuropathy	SCLC, thymoma, other
Anti-Ma proteins	Limbic, hypothalamic, brainstem encephalitis	Testicular (Ma2), other (Ma)
Anti-amphiphysin ^a	Stiff-person syndrome, encephalomyelitis	Breast, SCLC
Recoverin, bipolar cell antibodies, others ^b	Cancer-associated retinopathy (CAR) Melanoma-associated retinopathy (MAR)	SCLC (CAR), melanoma (MAR)
Anti-GAD	Stiff-person, cerebellar syndrome, limbic encephalitis	Infrequent tumor association (thymoma and several cancers)

^aAmphiphysin is likely exposed to the cell surface during synaptic vesicle endocytosis.

^bA variety of target antigens have been identified.

Abbreviations: CRMP, collapsing response-mediator protein; SCLC, small-cell lung cancer.

- *Dorsal root ganglionopathy* (sensory neuropathy) is characterized by sensory deficits that reflexes; all modalities of sensation can be involved.

TREATMENT

Encephalomyelitis and Focal Encephalitis

Most respond poorly to treatment. Stabilization of symptoms or partial neurologic improvement may occur, particularly if there is a satisfactory response of the tumor to treatment. Controlled trials of therapy are lacking; therapies aimed to remove antibodies against intracellular antigens, such as intravenous immunoglobulin (IVIg) or plasma exchange, usually fail. The main concern should be to treat the tumor and consider immunotherapies, such as cyclophosphamide or tacrolimus, aimed at controlling pathogenic cytotoxic T-cell responses.

■ ENCEPHALITIDES WITH ANTIBODIES TO CELL-SURFACE OR SYNAPTIC PROTEINS (TABLE 79-3)

These are a growing group of disorders that can occur with or without tumor association. An example is *N*-methyl-D-aspartate (NMDA) receptor autoantibodies that present as a virus-like syndrome followed by a prominent psychiatric

TABLE 79-3 Antibodies to Cell Surface or Synaptic Antigens, Syndromes, and Associated Tumors

ANTIBODY	NEUROLOGIC SYNDROME	TUMOR TYPE WHEN ASSOCIATED
Anti-AChR (muscle) ^a	Myasthenia gravis	Thymoma
Anti-AChR (neuronal) ^a	Autonomic ganglionopathy	SCLC
Anti-VGCC ^a	LEMS, cerebellar degeneration	SCLC
Anti-NMDAR ^a	Anti-NMDAR encephalitis	Teratoma in young women (children and men rarely have tumors)
Anti-LGI1 ^b	Limbic encephalitis, hyponatremia, faciobrachial tonic or dystonic seizures	Rarely thymoma
Anti-Caspr2 ^b	Morvan's syndrome, neuromyotonia, limbic encephalitis	Thymoma, prostate cancer
Anti-GABA _B R ^c	Limbic encephalitis, seizures	SCLC, neuroendocrine
Anti-GABA _A R ^a	Encephalitis with prominent seizures and status epilepticus; less often opsoclonus and stiff-person syndrome	Thymoma in ~30% of pts
Anti-AMPA ^a	Limbic encephalitis with relapses	SCLC, thymoma, breast
Glycine receptor	PERM, stiff-person syndrome	Rarely, thymoma, lung, Hodgkin lymphoma
Anti-DPPX ^a	Agitation, myoclonus, tremor, seizures, hyperekplexia, encephalomyelitis with rigidity	No cancer, but frequent diarrhea or cachexia suggesting paraneoplasia
Anti-Neurexin 3alpha	Autoimmune encephalitis without distinctive features	No cancer association
Anti-Dopamine-2R	Basal ganglia encephalitis	No cancer association
Anti-Tr (DNER)	Cerebellar syndrome	Hodgkin lymphoma, or no tumor
Anti-mGluR1	Cerebellar syndrome	Hodgkin lymphoma, or no tumor
Anti-mGluR5	Autoimmune encephalitis without distinctive features	Hodgkin lymphoma, or no tumor
IgLON5	NREM and REM sleep disorder, and brainstem dysfunction	No tumor association

^aA direct pathogenic role of these antibodies has been demonstrated in cultured neurons or animal models.

^bPreviously named voltage-gated potassium channel antibodies (VGKC); currently included under the term VGKC-complex proteins. Of note, the significance of antibodies to VGKC-complex proteins other than LGI1 and Caspr2 is uncertain (the antigens are unknown, and the response to immunotherapy is variable).

^cThis antibody is strongly suspected to be pathogenic.

Abbreviations: AChR, acetylcholine receptor; AMPAR, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Caspr2, contactin-associated protein-like 2; DNER, delta/notch-like epidermal growth factor-related receptor; DPPX, dipeptidyl-peptidase-like protein-6; GABA_BR, γ -aminobutyric acid B receptor; GAD, glutamic acid decarboxylase; mGluR, metabotropic glutamate receptor; LEMS, Lambert-Eaton myasthenic syndrome; LGI1, leucine-rich glioma-inactivated 1; NMDAR, N-methyl-D-aspartate receptor; NREM, non-rapid eye movement; PERM, progressive encephalomyelitis with rigidity and myoclonus; REM, rapid eye movement; SCLC, small-cell lung cancer; VGCC, voltage-gated calcium channel.

disturbance with involuntary movements; in young women, ovarian teratomas are frequently present. Relapses may occur. Despite dramatic severity at times, pts usually respond to treatment of the tumor (if found) and immunotherapy.

Encephalitis with leucine-rich glioma-inactivated 1 (LG1) antibodies predominates in pts aged >50 years and frequently presents with memory loss and seizures (limbic encephalopathy), with hyponatremia and sleep dysfunction. In some pts, the encephalitis is preceded by or occurs with myoclonic-like movements called faciobrachial dystonic seizures.

Encephalitis with contactin-associated protein-like 2 (Caspr2) antibodies predominates in pts aged >50 years and is associated with Morvan's syndrome (encephalitis, insomnia, confusion, hallucinations, autonomic dysfunction, and neuromyotonia), or a form of encephalitis with three or more of the following core symptoms: encephalopathy, cerebellar symptoms, peripheral nervous system hyperexcitability, dysautonomia, insomnia, neuropathic pain, or weight loss.

Encephalitis with γ -aminobutyric acid type B (GABA_B) receptor antibodies is usually associated with limbic encephalitis and seizures. In rare instances, pts develop cerebellar symptoms and opsoclonus.

Encephalitis with GABA_A receptor antibodies associates with prominent seizures and status epilepticus, often requiring pharmacologically induced coma.

Encephalitis with AMPA receptor antibodies affects middle-aged women, who develop acute limbic dysfunction or, less frequently, prominent psychiatric symptoms; 70% of the pts have an underlying tumor in the lung, breast, or thymus. Neurologic relapses may occur; not necessarily associated with tumor recurrence.

TREATMENT

Encephalitides with Antibodies to Cell-Surface or Synaptic Proteins

Most pts respond to immunotherapy and treatment of the tumor (if appropriate). Although there are no standardized treatment protocols, the most frequent approach employs progressive escalation of immunotherapy using first a combination of glucocorticoids, IVIg or plasma exchange, and if there is no response, either rituximab or cyclophosphamide.

PNDs of Nerve and Muscle

These disorders may develop anytime during the course of the neoplastic disease. Serum and urine immunofixation studies should be considered in pts with peripheral neuropathy of unknown cause; detection of a monoclonal gammopathy suggests the need for additional studies to uncover a B cell or plasma cell malignancy. If demyelinating features predominate (**Chap. 196**), IVIg, plasma exchange, or glucocorticoids may improve symptoms.

Myasthenia gravis is discussed in **Chap. 197** and dermatomyositis in **Chap. 198**.

80

Growing Threats in Infectious Disease



Infectious diseases remain the second leading cause of death worldwide. Despite numerous advances in the diagnosis, treatment, and prevention of infectious diseases, threats of antimicrobial resistance, and emerging/reemerging infectious diseases continue to pose challenges.

Antimicrobial Resistance

- Multidrug resistance has been increasing in prevalence in recent years and differs among different geographical regions and among institutions in the same area. The overall prevalence of antimicrobial resistance is affected by reservoirs in the pt population, use of antimicrobial drugs that favor resistant strains, and transmission of resistant strains to pts from their environment or other persons (e.g., health care workers with poor hand hygiene).
- The Centers for Disease Control and Prevention (CDC) has estimated that >2 million resistant bacterial infections occur in the United States each year, with 23,000 deaths, and has identified particular resistant pathogens that are of greatest concern, given their impact on public health (Table 80-1).
- Bacteria circumvent the activity of antibacterial agents by mechanisms that generally fall into three categories: (1) alteration or bypassing of targets that exhibit reduced binding of the drug, (2) altered access of the drug to its target by reductions in uptake or increases in active efflux, and (3) a modification of the drug that reduces its activity (Table 80-2).

TABLE 80-1 Antibiotic Resistance Threats in the United States, 2013

THREAT CATEGORY	ORGANISMS
Urgent	<i>Clostridium difficile</i> Carbapenem-resistant Enterobacteriaceae Drug-resistant <i>Neisseria gonorrhoeae</i>
Serious	Multidrug-resistant <i>Acinetobacter</i> Drug-resistant <i>Campylobacter</i> Extended-spectrum β -lactamase–producing Enterobacteriaceae Vancomycin-resistant <i>Enterococcus</i> Multidrug-resistant <i>Pseudomonas aeruginosa</i> Drug-resistant nontyphoidal <i>Salmonella</i> Drug-resistant <i>Salmonella typhi</i> Drug-resistant <i>Shigella</i> Methicillin-resistant <i>Staphylococcus aureus</i> Drug-resistant <i>Streptococcus pneumoniae</i> Drug-resistant <i>Mycobacterium tuberculosis</i>
Concerning	Vancomycin-resistant <i>S. aureus</i> Erythromycin-resistant group A <i>Streptococcus</i> Clindamycin-resistant group B <i>Streptococcus</i>

Source: U.S. Centers for Disease Control and Prevention.

TABLE 80-2 The Most Common Mechanisms of Resistance to Antibacterial Agents

ANTIBACTERIAL AGENT(S)	MAJOR TARGET	MECHANISM(S) OF ACTION	MECHANISM(S) OF RESISTANCE
β -Lactams (penicillins, cephalosporins, monobactams, carbapenems)	Cell wall synthesis	Bind cell-wall cross-linking enzymes (PBPs, transpeptidases)	<ol style="list-style-type: none"> 1. Drug inactivation by β-lactamases 2. Altered PBP targets 3. Reduced diffusion through porin channels
Glycopeptides and lipoglycopeptides (vancomycin, teicoplanin, telavancin, dalbavancin, oritavancin)	Cell wall synthesis	Block cell wall glycosyltransferases by binding D-Ala-D-Ala stem-peptide terminus Teicoplanin, telavancin, dalbavancin, and oritavancin: affect membrane function	<ol style="list-style-type: none"> 1. Altered D-Ala-D-Ala target (D-Ala-D-Lac) 2. Increased D-Ala-D-Ala target binding at sites distant from cell wall synthesis enzymes
Bacitracin	Cell wall synthesis	Blocks lipid carrier of cell wall precursors	Active drug efflux
Fosfomycin	Cell wall synthesis	Blocks linkage of stem peptide to NAG by enoyltransferase	<ol style="list-style-type: none"> 1. Target enzyme overexpression 2. Drug-modifying enzymes
Aminoglycosides (gentamicin, tobramycin, amikacin)	Protein synthesis	Bind 30S ribosomal subunit Block translocation of peptide chain Cause misreading of mRNA	<ol style="list-style-type: none"> 1. Drug-modifying enzymes 2. Methylation at ribosome binding site 3. Decreased permeation to target due to active efflux
Tetracyclines (tetracycline, doxycycline, minocycline)	Protein synthesis	Bind 30S ribosomal subunit Inhibit peptide elongation	<ol style="list-style-type: none"> 1. Active drug efflux 2. Ribosomal protection proteins
Tigecycline	Protein synthesis	Same as tetracyclines	Active drug efflux (pumps different from those affecting tetracyclines)
Macrolides (erythromycin, clarithromycin, azithromycin) and the ketolide telithromycin	Protein synthesis	Bind 50S ribosomal subunit Block peptide chain exit	<ol style="list-style-type: none"> 1. Methylation at ribosome binding site 2. Active drug efflux
Lincosamides (clindamycin)	Protein synthesis	Bind 50S ribosomal subunit Block peptide bond formation	Methylation at ribosome binding site
Streptogramins (quinupristin, dalfopristin)	Protein synthesis	Same as macrolides	<ol style="list-style-type: none"> 1. Same as macrolides 2. Drug-modifying enzymes

(Continued)

TABLE 80-2 The Most Common Mechanisms of Resistance to Antibacterial Agents (Continued)

ANTIBACTERIAL AGENT(S)	MAJOR TARGET	MECHANISM(S) OF ACTION	MECHANISM(S) OF RESISTANCE
Chloramphenicol	Protein synthesis	Binds 50S ribosomal subunit Blocks aminoacyl tRNA positioning	Drug-modifying enzymes
Oxazolidinones (linezolid, tedizolid)	Protein synthesis	Bind 50S ribosomal subunit Inhibit initiation of peptide synthesis	1. Altered rRNA binding site 2. Methylation of ribosome-binding site
Mupirocin	Protein synthesis	Blocks isoleucyl tRNA synthetase	1. Acquired resistant tRNA synthetase (drug bypass) 2. Altered native tRNA synthetase target
Sulfonamides (sulfadiazine, sulfisoxazole, and sulfamethoxazole)	Folate synthesis	Inhibit dihydropteroate synthetase	Acquired resistant dihydropteroate synthetase (drug bypass)
Trimethoprim	Folate synthesis	Inhibits dihydrofolate reductase	Acquired resistant dihydrofolate reductase (drug bypass)
Quinolones (norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gemifloxacin, delafloxacin)	DNA synthesis	Inhibit DNA gyrase and DNA topoisomerase IV Enzyme–DNA–drug complex: blocks DNA replication apparatus	1. Altered target(s) 2. Active efflux 3. Protection of target from drug 4. Drug-modifying enzyme (ciprofloxacin)
Rifamycins (rifampin, rifabutin, rifapentine)	RNA synthesis	Inhibit RNA polymerase	Altered target
Nitrofurantoin	Nucleic acid synthesis	Reduces reactive drug derivatives that damage DNA	Altered drug-activating enzymes
Metronidazole	Nucleic acid synthesis	Reduces reactive drug derivatives that damage DNA	1. Altered drug-activating enzyme 2. Acquired detoxifying enzymes 3. Active efflux
Polymyxins (polymyxin B and polymyxin E [colistin])	Cell membrane	Bind LPS and disrupt both outer and cytoplasmic membranes	Altered cell-membrane charge with reduced drug binding
Daptomycin	Cell membrane	Produces membrane channel and membrane leakage	Altered cell-membrane charge with reduced drug binding

Abbreviations: LPS, lipopolysaccharide; NAG, *N*-acetylglucosamine; PBP, penicillin-binding protein.

TABLE 80-3 Examples of Emerging and Reemerging Infectious Diseases

BACTERIAL AND RICKETTSIAL	VIRAL AND PRION	FUNGAL AND PARASITIC
Anaplasmosis	Chikungunya virus infection	Coccidioidomycosis
Anthrax	Variante Creutzfeldt-Jakob disease	<i>Cryptosporidium parvum</i> infection
Lyme disease	Dengue	<i>Cyclospora cayatanensis</i> infection
<i>Vibrio cholerae</i> O139 infection	Ebola virus, Marburg virus infection	Drug-resistant malaria
Diphtheria	Enterovirus D68 infection	
Ehrlichiosis	Hantavirus (Sin Nombre, Seoul) infection	
<i>Escherichia coli</i> O157:H7 infection	Hendra virus, Nipah virus infection	
<i>Escherichia coli</i> O154:H4 infection	Hepatitis C	
<i>Legionella pneumophila</i> infection	Hepatitis E	
Plague	HIV-1 and -2 infection	
Vancomycin-resistant <i>Staphylococcus aureus</i> infection	Human herpesvirus 6, 8 infection	
Tuberculosis	Human T-lymphotropic virus 1 and 2 infection	
	Influenza A H1N1pdm, H5N7, H7N7, H7N9	
	Lassa fever	
	Lyssavirus infection	
	Middle East respiratory syndrome (MERS)	
	Monkeypox	
	Rift Valley fever virus infection	
	Severe acute respiratory syndrome (SARS)	
	West Nile virus infection	
	Whitewater Arroyo virus infection	
	Yellow fever	
	Zika	

- The CDC has emphasized four actions to address the growing problem of antimicrobial resistance: (1) prevent infections, (2) track resistance patterns, (3) improve use of existing antimicrobial agents, and (4) develop new antimicrobial drugs and diagnostic tests.

Emerging/Reemerging Infectious Diseases

- Infectious diseases are considered to be emerging if the incidence in humans has increased within the past two decades or is anticipated to increase in the near future.

- Reemerging infectious diseases are those that were previously under control but have more recently increased—or are expected to increase—in incidence.
- Reasons for disease emergence or reemergence include human demographics and behavior, technology and industry, economic development and land use, international travel and commerce, microbial adaptation and change, and breakdown of public health measures.
- Examples of emerging and reemerging infectious diseases, as of 2017, are listed in [Table 80-3](#).

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Infections Acquired in Health Care Facilities



Hospital-acquired or *nosocomial* infections (defined as those not present or incubating at the time of admission to the hospital) and other health care–associated infections affect an estimated 1.7 million pts, cost \$10–33 billion, and contribute up to 99,000 deaths in U.S. hospitals each year. Although efforts to lower infection risks are challenged by the growing numbers of immunocompromised pts, antibiotic-resistant bacteria, fungal and viral superinfections, and invasive procedures and devices, the “zero-tolerance” viewpoint of consumer advocates holds that nearly all health care–associated infections should be avoidable. Accordingly, federal legislation now exists to prevent U.S. hospitals from upgrading Medicare charges to pay hospital costs resulting from at least 14 specific nosocomial events.

■ PREVENTION OF HOSPITAL-ACQUIRED INFECTIONS

Nosocomial pathogens have reservoirs, are transmitted by largely predictable routes, and require susceptible hosts—features that allow the implementation of monitoring and prevention strategies.

- *Surveillance*: Computerized algorithm-driven review of hospital databases is replacing manual review of microbiology laboratory results and surveys of nursing wards, but all these mechanisms keep track of infections acquired after hospital admission. Results of surveillance are expressed as rates and should include a denominator indicating the number of pts exposed to a specific risk (e.g., pts using a mechanical ventilator) or the number of intervention days (e.g., 1000 pt days on a ventilator).
- *Prevention and control measures*: Hand hygiene is the single most important measure to prevent cross-infection.
 - Health care workers’ rates of adherence to hand-hygiene recommendations are abysmally low at <50%.
 - Other measures include identifying and eradicating reservoirs of infection and minimizing use of invasive procedures and catheters.
- *Isolation techniques*: Isolation of infectious pts is a standard component of infection control programs.
 - Standard precautions include hand hygiene and use of gloves when there is a potential for contact with blood, other body fluids, nonintact skin, or mucous membranes during the care of all pts. In certain cases, masks, eye protection, and gowns are used as well.
 - Transmission-based guidelines: Airborne, droplet, and contact precautions—for which personnel don (at a minimum) N95 respirators, surgical

face masks, and gowns and gloves, respectively—are used to prevent transmission of disease from pts with contagious clinical syndromes. More than one precaution can be used for diseases that have more than one mode of transmission (e.g., contact and airborne isolation for varicella).

■ NOSOCOMIAL AND DEVICE-RELATED INFECTIONS

Nosocomial infections are due to the presence of invasive devices in 25–50% of cases. Intensive education, “bundling” of evidence-based interventions, use of checklists to facilitate adherence, and improvements in the design of these devices have reduced infection rates. [Table 81-1](#) summarizes effective interventions to reduce the incidence of the more common nosocomial infections.

- **Urinary tract infections:** UTIs represent ~14% of nosocomial infections and have an attributable cost of ~\$900.
 - Most nosocomial UTIs are associated with prior instrumentation or indwelling bladder catheterization. The 3–7% risk of infection for each day a catheter remains in place is due to the ascent of bacteria from the periurethral area or via intraluminal contamination of the catheter.
 - In men, condom catheters may lessen the risk of UTI.
 - The most common pathogens are *Escherichia coli*, nosocomial gram-negative bacilli, enterococci, and (particularly for pts in the ICU) *Candida*.
 - For suspected infection in the setting of chronic catheterization, the catheter should be replaced and a freshly voided urine specimen obtained for culture to confirm actual infection as opposed to simple colonization of the catheter.
 - As with all nosocomial infections, it is useful to repeat the culture to confirm the persistence of infection at the time therapy is initiated.
- **Pneumonia:** Accounting for 24% of nosocomial infections, pneumonia increases the duration of hospital stay by 12–14 days, accounts for ~\$40,000 in extra costs, and is associated with more deaths than are infections at any other body site. Of pts using mechanical ventilation, ~10% develop ventilator-associated events.
 - Risk factors include events that increase colonization with potential pathogens, such as prior antibiotic use, contaminated ventilator equipment, or decreased gastric acidity; events that increase risk of aspiration, such as nasogastric or endotracheal intubation or decreased level of consciousness; and conditions that compromise host defense mechanisms in the lung, such as chronic obstructive pulmonary disease, extremes of age, or upper abdominal surgery.
 - Etiologic organisms include community-acquired pathogens (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*) early during hospitalization and *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter*, and *Acinetobacter* later in the hospital stay.
 - Diagnosis can be difficult, as clinical criteria (e.g., fever, leukocytosis, purulent secretions, and new or changing pulmonary infiltrates on CXR) have high sensitivity but low specificity.
 - An etiology should be sought by studies of lower respiratory tract samples protected from upper-tract contamination; quantitative cultures have diagnostic sensitivities in the range of 80%.
 - Febrile pts with nasogastric or nasotracheal tubes should also have sinusitis or otitis media ruled out.
- **Surgical wound infections:** Making up ~24% of nosocomial infections, surgical wound infections increase the length of hospital stay by up to 11 days and increase costs by \$3000–\$29,000.

TABLE 81-1 Examples of Selected Components of Evidence-Based Bundled Interventions to Prevent Common Health Care–Associated Infections and Other Adverse Events^a

Prevention of Central Venous Catheter Infections

Catheter insertion bundle

- Educate personnel about catheter insertion and care.
- Use chlorhexidine to prepare the insertion site.
- Use maximal barrier precautions and asepsis during catheter insertion.
- Consolidate insertion supplies (e.g., in an insertion kit or cart).
- Use a checklist to enhance adherence to the insertion bundle.
- Empower nurses to halt insertion if asepsis is breached.

Catheter maintenance bundle

- Cleanse pts daily with chlorhexidine.
- Maintain clean, dry dressings.
- Enforce hand hygiene among health care workers.

Ask daily: Is the catheter needed? Remove catheter if not needed or used.

Prevention of Ventilator-Associated Events

- Avoid mechanical ventilation whenever possible.
- Elevate head of bed to 30–45°.
- Decontaminate oropharynx regularly with chlorhexidine (controversial).
- Give “sedation vacation” and assess readiness to extubate daily.
- Use deep-vein thrombosis prophylaxis (unless contraindicated).

Prevention of Surgical-Site Infections

- Choose a surgeon wisely.
- Administer prophylactic antibiotics within 1 h before surgery; discontinue within 24 h.
- Limit any hair removal to the time of surgery; use clippers or do not remove hair at all.
- Prepare surgical site with chlorhexidine-alcohol.

Prevention of Urinary Tract Infections

- Place bladder catheters only when absolutely needed (e.g., to relieve obstruction), not solely for the provider’s convenience.
- Use aseptic equipment and technique for catheter insertion and urinary tract instrumentation.
- Minimize manipulation or opening of drainage systems.
- Ask daily: Is the bladder catheter needed? Remove catheter if not needed.

Prevention of Pathogen Cross-Transmission

- Cleanse hands with alcohol hand rub before and after all contacts with pts or their environments.

^aSee text for additional interventions to prevent device- and procedure-associated infections; checklists and personnel education have been recommended as management tools for each of the prevention bundles.

Source: Adapted from information presented at the following websites: www.cdc.gov/hicpac/pubs.html; www.cdc.gov/HAI/index.html; www.ihl.org.

- These infections often become evident after pts have left the hospital; thus, it is difficult to assess the true incidence.
- Risk factors include the pt’s underlying conditions (e.g., diabetes mellitus or obesity) and age, inappropriate timing of antibiotic prophylaxis,

the presence of drains, prolonged preoperative hospital stays, shaving of the operative site the day before surgery (rather than just before the procedure), long duration of surgery, and infection at remote sites.

- These infections are typically caused by the pt's endogenous or hospital-acquired flora.
 - *S. aureus*, coagulase-negative staphylococci, and enteric and anaerobic bacteria are the most common pathogens.
 - A group A streptococcal or clostridial etiology should be considered in rapidly progressing postoperative infections (manifesting within 24–48 h of a procedure).
- Treatment of postoperative wound infections requires source control (drainage or surgical excision of infected or necrotic material) and use of antibiotics aimed at the most likely or laboratory-confirmed pathogens.
- **Intravascular device infections:** Intravascular device-related infections account for 10–15% of nosocomial infections, increase the duration of hospital stay by 7–15 days, add \$31,000–\$65,000 to hospital costs, and have an attributable mortality rate of 12–25%.
 - Catheterization of the femoral vessels is associated with a higher risk of infection in adults.
 - These infections are largely due to the skin flora at the site of catheter insertion, with pathogens migrating extraluminally to the catheter tip.
 - Contamination of the infusate is rare but can cause epidemic device-related bacteremias.
 - Coagulase-negative staphylococci, *S. aureus* ($\geq 50\%$ methicillin-resistant isolates), enterococci, nosocomial gram-negative bacilli, and *Candida* are the pathogens most frequently associated with these bacteremias.
 - Infection is suspected on the basis of the catheter site's appearance and/or the presence of fever or bacteremia without another source. The diagnosis is confirmed by isolation of the same bacteria from peripheral-blood cultures and from semiquantitative or quantitative cultures of samples from the vascular catheter tip.
 - In addition to the initiation of appropriate antibiotic treatment, considerations include the level of risk for endocarditis (relatively high in pts with *S. aureus* bacteremia) and the decision regarding catheter removal, which is often necessary to cure infection.
 - The decision to remove a surgically implanted catheter should be based on the severity of the pt's illness, the strength of evidence that the device is infected, the presence of local or systemic complications, an assessment of the specific pathogens, and the pt's response to antimicrobial therapy if the catheter is initially retained.
 - If salvage of the catheter is attempted, the "antibiotic lock" technique (allowing a concentrated antibiotic solution to dwell in the catheter lumen along with systemic antibiotic administration) should be used.

■ EPIDEMIC AND EMERGING PROBLEMS

Although outbreaks and emerging pathogens often receive a great deal of press, they account for <5% of nosocomial infections.

- **Influenza:** The main components of infection control—vaccination of the general public and health care workers, early use of antiviral agents for control of outbreaks, and adherence to surveillance and droplet precautions for symptomatic pts—have been effective in controlling influenza, including the 2009 H1N1 pandemic.

- *Nosocomial diarrhea*: Rates of health care–associated diarrhea have been increasing in recent years.
 - Rates of infection with *Clostridium difficile*—particularly the more virulent NAP1/BI/027 strain—are increasing, especially among older pts. Important infection-control components include judicious use of antibiotics (particularly fluoroquinolones); heightened suspicion in cases with atypical presentations; enhanced disinfection of isolation rooms; and early diagnosis, treatment, and implementation of contact precautions.
 - Outbreaks of norovirus infection should be suspected in bacterial culture–negative diarrheal syndromes in which nausea and vomiting are prominent aspects. Contact precautions may need to be augmented by environmental cleaning and active exclusion of ill staff and visitors, who often represent index cases.
- *Chickenpox*: Routine vaccination of children and VZV-susceptible employees has made nosocomial spread less common.
- *Tuberculosis*: Prompt recognition and isolation of cases, use of negative-pressure private rooms with 100% exhaust and at least 6–12 air changes per hour, use of approved N95 respirators, and follow-up serologic or skin testing of susceptible, exposed personnel are required.
- *Group A streptococcal infections*: One or two nosocomial cases, usually involving surgical wounds and the presence of an asymptomatic carrier in the operating room, should trigger an investigation. Health care workers linked to nosocomial transmission of group A streptococci should not be permitted to return to pt care settings until eradication of carriage via antimicrobial therapy has been documented.
- *Fungal infections*: Hospital renovations and disturbance of dusty surfaces can cause fungal spores to become airborne. Routine surveillance of neutropenic pts for infections with filamentous fungi (e.g., *Aspergillus*, *Fusarium*) helps determine whether there are extensive environmental risks. *Candida auris* is an emerging multidrug-resistant pathogen that causes invasive health care–associated infections.
- *Legionellosis*: If nosocomial cases are detected, environmental samples (e.g., tap water, water used in decorative fountains) should be cultured; eradication measures should be pursued if typing of clinical and environmental isolates reveals a correlation.
- *Antibiotic-resistant bacterial infection*: Close laboratory surveillance, strict infection-control practices, and aggressive antibiotic-control policies are the cornerstones of resistance-control efforts.
 - Molecular typing can help distinguish an outbreak of a single isolate (which necessitates an emphasis on hand hygiene and an evaluation of common-source exposures) from a polyclonal outbreak (which necessitates re-emphasis on antibiotic prudence and device bundles).
 - Organisms that raise concerns include methicillin-resistant *S. aureus*, gram-negative organisms that produce carbapenemases and/or extended-spectrum β -lactamases, pan-resistant strains of *Acinetobacter*, and vancomycin-resistant enterococci.
- *Bioterrorism preparedness*: Education, effective systems of internal and external communication, and risk assessment capabilities are key features.

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Infections in the
Immunocompromised Host

The immunocompromised pt is at increased risk for infection with both common and opportunistic pathogens.

INFECTIONS IN CANCER PTS

Table 82-1 lists the normal barriers to infection whose disruption may permit infections in immunocompromised pts, with particular relevance for the noted cancers. Infection-associated mortality rates among cancer pts have decreased as a result of an evolving approach entailing early use of empirical broad-spectrum antibiotics; empirical antifungal therapy in neutropenic pts who, after 4–7 days of antibiotic treatment, remain febrile without positive cultures; and use of antibiotics for afebrile neutropenic pts as broad-spectrum prophylaxis against infections.

■ SYSTEM-SPECIFIC SYNDROMES

- **Skin infections:** Skin lesions of various types are common in pts with cancer and may be the first sign of bacterial or fungal sepsis, particularly in neutropenic pts (those with <500 functional neutrophils/ μL).
 - *Cellulitis:* most often caused by group A *Streptococcus* and *Staphylococcus aureus*. Unusual organisms (e.g., *Escherichia coli*, *Pseudomonas*, fungi) may be involved in neutropenic pts.
 - *Macules or papules:* due to bacteria (e.g., *Pseudomonas aeruginosa* causing ecthyma gangrenosum) or fungi (e.g., *Candida*)
 - *Sweet's syndrome or febrile neutrophilic dermatosis:* Most often seen in neutropenic pts (particularly those with acute myeloid leukemia), it presents as red or bluish-red papules or nodules that form sharply bordered plaques; high fever; and an elevated ESR. The skin lesions are most common on the face, neck, and arms.
 - *Erythema multiforme with mucous membrane involvement:* Often due to HSV infection, it is distinct from Stevens-Johnson syndrome, which is associated with drugs and has a more widespread distribution. Both conditions are common in pts with cancer.
 - *Drug rashes:* Rashes associated with drugs, particularly cytokines used in cancer therapy, complicate the differential diagnosis of rashes in pts with cancer.
- **Catheter-related infections:** Exit-site infections, often with erythema around the insertion site, are most common.
 - Infections caused by coagulase-negative staphylococci can often be treated medically without catheter removal.
 - Infections caused by other organisms, including *S. aureus*, *P. aeruginosa*, *Candida*, *Stenotrophomonas*, and *Bacillus*, usually require catheter removal.
 - If a red streak develops over the SC part of a “tunneled” catheter, the device must be removed to prevent extensive cellulitis and tissue necrosis.
- **Upper GI infections:** Breakdown of mucosal surfaces due to chemotherapy and infection is common.
 - Oral mucositis is associated with viridans streptococci and HSV.
 - Oral candidal infections (thrush) are common.
 - Esophagitis can be caused by *Candida albicans* and HSV.

TABLE 82-1 Disruption of Normal Barriers in Pts with Cancer That May Predispose Them to Infections

TYPE OF DEFENSE	SPECIFIC LESION	CELLS INVOLVED	ORGANISM	CANCER ASSOCIATION	DISEASE
Physical barrier	Breaks in skin	Skin epithelial cells	Staphylococci, streptococci	Head and neck, squamous cell carcinoma	Cellulitis, extensive skin infection
Emptying of fluid collections	Occlusion of orifices: ureters, bile duct, colon	Luminal epithelial cells	Gram-negative bacilli	Renal, ovarian, biliary tree, metastatic diseases of many cancers	Rapid, overwhelming bacteremia; urinary tract infection
Lymphatic function	Node dissection	Lymph nodes	Staphylococci, streptococci	Breast cancer surgery	Cellulitis
Splenic clearance of microorganisms	Splenectomy	Splenic reticuloendothelial cells	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Neisseria meningitidis</i> , <i>Babesia</i> , <i>Capnocytophaga canimorsus</i>	Hodgkin's disease, leukemia	Rapid, overwhelming sepsis
Phagocytosis	Lack of granulocytes	Granulocytes (neutrophils)	Staphylococci, streptococci, enteric organisms, fungi	Acute myeloid and acute lymphocytic leukemias, hairy cell leukemia	Bacteremia
Humoral immunity	Lack of antibody	B cells	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>N. meningitidis</i>	Chronic lymphocytic leukemia, multiple myeloma	Infections with encapsulated organisms, sinusitis, pneumonia
Cellular immunity	Lack of T cells	T cells and macrophages	<i>Mycobacterium tuberculosis</i> , <i>Listeria</i> , herpesviruses, fungi, intracellular parasites	Hodgkin's disease, leukemia, T cell lymphoma	Infections with intracellular bacteria, fungi, parasites; virus reactivation

- **Lower GI infections:** Transmigration of bowel flora across the intestinal epithelium can lead to severe conditions.
 - *Chronic disseminated candidiasis:* results from seeding of organs (e.g., liver, spleen, kidneys) during neutropenia in pts with hematologic malignancy and generally presents symptomatically when neutropenia resolves. Pts have persistent fever unresponsive to antibiotics, abdominal pain, and increased alkaline phosphatase levels. Although biopsies may reveal granulomas, yeasts, or pseudohyphae, the diagnosis is often made on the basis of radiographic studies (CT, MRI). Treatment should be directed to the causative agent; *C. albicans* is usually responsible, but *Candida tropicalis* or other *Candida* species are sometimes involved.
 - *Typhlitis (necrotizing colitis):* more common among children than among adults and among pts with acute myeloid leukemia or acute lymphocytic leukemia than among pts with other forms of cancer. Pts have fever, RLQ tenderness, and diarrhea that is often bloody. The diagnosis is confirmed by documentation of a thickened cecal wall via imaging. Treatment should include antibiotics directed against bowel flora and surgery (in the case of perforation).
- **CNS infections:** The susceptibility of pts to specific infections depends on whether they have prolonged neutropenia, defects in cellular immunity (e.g., due to high-dose glucocorticoid therapy or cytotoxic chemotherapy), or defects in humoral immunity (e.g., pts with chronic lymphocytic leukemia, those who have previously undergone splenectomy or bone marrow transplantation [BMT]).
 - *Meningitis:* Consider *Cryptococcus* or *Listeria*, particularly for pts with defects in cellular immunity. Pts with defects in humoral immunity are also at risk for infection with encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*.
 - *Encephalitis:* Pts with defects in cellular immunity are particularly prone to infection with VZV, JC virus (the cause of progressive multifocal leukoencephalopathy), CMV, *Listeria*, HSV, and human herpesvirus type 6.
 - *Brain masses:* most often present as headache with or without fever or neurologic abnormalities. Pts with prolonged neutropenia are at increased risk for a brain abscess due to *Aspergillus*, *Nocardia*, or *Cryptococcus*. Pts with defects in cellular immunity are at increased risk for infection with *Toxoplasma* and EBV (lymphoproliferative disease). A definitive diagnosis may require a biopsy.
- **Pulmonary infections:** Pneumonia can be difficult to diagnose in immunocompromised pts, given that many of the conventional findings (e.g., purulent sputum, physical findings suggestive of chest consolidation) rely on the presence of neutrophils. Radiographic patterns of infiltration can help narrow the differential diagnosis.
 - *Localized infiltrate:* Consider bacterial pneumonia (including that due to *Legionella* and mycobacteria), local hemorrhage or embolism, and tumor.
 - *Nodular infiltrate:* Consider fungal infection (e.g., *Aspergillus*, *Mucor*), *Nocardia* infection, and recurrent tumor. In pts with *Aspergillus* infection, hemoptysis may be an ominous sign. A biopsy performed with direct visualization may be required for definitive diagnosis.
 - *Diffuse infiltrates:* Consider infection with viruses (particularly CMV), *Chlamydia*, *Pneumocystis*, *Toxoplasma*, or mycobacteria. Viruses that cause URIs in immunocompetent hosts (e.g., influenza, respiratory syncytial) can cause fatal pneumonitis in immunocompromised pts. Noninfectious causes include radiation pneumonitis, CHF, diffuse alveolar hemorrhage

(after BMT), and drug-induced lung injury (e.g., bleomycin, alkylating agents).

- **Renal and ureteral infections:** These infections are usually associated with obstructing tumor masses.
 - *Candida* has a predilection for the kidneys, reaching this site via either hematogenous seeding or retrograde spread from the bladder. Persistent funguria should prompt a search for infection in the kidney (e.g., fungus ball).
 - BK virus and adenovirus can cause hemorrhagic cystitis.

APPROACH TO THE PATIENT

Febrile Neutropenia

Figure 82-1 presents an algorithm for the diagnosis and treatment of pts with febrile neutropenia.

- The initial regimen should be refined on the basis of culture data; surface cultures of skin and mucous membranes may be misleading.
- Adding antibiotics to the initial regimen is not appropriate unless there is a clinical or microbiologic reason to do so. Administering additional antibiotics for fear of a gram-negative infection (e.g., “double coverage,”

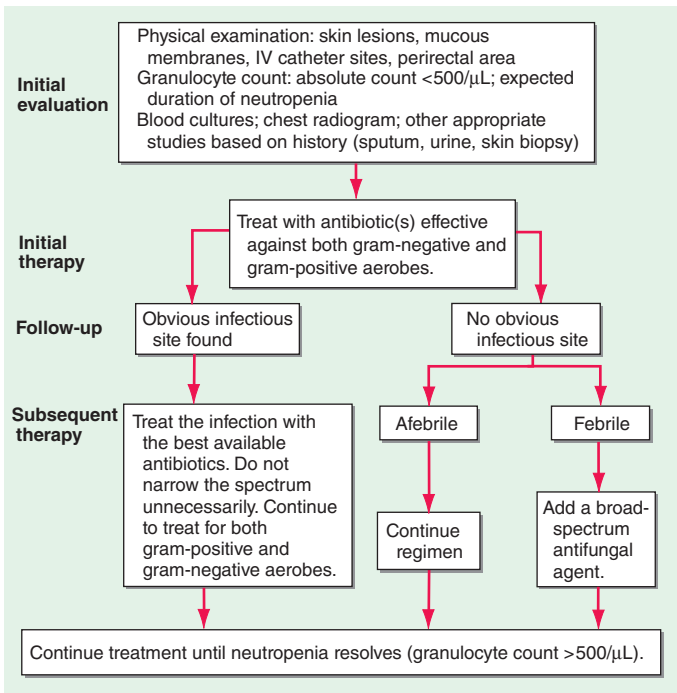


FIGURE 82-1 Algorithm for the diagnosis and treatment of fever and neutropenia.

synergistic addition of aminoglycosides to β -lactam therapy) does not enhance efficacy (but does increase toxicity), even for infections involving *P. aeruginosa*.

- For empirical antifungal treatment, amphotericin B deoxycholate is being supplanted by liposomal formulations of amphotericin B, newer azoles (e.g., voriconazole or posaconazole), and echinocandins (e.g., caspofungin). Echinocandins are useful against infections with azole-resistant *Candida*.
- Clinical experience related to antiviral therapy is most extensive with acyclovir for HSV and VZV infections. Newer agents (e.g., cidofovir, foscarnet) with a broader spectrum of action have heightened the focus on treatment of viral infections.
 - Prophylactic antibiotics (e.g., fluoroquinolones) in pts expected to have prolonged neutropenia or antifungal agents (e.g., fluconazole) in pts with hematopoietic stem cell transplants (see below) may prevent infections. *Pneumocystis* prophylaxis is mandatory for pts with acute lymphocytic leukemia and for those receiving glucocorticoid-containing regimens.

INFECTIONS IN TRANSPLANT RECIPIENTS

Evaluation of infections in transplant recipients must involve consideration of infectious agents harbored by the donor organ and the recipient's immunosuppressive drug regimen, which increases susceptibility to latent infections (among other infections).

- Pretransplantation evaluation of the donor should include a thorough serologic evaluation for viral pathogens (e.g., HSV-1, HSV-2, VZV, CMV, EBV, HIV, and hepatitis A, B, and C viruses) and mycobacterial disease; other evaluations should be directed by the donor's history, including diet, exposures, and travel.
- Pretransplantation evaluation of the recipient is generally more comprehensive than that of the donor and should include assessment for respiratory viruses and GI pathogens. Given the effects of underlying chronic disease and chemotherapy, serologic testing of the recipient may not be reliable.

■ HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

- **Pathogenesis:** The myeloablative processes involved in HSCT result in the complete absence of innate and adaptive immune cells. This transient state of complete immunologic incompetence and the reconstitution that follows make the host extremely susceptible to infections.
- **Etiology:** Most infections occur in a predictable time frame after HSCT (Table 82-2).
 - *Bacterial infections:* Neutropenia-related infectious complications are most common during the first month. Some centers give prophylactic antibiotics (e.g., quinolones) that may decrease the risk of gram-negative bacteremia but increase the risk of *Clostridium difficile* colitis.
 - Skin and bowel flora (e.g., *S. aureus*, coagulase-negative staphylococci, *E. coli*) are responsible for most infections in the first few days following HSCT, after which nosocomial pathogens and filamentous bacteria (e.g., vancomycin-resistant enterococci, *Acinetobacter*, antibiotic-resistant gram-negative bacteria, and *Nocardia* species) become more common.

TABLE 82-2 Common Sources of Infection after Hematopoietic Stem Cell Transplantation

INFECTION SITE	PERIOD AFTER TRANSPLANTATION		
	EARLY (<1 MONTH)	MIDDLE (1–4 MONTHS)	LATE (>6 MONTHS)
Disseminated	Aerobic bacteria (gram-negative, gram-positive)	<i>Candida</i> , <i>Aspergillus</i> , EBV	Encapsulated bacteria (<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Neisseria meningitidis</i>)
Skin and mucous membranes	HSV	HHV-6	VZV, HPV (warts)
Lungs	Aerobic bacteria (gram-negative, gram-positive), <i>Candida</i> , <i>Aspergillus</i> , other molds, HSV	CMV, seasonal respiratory viruses, <i>Pneumocystis</i> , <i>Toxoplasma</i>	<i>Pneumocystis</i> , <i>Nocardia</i> , <i>S. pneumoniae</i>
Gastrointestinal tract	<i>Clostridium difficile</i>	CMV, adenovirus	EBV, CMV
Kidney		BK virus, adenovirus	
Brain		HHV-6, <i>Toxoplasma</i>	<i>Toxoplasma</i> , JC virus (rare)
Bone marrow		CMV, HHV-6	CMV, HHV-6

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpesvirus type 6; HPV, human papillomavirus; HSV, herpes simplex virus; VZV, varicella-zoster virus.

- In the late post-transplantation period (>6 months after reconstitution), bacteremia due to encapsulated organisms is most common, particularly among pts who are asplenic or hypogammaglobulinemic.
- **Fungal infections:** Fungal infections are increasingly common beyond the first week after HSCT, particularly among pts who receive broad-spectrum antibiotics. Infections with *Candida* species are most common, although resistant fungi (e.g., *Aspergillus*, *Fusarium*) are becoming more common because of the increased use of prophylactic fluconazole.
 - Prolonged treatment with glucocorticoids or other immunosuppressive agents increases the risk of infection with *Candida* or *Aspergillus* and of reactivation of endemic fungi even after resolution of neutropenia.
 - Maintenance prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX; 160/800 mg/d starting after engraftment and continuing for at least 1 year) is recommended to prevent *Pneumocystis jirovecii* pneumonia.
- **Parasitic infections:** Prophylaxis with TMP-SMX is also protective against disease caused by *Toxoplasma* as well as against late infections caused by certain bacteria, including *Nocardia*, *Listeria monocytogenes*, *S. pneumoniae*, and *H. influenzae*.
 - Given increasing international travel, parasitic diseases (e.g., caused by *Strongyloides*, *Leishmania*, *Giardia*, *Cryptosporidium*) that are typically

restricted to particular environments may be more likely to be reactivated in pts after HSCT.

- *Viral infections*: Prophylactic acyclovir or valacyclovir for HSV-seropositive pts reduces rates of mucositis and prevents pneumonia and other HSV manifestations.
 - Zoster generally occurs several months after HSCT and usually is managed readily with acyclovir.
 - Human herpesvirus type 6 delays monocyte and platelet engraftment and may be linked to encephalitis or pneumonitis; the efficacy of antiviral treatment has not been well studied.
 - CMV disease (e.g., interstitial pneumonia, bone marrow suppression, colitis, and graft failure) usually occurs 30–90 days after HSCT. Severe disease is more common among allogeneic transplant recipients and is often associated with graft-versus-host disease, with pneumonia as the foremost cause of death. Preemptive therapy (initiation of antiviral therapy only after CMV is detected in blood) has supplanted prophylactic therapy (treatment of all transplant recipients when either the recipient or the donor is seropositive) because of the toxic side effects associated with ganciclovir.
 - EBV lymphoproliferative disease as well as infections caused by respiratory viruses (e.g., respiratory syncytial virus, parainfluenza virus, metapneumovirus, influenza virus, adenovirus) can occur. BK virus (a polyomavirus) has been found in the urine of pts after HSCT and may be associated with hemorrhagic cystitis.

■ SOLID ORGAN TRANSPLANTATION (SOT)

- **Pathogenesis**: After SOT, pts do not go through a stage of neutropenia like that seen after HSCT; thus the infections in these two groups of pts differ. However, solid organ transplant recipients are immunosuppressed for longer periods with agents that chronically impair T-cell immunity. Moreover, the persistent HLA mismatch between recipient immune cells (e.g., effector T cells) and the donor organ (allograft) places the organ at permanently increased risk of infection.
- **Etiology**: As in HSCT, the infection risk in SOT depends on the interval since transplantation.
 - *Early infections (<1 month)*: Infections are most commonly caused by extracellular organisms, which originate in surgical wound or anastomotic sites.
 - *Middle-period infections (1–6 months)*: The consequences of suppressing cell-mediated immunity become apparent, and infections result from acquisition—or reactivation—of viruses, mycobacteria, endemic fungi, and parasites.
 - CMV can cause severe systemic disease or infection of transplanted organs; the latter increases the risk of organ rejection, prompting increased immunosuppression that, in turn, increases CMV replication.
 - Diagnosis, treatment, and prophylaxis of CMV infection are the keys to interrupting this cycle.
 - *Late infections (>6 months)*: Infections in this period are similar to those in pts with chronically impaired T-cell immunity (e.g., *Listeria*, *Nocardia*, *Rhodococcus*, mycobacteria, various fungi, other intracellular organisms).
 - EBV lymphoproliferative disease occurs most commonly in pts who receive a heart or lung transplant (as well as the most intense immunosuppressive regimens); in these cases, immunosuppression should

- be decreased or discontinued, if possible, and consideration should be given to treatment with anti-B cell antibodies.
- Prophylaxis against *Pneumocystis* pneumonia for at least 1 year is generally recommended for all solid organ transplant recipients.
 - The incidence of tuberculosis within the first 12 months after SOT is greater than that after HSCT and reflects the prevalence of tuberculosis in the local population.
 - **Specific issues:** While the information given earlier is generally valid for all organ transplants, there are some organ-specific considerations.
 - *Kidney transplantation:* TMP-SMX prophylaxis for the first 4–6 months decreases the incidence of early and middle-period infections, particularly UTIs related to anatomic alterations resulting from surgery. CMV is the predominant pathogen in the middle period; disease is evident in 50% of renal transplant pts presenting with fever 1–4 months after transplantation, prompting many centers to use valganciclovir prophylaxis for high-risk pts. BK viruria and viremia, often diagnosed as a late-onset disease, are associated with ureteral strictures, nephropathy, and vasculopathy and require a reduction of immunosuppression to lower rates of graft loss.
 - *Heart transplantation:* Mediastinitis, generally caused by typical skin flora and rarely caused by *Mycoplasma hominis*, is an early complication of heart transplantation. The overall incidence of toxoplasmosis (a middle-period infection) is so high in the setting of heart transplantation that serologic screening and some prophylaxis (e.g., with TMP-SMX) are always warranted.
 - *Lung transplantation:* Pts receiving a lung transplant are predisposed to pneumonia and mediastinitis in the early period. The high incidence of CMV disease (75–100% if either the donor or the recipient is seropositive) indicates the importance of antiviral prophylaxis; late disease may occur once prophylaxis is discontinued, although the pt is generally better able to handle it because of reduced immunosuppression.
 - *Liver transplantation:* Bacterial abscesses and peritonitis are common early complications and often result from biliary leaks. Pts receiving a liver transplant have a high incidence of fungal infections correlated with preoperative glucocorticoid use, long-term antimicrobial use, and a high degree of immunosuppression. Recurrent (reactivated) hepatitis B and C infections are problematic. Administration of hepatitis B immunoglobulin and prophylaxis with antiviral agents active against hepatitis B virus has been successful in preventing reinfection with hepatitis B virus. Reinfection with hepatitis C virus occurs in all untreated pts, but direct-acting antivirals are now effective in both treating hepatitis C infections before transplantation and preventing reinfection of the graft after transplantation.

IMMUNIZATIONS IN IMMUNOSUPPRESSED PTS

Recommendations for vaccination of cancer pts receiving chemotherapy, pts with Hodgkin's disease, and hematopoietic stem cell transplant recipients are listed in [Table 82-3](#). In solid organ transplant recipients, the usual vaccines and boosters should be given before immunosuppression. Pts with continued immunosuppression should have pneumococcal vaccination repeated every 5 years and should generally not receive live vaccines.

TABLE 82-3 Vaccination of Cancer and Transplant Pts Receiving Chemotherapy^a

VACCINE	USE IN INDICATED PTS			
	INTENSIVE CHEMOTHERAPY	HODGKIN'S DISEASE	HEMATOPOIETIC STEM CELL TRANSPLANTATION	SOLID ORGAN TRANSPLANTATION
Diphtheria-tetanus ^b	Primary series and boosters as necessary	No special recommendation	Three doses given 6–12 months after transplantation	Administer TDaP before transplantation.
Poliomyelitis ^c	Complete primary series and boosters	No special recommendation	Three doses given 6–12 months after transplantation	Administer before transplantation.
<i>Haemophilus influenzae</i> type b conjugate	Primary series and booster for children	Single dose for adults	Three doses given 6–12 months after transplantation (separated by 1 month)	Administer before transplantation.
Human papillomavirus ^d	A 9-valent vaccine is approved for males and females 9–45 years of age.	A 9-valent vaccine is approved for males and females 9–45 years of age.	A 9-valent vaccine is approved for males and females 9–45 years of age.	A 9-valent vaccine is approved for males and females 9–45 years of age.
Hepatitis A	As indicated for normal hosts on the basis of occupation and lifestyle	As indicated for normal hosts on the basis of occupation and lifestyle	As indicated for normal hosts on the basis of occupation and lifestyle	Administer before transplantation.
Hepatitis B	Same as for normal hosts	As indicated for normal hosts on the basis of occupation and lifestyle	Three doses given 6–12 months after transplantation	Administer before transplantation.

Pneumococcal conjugate, pneumococcal polysaccharide ^e	Finish series prior to chemotherapy if possible	Pts with splenectomy should receive PPSV23.	Three doses of PCV13, beginning 3–6 months after transplantation, are followed by a dose of PPSV23 at least 8 weeks later. A second PPSV23 dose can be given 5 years later.	Administer in 2 steps. ^f
Quadrivalent meningococcal vaccine ^g	Should be administered to splenectomized pts and to pts living in endemic areas, including college students in dormitories	Should be administered to splenectomized pts and to pts living in endemic areas, including college students in dormitories. An additional dose can be given after 5 years.	Should be administered to splenectomized pts and to pts living in endemic areas, including college students in dormitories. An additional dose can be given after 5 years.	Administer before transplantation.
Influenza	Seasonal immunization	Seasonal immunization	Seasonal immunization (A seasonal dose is recommended and can be given as early as 4 months after transplantation; if given <6 months after transplantation, an additional dose is recommended.)	Seasonal immunization
Measles/mumps/rubella	Contraindicated	Contraindicated during chemotherapy	After 24 months in pts without graft-versus-host disease	Administer before transplantation.

(Continued)

TABLE 82-3 Vaccination of Cancer and Transplant Pts Receiving Chemotherapy^a (Continued)

VACCINE	USE IN INDICATED PTS			
	INTENSIVE CHEMOTHERAPY	HODGKIN'S DISEASE	HEMATOPOIETIC STEM CELL TRANSPLANTATION	SOLID ORGAN TRANSPLANTATION
Varicella-zoster virus ^h	Contraindicated ^d	Contraindicated	Contraindicated (CDC recommends use on a case-by-case basis following reevaluation.)	Administer before transplantation.

^aThe latest recommendations by the Advisory Committee on Immunization Practices and the CDC guidelines can be found at <http://www.cdc.gov/vaccines>.

^bA single dose of tetanus–diphtheria–acellular pertussis (TDaP), followed by a booster dose of tetanus-diphtheria (Td) every 10 years, is recommended for adults.

^cLive-virus vaccine is contraindicated; inactivated vaccine should be used.

^dCheck the CDC website (www.cdc.gov/vaccines) for updated recommendations.

^eTwo types of vaccine are used to prevent pneumococcal disease. A conjugate vaccine active against 13 serotypes (13-valent pneumococcal conjugate vaccine, or PCV13) is currently administered in three separate doses to all children. A polysaccharide vaccine active against 23 serotypes (23-valent pneumococcal polysaccharide vaccine, or PPSV23) elicits titers of antibody lower than those achieved with the conjugate vaccine, and immunity may wane more rapidly. Because the ablative chemotherapy given to recipients of hematopoietic stem cell transplants eradicates immunologic memory, revaccination is recommended for all such pts. Vaccination is much more effective once immunologic reconstitution has occurred; however, because of the need to prevent serious disease, pneumococcal vaccine should be administered 6–12 months after transplantation in most cases. Because PPSV23 includes serotypes not present in PCV13, recipients of stem cell transplants should receive a dose of PPSV23 at least 8 weeks after the last dose of PCV13. Although antibody titers from PPSV23 clearly decay, experience with multiple doses of PPSV23 is limited, as are data on the safety, toxicity, or efficacy of such a regimen. For this reason, the CDC currently recommends the administration of one additional dose of PPSV23 at least 5 years after the last dose to immunocompromised pts, including transplant recipients, as well as pts with Hodgkin's disease, multiple myeloma, lymphoma, or generalized malignancies. Beyond this single additional dose, further doses are not recommended at this time.

^fStep 1: Administer one dose of the pneumococcal conjugate vaccine Prevnar[®] (13-valent pneumococcal vaccine, PCV13) to all transplant candidates. If a candidate has previously been vaccinated with Pneumovax[®] (23-valent pneumococcal vaccine, PPSV23), at least 6 months should have elapsed before Prevnar is administered. Step 2: Administer one dose of Pneumovax at least 8 weeks after vaccination with PCV13; follow with a booster dose of Pneumovax 5 years later. If the pt has previously been vaccinated with Pneumovax (i.e., before receiving Prevnar), at least 3 years should have elapsed before the second dose of Pneumovax is administered.

^gMeningococcal conjugate vaccine MenACWY is recommended for adults ≤55 years old, and meningococcal polysaccharide vaccine (MPSV4) is recommended for those ≥56 years old.

^hIncludes both varicella vaccine for children and zoster vaccine for adults.

ⁱContact the manufacturer for more information on use in children with acute lymphocytic leukemia.

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Infective Endocarditis



Acute endocarditis is a febrile illness that rapidly damages cardiac structures, seeds extracardiac sites hematogenously, and can progress to death within weeks. *Subacute* endocarditis follows an indolent course, rarely causes metastatic infection, and progresses gradually unless complicated by a major embolic event or a ruptured mycotic aneurysm.

- **Epidemiology:** In developed countries, the incidence of endocarditis ranges from 4 to 7 cases per 100,000 population per year, with higher rates among the elderly.
 - Predisposing conditions include association with health care, congenital heart disease, illicit IV drug use, degenerative valve disease, and the presence of intracardiac devices.
 - Chronic rheumatic heart disease is a risk factor in low-income countries.
 - Of endocarditis cases, 16–30% involve prosthetic valves, with the greatest risk during the first 6–12 months after valve replacement.
- **Etiology and microbiology:** Because of their different portals of entry, the causative microorganisms vary among clinical types of endocarditis.
 - In *native-valve endocarditis* (NVE), viridans streptococci, staphylococci, and HACEK organisms (*Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium* spp., *Eikenella corrodens*, and *Kingella kingae*) enter the bloodstream from oral, skin, and upper respiratory tract portals. *Streptococcus gallolyticus* subspecies *gallolyticus* (formerly *S. bovis* biotype 1) originates from the gut and is associated with polyps or colon cancer.
 - *Health care-associated NVE*, frequently due to *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and enterococci, may have a nosocomial onset (55%) or a community onset (45%) in pts who have had extensive contact with the health care system in the preceding 90 days.
 - *Prosthetic-valve endocarditis* (PVE) developing within 2 months of surgery is due to intraoperative contamination or a bacteremic postoperative complication and is typically caused by CoNS, *S. aureus*, facultative gram-negative bacilli, diphtheroids, or fungi. Cases beginning >1 year after valve surgery are caused by the same organisms that cause community-acquired NVE. PVE due to CoNS that presents 2–12 months after surgery often represents delayed-onset nosocomial infection.
 - *Cardiovascular implantable electronic device (CIED)-related endocarditis* involves the device itself or the endothelium at points of device contact, with occasional concurrent aortic or mitral valve infection. One-third of cases of CIED endocarditis present within 3 months after device implantation or manipulation, one-third present at 4–12 months, and one-third present at >1 year. *S. aureus* and CoNS (often methicillin-resistant strains) cause the majority of cases.
 - *Endocarditis occurring among IV drug users*, especially that involving the tricuspid valve, is commonly caused by *S. aureus* (often a methicillin-resistant strain). Left-sided valve infections among IV drug users are caused by *Pseudomonas aeruginosa* and *Candida*, *Bacillus*, *Lactobacillus*, and *Corynebacterium* spp. in addition to the usual causes of endocarditis.
 - About 5–15% of endocarditis cases are *culture negative*, and one-third to one-half of these cases are due to prior antibiotic exposure. The remainder of culture-negative cases represent infection by fastidious organisms, such as the nutritionally variant bacteria *Granulicatella* and *Abiotrophia* spp., HACEK organisms, *Coxiella burnetii*, *Bartonella* spp., *Brucella* spp., and *Tropheryma whipplei*.

- **Pathogenesis:** Endothelial injury allows direct infection by more virulent pathogens (e.g., *S. aureus*) or the development of a platelet–fibrin thrombus (a condition referred to as *nonbacterial thrombotic endocarditis* [NBTE]) that may become infected during transient bacteremia.
 - NBTE arises from cardiac conditions (e.g., mitral regurgitation, aortic stenosis, aortic regurgitation), hypercoagulable states (giving rise to *marantic endocarditis*, which consists of uninfected vegetations), and the antiphospholipid antibody syndrome.
 - After entering the bloodstream, organisms adhere to the endothelium or sites of NBTE via surface adhesin molecules.
 - The clinical manifestations of endocarditis arise from cytokine production, damage to intracardiac structures, embolization of vegetation fragments, hematogenous infection of sites during bacteremia, and tissue injury due to the deposition of immune complexes.
- **Clinical manifestations:** The clinical syndrome is variable and spans a continuum between acute and subacute presentations. The temporal course of disease is dictated in large part by the causative organism: *S. aureus*, β -hemolytic streptococci, pneumococci, and *Staphylococcus lugdunensis* typically present acutely, whereas viridans streptococci, enterococci, CoNS (other than *S. lugdunensis*), and the HACEK group typically present subacutely.
 - *Constitutional symptoms:* generally nonspecific, but may include fever, chills, weight loss, myalgias, or arthralgias
 - *Cardiac manifestations:* Heart murmurs, particularly new or worsened regurgitant murmurs, are ultimately heard in 85% of pts with acute NVE.
 - CHF develops in 30–40% of pts and is usually due to valvular dysfunction.
 - Extension of infection can result in perivalvular abscesses, which in turn may cause intracardiac fistulae. Abscesses may burrow from the aortic root into the ventricular septum and interrupt the conduction system or may burrow through the epicardium and cause pericarditis.
 - *Noncardiac manifestations:* Arterial emboli, one-half of which precede the diagnosis of endocarditis, are present in 50% of pts, with hematogenously seeded focal infection most often evident in the skin, spleen, kidneys, bones, and meninges.
 - The risk of embolization increases with endocarditis caused by *S. aureus*, mobile vegetations >10 mm in diameter, and infection involving the mitral valve (particularly the anterior leaflet).
 - Cerebrovascular emboli presenting as stroke or encephalopathy complicate 15–35% of cases, with one-half of these cases preceding the diagnosis of endocarditis; however, evidence of clinically asymptomatic emboli is found on MRI in 30–65% of pts with left-sided endocarditis.
 - The incidence of stroke decreases dramatically with antibiotic therapy and does not correlate with change in vegetation size; 3% of strokes occur after 1 week of effective therapy, but these late-occurring embolic events do not specifically constitute evidence of failed antimicrobial therapy.
 - Other neurologic complications include aseptic or purulent meningitis, intracranial hemorrhage due to ruptured mycotic aneurysms (focal dilations of arteries at points in the artery wall that have been weakened by infection or where septic emboli have lodged) or hemorrhagic infarcts, seizures, and microabscesses (especially with *S. aureus*).
 - Immune complex deposition on the glomerular basement membrane causes glomerulonephritis and renal dysfunction, which improve with antibiotic therapy.
 - Nonsuppurative peripheral manifestations of subacute endocarditis (e.g., Janeway lesions, Roth's spots) are related to duration of infection and are now rare because of early diagnosis and treatment.

- *Manifestations of specific predisposing conditions:* Underlying conditions may affect the presenting signs and symptoms.
 - *IV drug use:* Of endocarditis cases associated with IV drug use, ~50% are limited to the tricuspid valve and present as fever, faint or no murmur, septic pulmonary emboli (evidenced by cough, pleuritic chest pain, nodular pulmonary infiltrates, or occasional empyema or pyopneumothorax), and the absence of peripheral manifestations. Pts with left-sided cardiac infections present with the typical clinical features of endocarditis.
 - *Health care-associated endocarditis:* Manifestations are typical in the absence of a retained intracardiac device. Endocarditis associated with a transvenous pacemaker or an implanted defibrillator may be associated with a generator pocket infection and result in fever, minimal murmur, and pulmonary symptoms due to septic emboli.
 - *PVE:* In cases of endocarditis occurring within 60 days of valve surgery, typical symptoms may be masked by comorbidity associated with recent surgery. Paravalvular infection is common in PVE, resulting in partial valve dehiscence, regurgitant murmurs, CHF, or disruption of the conduction system.
- **Diagnosis:** A diagnosis of infective endocarditis is established definitively only when vegetations are examined histologically and microbiologically.
 - The modified Duke criteria (**Table 83-1**) constitute a highly sensitive and specific diagnostic schema that emphasizes the roles of bacteremia and echocardiographic findings.
 - A clinical diagnosis of *definite* endocarditis requires fulfillment of two major criteria, one major criterion plus three minor criteria, or five minor criteria.
 - A diagnosis of *possible* endocarditis requires documentation of one major criterion plus one minor criterion or three minor criteria.
 - For antibiotic-naïve pts, three 2-bottle sets of blood culture samples—separated from one another by at least 2 h—should be obtained from different sites within the first 24 h. If blood cultures are negative after 48–72 h, two or three additional sets of samples should be cultured.
 - Serology is helpful in implicating *Brucella*, *Bartonella*, *Legionella*, *Chlamydia psittaci*, or *C. burnetii* in endocarditis. Examination of the vegetation by histology, culture, direct fluorescent antibody techniques, and/or PCR may be helpful in identifying the causative organism in the absence of a positive blood culture.
 - Echocardiography should be performed to confirm the diagnosis, to verify the size of vegetations, to detect intracardiac complications, and to assess cardiac function.
 - *Transthoracic* echocardiography (TTE) does not detect vegetations <2 mm in diameter, is not adequate for evaluation of prosthetic valves or detection of intracardiac complications, and is technically inadequate in 20% of pts because of emphysema or body habitus; however, TTE may suffice when pts have a low pretest likelihood of endocarditis.
 - *Transesophageal* echocardiography (TEE) detects vegetations in >90% of cases of definite endocarditis and is optimal for evaluation of prosthetic valves and detection of abscesses, valve perforation, or intracardiac fistulas.
 - When endocarditis is likely, a negative TEE result does not exclude the diagnosis but warrants repetition of the study once or twice within 7–10 days.
 - Routine echocardiography (preferably TEE) is recommended in pts with *S. aureus* bacteremia.

TABLE 83-1 The Modified Duke Criteria for the Clinical Diagnosis of Infective Endocarditis^a**Major Criteria**

1. Positive blood culture

Typical microorganism for infective endocarditis from two separate blood cultures

Viridans streptococci, *Streptococcus gallolyticus*, HACEK group organisms, *Staphylococcus aureus*, or

Community-acquired enterococci in the absence of a primary focus,

or

Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:

Blood cultures drawn >12 h apart; or

All of 3 or a majority of ≥ 4 separate blood cultures, with first and last drawn at least 1 h apart

or

Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer of >1:800

2. Evidence of endocardial involvement

Positive echocardiogram^b

Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or in implanted material, in the absence of an alternative anatomic explanation, or

Abscess, or

New partial dehiscence of prosthetic valve,

or

New valvular regurgitation (increase or change in preexisting murmur not sufficient)

Minor Criteria1. Predisposition: predisposing heart conditions^c or injection drug use2. Fever $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$)

3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions

4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor

5. Microbiologic evidence: positive blood culture but not meeting major criterion, as noted previously,^d or serologic evidence of active infection with an organism consistent with infective endocarditis

^aDefinite endocarditis is defined by documentation of two major criteria, of one major criterion and three minor criteria, or of five minor criteria. See text for further details.

^bTransesophageal echocardiography is required for optimal assessment of possible prosthetic valve endocarditis or complicated endocarditis.

^cValvular disease with stenosis or regurgitation, presence of a prosthetic valve, congenital heart disease including corrected or partially corrected conditions (except isolated atrial septal defect, repaired ventricular septal defect, or closed patent ductus arteriosus), prior endocarditis, or hypertrophic cardiomyopathy.

^dExcluding single positive cultures for coagulase-negative staphylococci and diphtheroids, which are common culture contaminants, or for organisms that do not cause endocarditis frequently, such as gram-negative bacilli.

Source: Adapted from Li JS et al: Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 30:633, 2000. With permission from Oxford University Press.

TREATMENT**Endocarditis****ANTIMICROBIAL THERAPY**

- Antimicrobial therapy must be bactericidal and prolonged. See [Table 83-2](#) for organism-specific regimens.
 - Blood cultures should be repeated until sterile. Results should be rechecked if there is recrudescence of fever and at 4–6 weeks after therapy to document cure.
 - If pts are febrile for 7 days despite antibiotic therapy, an evaluation for paravalvular or extracardiac abscesses should be performed.
- Pts with acute endocarditis require antibiotic treatment as soon as three sets of blood culture samples are obtained, but pts with subacute disease who are clinically stable should have antibiotics withheld until a diagnosis is made.
- Pts treated with vancomycin or an aminoglycoside should have serum drug levels monitored. Tests to detect renal, hepatic, and/or hematologic toxicity should be performed periodically.

ORGANISM-SPECIFIC THERAPIES

- Endocarditis due to group B, C, or G streptococci should be treated with the regimen recommended for relatively penicillin-resistant streptococci ([Table 83-2](#)).
- Killing of enterococci requires the synergistic activity of a cell wall–active agent and an aminoglycoside (gentamicin or streptomycin) to which the isolate does not exhibit high-level resistance. If toxicity develops after 2–3 weeks of treatment, the aminoglycoside can be discontinued in pts who have responded satisfactorily. If there is high-level resistance to both aminoglycosides, the cell wall–active agent should be given alone for 8–12 weeks, or—for *Enterococcus faecalis*—high-dose ampicillin plus ceftriaxone or cefotaxime can be given. If the isolate is resistant to all commonly used agents, surgical therapy is advised (see next and [Table 83-3](#)).
- For staphylococcal NVE, the addition of 3–5 days of gentamicin to a β -lactam antibiotic does not improve survival rates and is not recommended.
- Although this regimen has not yet been approved by the FDA, daptomycin (8–10 mg/kg IV qd) has been effective for endocarditis caused by *S. aureus* isolates with a vancomycin MIC of ≥ 2 $\mu\text{g}/\text{mL}$. These isolates should be tested to document daptomycin sensitivity.
- Staphylococcal PVE is treated for 6–8 weeks with a multidrug regimen. Rifampin is important because it kills organisms adherent to foreign material. The inclusion of two other agents in addition to rifampin helps prevent the emergence of rifampin resistance in vivo. Testing for gentamicin susceptibility should be performed before rifampin is given; if the strain is resistant, another aminoglycoside, a fluoroquinolone, ceftaroline, or another active agent should be substituted.
- Empirical therapy (either before culture results are known or when cultures are negative) depends on epidemiologic clues to etiology (e.g., endocarditis in an IV drug user, health care–associated endocarditis).
 - In the setting of no prior antibiotic therapy and negative blood cultures, *S. aureus*, CoNS, and enterococcal infection are unlikely; empirical therapy in this situation should target nutritionally variant organisms, the HACEK group, and *Bartonella*.

TABLE 83-2 Antibiotic Treatment for Infective Endocarditis Caused by Common Organisms^a

ORGANISM(S)	DRUG (DOSE, DURATION)	COMMENTS
Streptococci		
Penicillin-susceptible streptococci, <i>S. gallolyticus</i> (MIC ≤ 0.12 $\mu\text{g}/\text{mL}^b$)	• Penicillin G (2–3 mU IV q4h for 4 weeks)	Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable.
	• Ceftriaxone (2 g/d IV as a single dose for 4 weeks) • Vancomycin ^c (15 mg/kg IV q12h for 4 weeks)	Can use ceftriaxone in pts with non-immediate penicillin allergy. Use vancomycin in pts with severe or immediate β -lactam allergy.
	• Penicillin G (2–3 mU IV q4h) or ceftriaxone (2 g IV qd) for 2 weeks plus Gentamicin ^d (3 mg/kg qd IV or IM, as a single dose ^e or divided into equal doses q8h for 2 weeks)	Avoid 2-week regimen when risk of aminoglycoside toxicity is increased and in prosthetic–valve or complicated endocarditis.
Relatively penicillin-resistant streptococci, <i>S. gallolyticus</i> (MIC >0.12 $\mu\text{g}/\text{mL}$ and <0.5 $\mu\text{g}/\text{mL}^f$)	• Penicillin G (4 mU IV q4h) or ceftriaxone (2 g IV qd) for 4 weeks plus Gentamicin ^d (3 mg/kg qd IV or IM, as a single dose ^e or divided into equal doses q8h for 2 weeks)	Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable. Penicillin alone at this dose for 6 weeks or with gentamicin during the initial 2 weeks is preferred for prosthetic–valve endocarditis caused by streptococci with penicillin MICs of ≤ 0.1 $\mu\text{g}/\text{mL}$.
	• Vancomycin ^c as noted earlier for 4 weeks	Use vancomycin if unable to tolerate penicillins. Ceftriaxone alone or with gentamicin can be used in pts with non-immediate β -lactam allergy.
Moderately penicillin-resistant streptococci (MIC, ≥ 0.5 $\mu\text{g}/\text{mL}$ and <8 $\mu\text{g}/\text{mL}^g$); <i>Granulicatella</i> , <i>Abiotrophia</i> , or <i>Gemella</i> spp.	• Penicillin G (4–5 mU IV q4h) or ceftriaxone (2 g IV qd) for 6 weeks plus Gentamicin ^d (3 mg/kg qd IV or IM as a single dose ^e or divided into equal doses q8h for 6 weeks)	Preferred for PVE caused by streptococci with penicillin MICs of >0.1 $\mu\text{g}/\text{mL}$.
	• Vancomycin ^c as noted earlier for 4 weeks	Regimen is preferred by some.

Enterococci^h		
	Penicillin G (4–5 mU IV q4h) <i>plus</i> gentamicin ^d (1 mg/kg IV q8h), both for 4–6 weeks	Can treat NVE for 4 weeks if symptoms last <3 months. Treat PVE and NVE with >3 months of symptoms for 6 weeks. Can abbreviate gentamicin course in some pts (see text). Can use streptomycin (7.5 mg/kg q12h) in lieu of gentamicin if there is not high-level resistance to streptomycin.
	• Ampicillin (2 g IV q4h) <i>plus</i> gentamicin ^d (1 mg/kg IV q8h), both for 4–6 weeks	Can use amoxicillin in lieu of ampicillin (same dose).
	• Vancomycin ^c (15 mg/kg IV q12h) <i>plus</i> gentamicin ^d (1 mg/kg IV q8h), both for 6 weeks	Use vancomycin <i>plus</i> gentamicin only for penicillin-allergic pts (preferable to desensitize to penicillin) and for isolates resistant to penicillin/ampicillin.
	• Ampicillin (2 g IV q4h) <i>plus</i> ceftriaxone (2 g IV q12h), both for 6 weeks	Use for <i>E. faecalis</i> isolates with or without high-level resistance to gentamicin and streptomycin or for pts at high risk for aminoglycoside nephrotoxicity (creatinine clearance rate <50 mL/min; see text).
Staphylococci (<i>S. aureus</i> and coagulase-negative)		
MSSA infecting native valves (no foreign devices)	• Nafcillin, oxacillin, or flucloxacillin (2 g IV q4h for 4–6 weeks)	Can use penicillin (4 mU q4h) if isolate is penicillin susceptible (i.e., does not produce β -lactamase); 6-week course preferred
	• Cefazolin (2 g IV q8h for 4–6 weeks)	Can use cefazolin regimen for pts with non-immediate penicillin allergy; 6-week course preferred
	• Vancomycin ^c (15 mg/kg IV q12h for 4–6 weeks)	Only use vancomycin for pts with immediate (urticarial) or severe penicillin allergy; see text regarding addition of gentamicin, fusidic acid, or rifampin. A 6-week course is preferred.
MRSA infecting native valves (no foreign devices)	• Vancomycin ^c (15 mg/kg IV q8–12h for 4–6 weeks)	No role for routine use of rifampin (see text). Consider high-dose daptomycin treatment (see text) for MRSA with vancomycin MIC >1.0 or persistent bacteremia during vancomycin therapy.

(Continued)

TABLE 83-2 Antibiotic Treatment for Infective Endocarditis Caused by Common Organisms^a (Continued)

ORGANISM(S)	DRUG (DOSE, DURATION)	COMMENTS
MSSA infecting prosthetic valves	<ul style="list-style-type: none"> • Nafcillin, oxacillin, or flucloxacillin (2 g IV q4h for 6–8 weeks) <i>plus</i> Gentamicin^d (1 mg/kg IM or IV q8h for 2 weeks) <i>plus</i> • Rifampinⁱ (300 mg PO q8h for 6–8 weeks) 	Use gentamicin during initial 2 weeks; determine susceptibility to gentamicin before initiating rifampin (see text); if pt is highly allergic to penicillin, use regimen for MRSA; if β -lactam allergy is of the minor non-immediate type, cefazolin can be substituted for oxacillin, nafcillin, or flucloxacillin.
MRSA infecting prosthetic valves	<ul style="list-style-type: none"> • Vancomycin^c (15 mg/kg IV q12h for 6–8 weeks) <i>plus</i> Gentamicin^d (1 mg/kg IM or IV q8h for 2 weeks) <i>plus</i> Rifampinⁱ (300 mg PO q8h for 6–8 weeks) 	Use gentamicin during initial 2 weeks; determine gentamicin susceptibility before initiating rifampin.
HACEK Organisms		
	<ul style="list-style-type: none"> • Ceftriaxone (2 g/d IV as a single dose for 4 weeks) 	Can use another third-generation cephalosporin at comparable dose.
	<ul style="list-style-type: none"> • Ampicillin/sulbactam (3 g IV q6h for 4 weeks) 	If the isolate is susceptible, ciprofloxacin (400 mg IV q12h) can be used.
<i>Coxiella burnetii</i>		
	<ul style="list-style-type: none"> • Doxycycline (100 mg PO q12h) <i>plus</i> hydroxychloroquine (200 mg PO q8h), both for at least 18 (native valve) or 24 (prosthetic valve) months 	Follow serology to monitor response during treatment (antiphase I IgG and IgA decreased 4-fold and IgM antiphase II negative) and thereafter for relapse.

<i>Bartonella</i> spp.	<ul style="list-style-type: none"> • Doxycycline (100 mg q12h PO) for 6 weeks <p>plus</p> <p>Gentamicin (1 mg/kg IV q8h for 2 weeks)</p>	<p>If doxycycline is not tolerated, use azithromycin (500 mg PO qd). Some experts recommend that doxycycline be continued for 3–6 months unless all infection is resected surgically.</p>
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^aRegimens adapted from the guidelines of the American Heart Association, the European Society of Cardiology (ESC), and to a lesser extent the British Society for Antimicrobial Chemotherapy (BSAC). Doses of gentamicin, streptomycin, and vancomycin must be adjusted for reduced renal function. Ideal body weight is used to calculate doses of gentamicin and streptomycin per kilogram (men = 50 kg + 2.3 kg per inch over 5 feet; women = 45.5 kg + 2.3 kg per inch over 5 feet).

^bMIC \leq 0.125 $\mu\text{g}/\text{mL}$ per ESC and BSAC.

^cVancomycin dose is based on actual body weight. Adjust for trough level of 10–15 $\mu\text{g}/\text{mL}$ for streptococcal and enterococcal infections and 15–20 $\mu\text{g}/\text{mL}$ for staphylococcal infections.

^dAminoglycosides should not be administered as single daily doses for enterococcal endocarditis and should be introduced as part of the initial treatment. Target peak and trough serum concentrations of divided-dose gentamicin 1 h after a 20- to 30-min infusion or IM injection are \sim 3.5 $\mu\text{g}/\text{mL}$ and \leq 1 $\mu\text{g}/\text{mL}$, respectively; target peak and trough serum concentrations of streptomycin (timing as with gentamicin) are 20–35 $\mu\text{g}/\text{mL}$ and $<$ 10 $\mu\text{g}/\text{mL}$, respectively.

^eNetilmicin (4 mg/kg qd, as a single dose) can be used in lieu of gentamicin.

^fMIC $>$ 0.125 $\mu\text{g}/\text{mL}$ and \leq 2.0 $\mu\text{g}/\text{mL}$ per ESC; MIC $>$ 0.125 $\mu\text{g}/\text{mL}$ and \leq 0.5 $\mu\text{g}/\text{mL}$ per BSAC.

^gMIC $>$ 2.0 $\mu\text{g}/\text{mL}$ per ESC; treat with regimen for enterococci (BSAC).

^hAntimicrobial susceptibility must be evaluated; see text.

ⁱRifampin increases warfarin and dicumarol requirements for anticoagulation.

Abbreviations: MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; NVE, native-valve endocarditis; PVE, prosthetic-valve endocarditis.

TABLE 83-3 Timing of Cardiac Surgical Intervention in Pts with Endocarditis

TIMING	INDICATION FOR SURGICAL INTERVENTION	
	STRONG SUPPORTING EVIDENCE	CONFLICTING EVIDENCE, BUT MAJORITY OF OPINIONS FAVOR SURGERY
Emergent (same day)	Valve dysfunction with pulmonary edema or cardiogenic shock Acute aortic regurgitation plus preclosure of mitral valve Sinus of Valsalva abscess ruptured into right heart Rupture into pericardial sac	
Urgent (within 1–2 days)	Valve obstruction by vegetation Unstable (dehiscenced) prosthesis Acute aortic or mitral regurgitation with heart failure (New York Heart Association class III or IV)	Vegetation diameter >10 mm plus severe but not urgent aortic or mitral valve dysfunction ^a Major embolus plus persisting large vegetation (>10 mm)
	Septal perforation	Mobile vegetation >30 mm
	Perivalvular extension of infection with or without new electrocardiographic conduction system changes	
	Lack of effective antibiotic therapy	
Elective (earlier usually preferred)	Progressive paravalvular prosthetic regurgitation Valve dysfunction plus persisting infection after ≥7–10 days of antimicrobial therapy Fungal (mold) endocarditis	Staphylococcal prosthetic-valve endocarditis with intracardiac complications Early prosthetic-valve endocarditis (≤2 months after valve surgery) <i>Candida</i> spp. endocarditis Antibiotic-resistant organisms

^aSupported by a single-institution randomized trial showing benefit from early surgery. Implementation requires clinical judgment. If surgery is elected, it must be done early.

Source: Adapted from Olaison L, Petttersson G: Current best practices and guidelines indications for surgical intervention in infective endocarditis. *Infect Dis Clin North Am* 16:453, 2002.

- If negative cultures are confounded by prior antibiotic therapy, broader empirical therapy is indicated and should cover pathogens inhibited by the prior therapy.

SURGICAL TREATMENT

- The timing and indications for surgical intervention are listed in Table 83-3; most of these indications are not absolute, and recommendations are derived from observational studies and expert opinion. Moderate or severe refractory CHF is the major indication for surgical treatment of endocarditis.

- Cardiac surgery should be delayed for 2–3 weeks if possible when the pt has had a nonhemorrhagic embolic stroke and for 4 weeks when the pt has had a hemorrhagic embolic stroke. Ruptured mycotic aneurysms should be treated prior to cardiac surgery.
 - The duration of antibiotic therapy after cardiac surgery depends on the indication for surgery.
 - For cases of uncomplicated NVE caused by susceptible organisms with negative valve cultures at surgery, the duration of pre- and postoperative treatment should equal the total duration of recommended therapy, with ~2 weeks of treatment given postoperatively.
 - For endocarditis with paravalvular abscess, partially treated PVE, or culture-positive valves, pts should receive a full course of therapy postoperatively.
-
- **Outcome:** Death and other poor outcomes are related not to failure of antibiotic therapy but rather to interactions of comorbidities and endocarditis-related end-organ complications.
 - Survival rates are 85–90% for NVE due to viridans streptococci, HACEK organisms, or enterococci as opposed to 55–70% for NVE due to *S. aureus* in pts who are not IV drug users.
 - PVE beginning within 2 months of valve replacement results in mortality rates of 40–50%, whereas rates are only 10–20% in later-onset cases.
 - **Prevention:** The American Heart Association and the European Society of Cardiology have narrowed recommendations for antibiotic prophylaxis, limiting its use to pts at highest risk of severe morbidity and death from endocarditis.
 - Prophylaxis is recommended only for those dental procedures involving manipulation of gingival tissue or the periapical region of the teeth or perforation of the oral mucosa (including respiratory tract surgery). Prophylaxis is not advised for pts undergoing GI or genitourinary tract procedures unless the genitourinary tract is infected.
 - **Table 83-4** lists the high-risk cardiac lesions for which prophylaxis is advised, and **Table 83-5** lists the recommended antibiotic regimens for this purpose.

TABLE 83-4 High-Risk Cardiac Lesions for Which Endocarditis Prophylaxis Is Advised before Dental Procedures

Prosthetic heart valves

Prior endocarditis

Unrepaired cyanotic congenital heart disease, including palliative shunts or conduits

Completely repaired congenital heart defects during the 6 months after repair

Incompletely repaired congenital heart disease with residual defects adjacent to prosthetic material

Valvulopathy developing after cardiac transplantation^a

^aNot a target population for prophylaxis according to recommendations of the European Society for Cardiology.

Source: Wilson W et al: Prevention of infective endocarditis. *Circulation* 116:1736, 2007; Habib G et al: Guidelines on the prevention, diagnosis, and treatment of infective endocarditis. *Eur Heart J* 30:2369, 2009.

TABLE 83-5 Antibiotic Regimens for Prophylaxis of Endocarditis in Adults with High-Risk Cardiac Lesions^{a,b}

- A. Standard oral regimen
Amoxicillin: 2 g PO 1 h before procedure
- B. Inability to take oral medication
Ampicillin: 2 g IV or IM within 1 h before procedure
- C. Penicillin allergy
1. Clarithromycin or azithromycin: 500 mg PO 1 h before procedure
 2. Cephalexin^c: 2 g PO 1 h before procedure
 3. Clindamycin: 600 mg PO 1 h before procedure
- D. Penicillin allergy, inability to take oral medication
1. Cefazolin^c or ceftriaxone^c: 1 g IV or IM 30 min before procedure
 2. Clindamycin: 600 mg IV or IM 1 h before procedure

^aDosing for children: for amoxicillin, ampicillin, cephalexin, or cefadroxil, use 50 mg/kg PO; cefazolin, 25 mg/kg IV; clindamycin, 20 mg/kg PO or 25 mg/kg IV; clarithromycin, 15 mg/kg PO; and vancomycin, 20 mg/kg IV.

^bFor high-risk lesions, see Table 83-4. Prophylaxis is not advised for other lesions.

^cDo not use cephalosporins in pts with immediate hypersensitivity (urticaria, angioedema, anaphylaxis) to penicillin.

Source: Wilson W et al: Prevention of infective endocarditis. *Circulation* 116:1736, 2007; Habib G et al: Guidelines on the prevention, diagnosis, and treatment of infective endocarditis. *Eur Heart J* 30:2369, 2009.

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Intraabdominal Infections



Intraperitoneal infections result when normal anatomic barriers are disrupted. Organisms contained within the bowel or an intraabdominal organ enter the sterile peritoneal cavity, causing peritonitis and—if the infection goes untreated and the pt survives—abscesses.

PERITONITIS

Peritonitis is a life-threatening event that is often accompanied by bacteremia and sepsis. *Primary* peritonitis has no apparent source, whereas *secondary* peritonitis is caused by spillage from an intraabdominal viscus. The etiologic organisms and the clinical presentations of these two processes are different.

■ PRIMARY (SPONTANEOUS) BACTERIAL PERITONITIS

- **Epidemiology:** Primary bacterial peritonitis (PBP) is most common among pts with cirrhosis (usually due to alcoholism) and preexisting ascites, but $\leq 10\%$ of these pts develop PBP. PBP is also described in other settings (e.g., malignancy, hepatitis).
- **Pathogenesis:** PBP is due to hematogenous spread of organisms to ascitic fluid in pts in whom a diseased liver and altered portal circulation compromise the liver's filtration function.

- **Microbiology:** Enteric gram-negative bacilli such as *Escherichia coli* or gram-positive organisms such as streptococci, enterococci, and pneumococci are the most common etiologic agents.
 - A single organism is typically isolated.
 - If a polymicrobial infection including anaerobes is identified, the diagnosis of PBP should be reconsidered and a source of secondary peritonitis sought.
- **Clinical manifestations:** Although some pts experience acute-onset abdominal pain or signs of peritoneal irritation, other pts have only nonspecific and nonlocalizing manifestations (e.g., malaise, fatigue, encephalopathy). Fever is common (~80% of pts).
- **Diagnosis:** PBP is diagnosed if peritoneal fluid is sampled and contains >250 PMNs/ μ L.
 - Culture yield is improved if a 10-mL volume of peritoneal fluid is placed directly into blood culture bottles.
 - Blood cultures should be performed because bacteremia is common.
- **Prevention:** Up to 70% of pts have a recurrence of PBP within 1 year. Prophylaxis with fluoroquinolones (e.g., ciprofloxacin, 500 mg weekly) or trimethoprim-sulfamethoxazole (TMP-SMX; one double-strength tablet daily) reduces this rate to 20% but increases the risk of serious staphylococcal infections over time.

TREATMENT

Primary (Spontaneous) Bacterial Peritonitis

A third-generation cephalosporin (e.g., ceftriaxone, 2 g q24h IV; or cefotaxime, 2 g q8h IV) or piperacillin/tazobactam (3.375 g qid IV) constitutes appropriate empirical treatment.

- The regimen should be narrowed after the etiology is identified.
- Treatment should continue for at least 5 days, but longer courses (up to 2 weeks) may be needed for pts with coexisting bacteremia or for those whose improvement is slow.
- Albumin (1.5 g/kg of body weight within 6 h of detection and 1.0 g/kg on day 3) improves survival rates among pts with serum creatinine levels ≥ 1 mg/dL, BUN levels ≥ 30 mg/dL, or total bilirubin levels ≥ 4 mg/dL.

■ SECONDARY PERITONITIS

- **Pathogenesis:** Secondary peritonitis develops when bacteria contaminate the peritoneum as a result of spillage from an intraabdominal viscus.
- **Microbiology:** Infection almost always involves a mixed flora in which gram-negative bacilli and anaerobes predominate, especially when the contaminating source is colonic. The specific organisms depend on the flora present at the site of the initial process.
- **Clinical manifestations:** Initial symptoms may be localized or vague and depend on the primary organ involved. Once infection has spread to the peritoneal cavity, pain increases; pts lie motionless, often with knees drawn up to avoid stretching the nerve fibers of the peritoneal cavity. Coughing or sneezing causes severe, sharp pain. There is marked voluntary and involuntary guarding of anterior abdominal musculature, tenderness (often with rebound), and fever.

- **Diagnosis:** Although recovery of organisms from peritoneal fluid is easier in secondary than in primary peritonitis, radiographic studies to find the source of peritoneal contamination or immediate surgical intervention should usually be part of the initial diagnostic evaluation. Abdominal taps are done only to exclude hemoperitoneum in trauma cases.

TREATMENT

Secondary Peritonitis

- Antibiotics aimed at the inciting microbes—e.g., penicillin/ β -lactamase inhibitor combinations or a combination of a fluoroquinolone or a third-generation cephalosporin plus metronidazole—should be administered early.
 - Critically ill pts in the ICU and/or those with health care-associated infections should be treated for the possibility of resistant gram-negative organisms, including *Pseudomonas aeruginosa*, with a carbapenem—e.g., imipenem (500 mg q6h IV), meropenem (1 g q8h IV), higher-dose piperacillin/tazobactam (4.5 g q6h IV), or drug combinations such as metronidazole plus either cefepime (2 g IV q8h) or ceftazidime (2 g IV q8h). These regimens can be altered on the basis of the pt's history of resistant organisms and/or concern about enterococcal or fungal involvement.
 - Surgical intervention is often needed.

■ PERITONITIS IN PTS UNDERGOING CAPD

- **Pathogenesis:** In a phenomenon similar to that seen in intravascular device-related infections, organisms migrate along the catheter—a foreign body that serves as an entry point.
- **Microbiology:** CAPD-associated peritonitis usually involves skin organisms, with *Staphylococcus* spp. such as coagulase-negative staphylococci and *Staphylococcus aureus* accounting for ~45% of cases; gram-negative bacilli and fungi (e.g., *Candida*) are occasionally identified. A polymicrobial infection should prompt evaluation for secondary peritonitis.
- **Clinical manifestations:** CAPD-associated peritonitis presents similarly to secondary peritonitis, in that diffuse pain and peritoneal signs are common.
- **Diagnosis:** Several hundred milliliters of removed dialysis fluid should be centrifuged and sent for culture.
 - Use of blood culture bottles improves the diagnostic yield.
 - The dialysate is usually cloudy and contains >100 WBCs/ μ L, with $>50\%$ neutrophils; the percentage of neutrophils is more important than the absolute WBC count.

TREATMENT

Peritonitis in Pts Undergoing CAPD

- Empirical therapy should be directed against staphylococcal species and gram-negative bacilli (e.g., ceftazidime plus a fluoroquinolone or a third-generation cephalosporin such as ceftazidime). Vancomycin should be used instead of ceftazidime if methicillin resistance is prevalent, if the pt has an overt exit-site infection, or if the pt appears toxic.
 - Antibiotics are given by the IP route either continuously (e.g., with each exchange) or intermittently (e.g., once daily, with the dose allowed to

remain in the peritoneal cavity for 6 h). Severely ill pts should be given the same regimen by the IV route.

- Catheter removal should be considered in fungal infection, for pts with exit-site or tunnel infection, or if the pt's condition does not improve within 48–96 h.
- Uncomplicated CAPD-associated peritonitis should be treated for 14 days; up to 21 days may be necessary in pts with exit-site or tunnel infection.

INTRAABDOMINAL ABSCESSES

Intraabdominal abscesses are generally diagnosed through radiographic studies, of which abdominal CT is typically most useful.

■ INTRAPERITONEAL ABSCESSES

- **Epidemiology:** Of intraabdominal abscesses, 74% are IP or retroperitoneal, not visceral.
- **Pathogenesis:** Most IP abscesses arise from colonic sources. Abscesses develop in untreated peritonitis as an extension of the disease process and represent host defense activity aimed at containing the infection.
- **Microbiology:** Infection is typically polymicrobial; the most frequently isolated anaerobe is *Bacteroides fragilis*.

TREATMENT

Intraperitoneal Abscesses

- Antimicrobial therapy is adjunctive to drainage and/or surgical correction of an underlying lesion or process.
 - Diverticular abscesses usually wall off locally, and surgical intervention is not routinely needed.
 - Antimicrobial agents with activity against gram-negative bacilli and anaerobic organisms are indicated (see “Secondary Peritonitis,” above). With adequate source control, antibiotic treatment may be limited to 4 or 5 days.

VISCERAL ABSCESSES

■ LIVER ABSCESS

- **Epidemiology, pathogenesis, and microbiology:** Liver abscesses account for up to half of visceral intraabdominal abscesses and are caused most commonly by biliary tract disease (due to aerobic gram-negative bacilli or enterococci) and less often by local spread from pelvic and other IP sources (due to mixed flora including aerobic and anaerobic species, among which *B. fragilis* is most common) or hematogenous seeding (infection with a single species, usually *S. aureus* or streptococci such as *Streptococcus milleri*).
 - Amebic liver abscesses are not uncommon, with positive serology in >95% of affected pts.
- **Clinical manifestations:** Pts have fever, anorexia, weight loss, nausea, and vomiting, but only ~50% have signs localized to the RUQ, such as tenderness, hepatomegaly, and jaundice. Serum levels of alkaline phosphatase are elevated in ~70% of pts, and leukocytosis is common. One-third to one-half of pts are bacteremic.

TREATMENT

Liver Abscess

- Drainage is the mainstay of treatment (Fig. 84-1), but medical management with long courses of antibiotics can be successful.
 - Empirical therapy is the same as for intraabdominal sepsis and secondary bacterial peritonitis.
 - Percutaneous drainage tends to fail in cases with multiple, sizable abscesses; with viscous abscess contents that plug the pigtail catheter; with associated disease (e.g., of the biliary tract) requiring surgery; with the presence of yeast; or with lack of response in 4–7 days.

Splenic Abscess

- **Epidemiology and pathogenesis:** Splenic abscesses are much less common than liver abscesses and usually develop via hematogenous spread of infection (e.g., due to endocarditis). The diagnosis is often made only after the pt's death; the condition is frequently fatal if left untreated.
- **Microbiology:** Splenic abscesses are most often caused by streptococci; *S. aureus* is the next most common cause. Gram-negative bacilli can cause splenic abscess in pts with urinary tract foci, with associated bacteremia, or with infection from another intraabdominal source; salmonellae are fairly commonly isolated, particularly from pts with sickle cell disease.
- **Clinical manifestations:** Abdominal pain or splenomegaly occurs in ~50% of cases and pain localized to the LUQ in ~25%. Fever and leukocytosis are common.

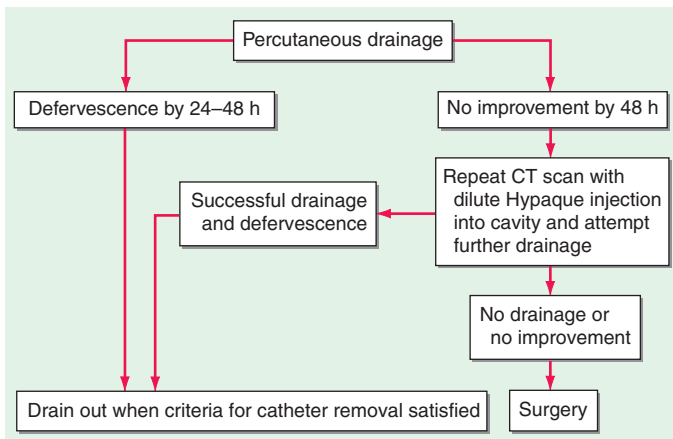


FIGURE 84-1 Algorithm for the management of pts with intraabdominal abscesses by percutaneous drainage. Antimicrobial therapy should be administered concomitantly. (Reprinted with permission from Lorber B [ed]: *Atlas of Infectious Diseases, vol VII: Intra-abdominal Infections, Hepatitis, and Gastroenteritis*. Philadelphia, Current Medicine, 1996, p 1.30, as adapted from Rotstein OD, Simmons RL, in Gorbach SL et al [eds]: *Infectious Diseases*. Philadelphia, Saunders, 1992, p 668.)

TREATMENT**Splenic Abscess**

Pts with multiple or complex multilocular abscesses should undergo splenectomy, receive adjunctive antibiotics, and be vaccinated against encapsulated organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*). Percutaneous drainage has been successful for single, small (<3-cm) abscesses and may also be useful for pts at high surgical risk.

Perinephric and Renal Abscesses

- **Epidemiology and pathogenesis:** Perinephric and renal abscesses are uncommon. More than 75% of these abscesses are due to ascending infection and are preceded by pyelonephritis. The most important risk factor is the presence of renal calculi that produce local obstruction to urinary flow.
- **Microbiology:** *E. coli*, *Proteus* spp. (associated with struvite stones), and *Klebsiella* spp. are the most common etiologic agents; *Candida* spp. are sometimes identified.
- **Clinical manifestations:** Clinical signs are nonspecific and include flank pain, abdominal pain, and fever. This diagnosis should be considered if pts with pyelonephritis have persistent fever after 4 or 5 days of treatment, if a urine culture yields a polymicrobial flora, if the pt has known renal stone disease, or if fever and pyuria occur in conjunction with a sterile urine culture.

TREATMENT**Perinephric and Renal Abscesses**

Drainage and the administration of antibiotics active against the organisms recovered are essential. Percutaneous drainage is usually successful for perinephric abscesses.

85

Infectious Diarrheas and Bacterial Food Poisoning

Acute diarrheal disease, which is associated with ~1.7 million deaths per year, is the second most common infectious cause of death worldwide among children <5 years old (after lower respiratory tract infection). The wide range of clinical manifestations is matched by the wide variety of infectious agents involved (Table 85-1). An approach to pts with infectious diarrhea is presented in Fig. 85-1.

NONINFLAMMATORY DIARRHEA**■ BACTERIAL FOOD POISONING**

If there is evidence of a common-source outbreak, questions concerning the ingestion of specific foods and the timing of diarrhea after a meal can provide clues to the bacterial cause of the illness.

- *Staphylococcus aureus*: Enterotoxin is elaborated in food left at room temperature (e.g., at picnics).

TABLE 85-1 Gastrointestinal Pathogens Causing Acute Diarrhea

MECHANISM	LOCATION	ILLNESS	STOOL FINDINGS	EXAMPLES OF PATHOGENS INVOLVED
Noninflammatory (enterotoxin)	Proximal small bowel	Watery diarrhea	No fecal leukocytes; mild or no increase in fecal lactoferrin	<i>Vibrio cholerae</i> , enterotoxigenic <i>Escherichia coli</i> (LT and/or ST), enteroaggregative <i>E. coli</i> , <i>Clostridium perfringens</i> , <i>Bacillus cereus</i> , <i>Staphylococcus aureus</i> , <i>Aeromonas hydrophila</i> , <i>Plesiomonas shigelloides</i> , rotavirus, norovirus, enteric adenoviruses, <i>Giardia lamblia</i> , <i>Cryptosporidium</i> spp., <i>Cyclospora</i> spp., microsporidia
Inflammatory (invasion or cytotoxin)	Colon or distal small bowel	Dysentery or inflammatory diarrhea	Fecal polymorphonuclear leukocytes; substantial increase in fecal lactoferrin	<i>Shigella</i> spp., <i>Salmonella</i> spp., <i>Campylobacter jejuni</i> , enterohemorrhagic <i>E. coli</i> , enteroinvasive <i>E. coli</i> , <i>Yersinia enterocolitica</i> , <i>Listeria monocytogenes</i> , <i>Vibrio parahaemolyticus</i> , <i>Clostridium difficile</i> , <i>A. hydrophila</i> , <i>P. shigelloides</i> , <i>Entamoeba histolytica</i> , <i>Klebsiella oxytoca</i>
Penetrating	Distal small bowel	Enteric fever	Fecal mononuclear leukocytes	<i>Salmonella</i> Typhi, <i>Y. enterocolitica</i>

Abbreviations: LT, heat-labile enterotoxin; ST, heat-stable enterotoxin.

- The incubation period is 1–6 h. Disease lasts <12 h and consists of diarrhea, nausea, vomiting, and abdominal cramping, usually without fever.
- Most cases are due to contamination from infected human carriers.
- *Bacillus cereus*: Either an *emetic* or a *diarrheal* form of food poisoning can occur.
 - The *emetic* form presents like *S. aureus* food poisoning, is due to a staphylococcal type of enterotoxin, has an incubation period of 1–6 h, and is associated with contaminated fried rice.
 - The *diarrheal* form has an incubation period of 8–16 h, is caused by an enterotoxin resembling *Escherichia coli* heat-labile toxin (LT), and presents as diarrhea and abdominal cramps without vomiting.
- *Clostridium perfringens*: Ingestion of heat-resistant spores in undercooked meat, poultry, or legumes leads to toxin production in the intestinal tract. The incubation period is 8–14 h, after which pts develop ≤24 h of diarrhea and abdominal cramps, without vomiting or fever.

■ CHOLERA

Microbiology

Cholera is caused by *Vibrio cholerae* serogroups O1 (classic and El Tor biotypes) and O139—highly motile, facultatively anaerobic, curved gram-negative rods.

The natural habitat of *V. cholerae* is coastal salt water and brackish estuaries. Toxin production causes disease manifestations.

Epidemiology

Currently, Africa, Asia, and the Americas are the source of >40%, 35%, and 20% of cases reported to the World Health Organization (WHO), respectively; however, an estimated 90% of cases go unreported or do not have a specific bacterial etiology identified.

- It is estimated that there are >2–3 million cases annually, with >50,000–100,000 deaths.
- Spread takes place by fecal contamination of water and food sources. Infection requires ingestion of a relatively large inoculum (compared with that required for other pathogens) of 10^5 – 10^8 organisms.

Clinical Manifestations

After an incubation period of 24–48 h, pts develop painless watery diarrhea and vomiting that can cause profound, rapidly progressive dehydration and death within hours.

- Volume loss can be >250 mL/kg in the first day.
- Stool has a characteristic “rice-water” appearance: gray cloudy fluid with flecks of mucus; no blood; and a fishy, inoffensive odor.

Diagnosis

Stool cultures on selective medium (e.g., thiosulfate–citrate–bile salts–sucrose [TCBS] agar) can isolate the organism. A point-of-care antigen-detection assay is available for field use.

TREATMENT

Cholera

Rapid fluid replacement is critical, preferably with the WHO’s reduced-osmolarity oral rehydration solution (ORS), which contains (per liter of water) Na^+ , 75 mmol; K^+ , 20 mmol; Cl^- , 65 mmol; citrate, 10 mmol; and glucose, 75 mmol.

- If available, rice-based ORS is considered superior to standard ORS for cholera.
- If ORS is not available, a substitute can be made by adding 0.5 teaspoon of table salt and 6 teaspoons of table sugar to 1 L of safe water, with potassium provided separately (e.g., in bananas or green coconut water).
- Severely dehydrated pts should be managed initially with IV hydration (preferably with Ringer’s lactate), with the total fluid deficit replaced in the first 3–4 h (half within the first hour).
- Antibiotic therapy (azithromycin, a single 1-g dose; erythromycin, 250 mg PO qid for 3 days; tetracycline, 500 mg PO qid for 3 days; or ciprofloxacin, 500 mg PO bid for 3 days) diminishes the duration and volume of stool.

■ VIBRIO PARAHAEMOLYTICUS AND NON-O1 V. CHOLERAЕ

These infections are linked to ingestion of contaminated seawater or undercooked seafood. After an incubation period of 4 h to 4 days, watery diarrhea, abdominal cramps, nausea, vomiting, and occasionally fever and chills develop. The disease lasts <7 days. Dysentery is a less common presentation. Pts with comorbid disease (e.g., liver disease) sometimes have extraintestinal infections that require antibiotic treatment.

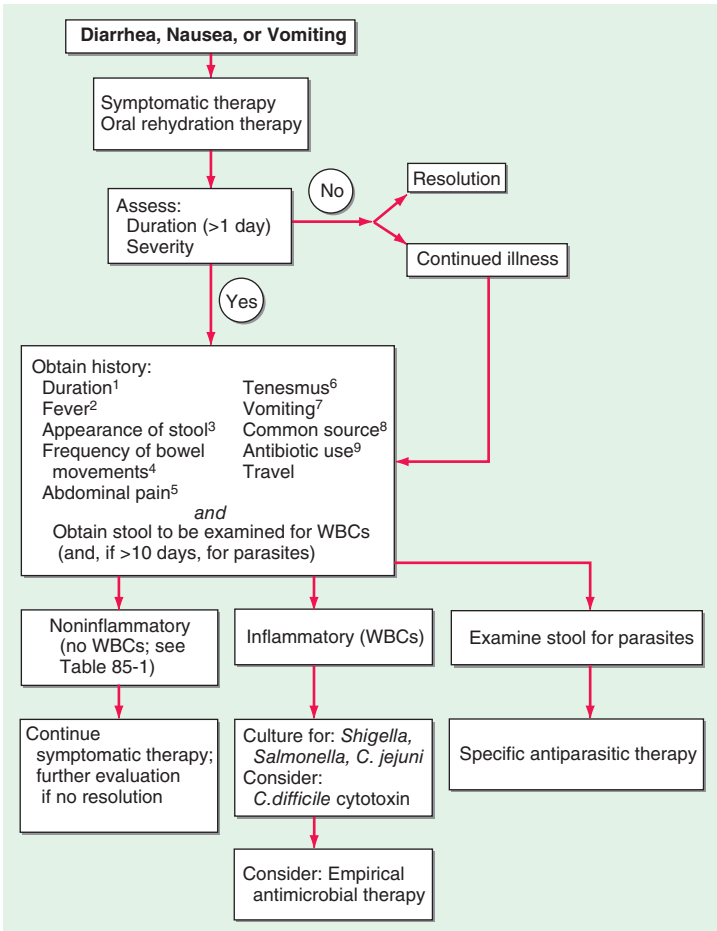


FIGURE 85-1 Clinical algorithm for the approach to pts with community-acquired infectious diarrhea or bacterial food poisoning. Key to superscripts: 1. Diarrhea lasting >2 weeks is generally defined as chronic; in such cases, many of the causes of acute diarrhea are much less likely, and a new spectrum of causes needs to be considered. 2. Fever often implies invasive disease, although fever and diarrhea may also result from infection outside the gastrointestinal tract, as in malaria. 3. Stools that contain blood or mucus indicate ulceration of the large bowel. Bloody stools without fecal leukocytes should alert the laboratory to the possibility of infection with Shiga toxin-producing enterohemorrhagic *Escherichia coli*. Bulky white stools suggest a small-intestinal process that is causing malabsorption. Profuse “rice-water” stools suggest cholera or a similar toxigenic process. 4. Frequent stools over a given period can provide the first warning of impending dehydration. 5. Abdominal pain may be most severe in inflammatory processes like those due to *Shigella*, *Campylobacter*, and necrotizing toxins. Painful abdominal muscle cramps, caused by electrolyte loss, can develop in severe cases of cholera. Bloating is common in giardiasis. An appendicitis-like syndrome should prompt a culture for *Yersinia enterocolitica* with cold enrichment. 6. Tenesmus (painful rectal spasms with a strong urge to defecate but little passage of stool) may be a feature of cases with proctitis, as in shigellosis or amebiasis.

■ NOROVIRUSES AND RELATED HUMAN CALCIVIRUSES

Microbiology and Epidemiology

These single-stranded RNA viruses are common causes of traveler's diarrhea and of viral gastroenteritis in pts of all ages as well as of epidemics worldwide, with a higher prevalence in cold-weather months. In the United States, ~50% of outbreaks of nonbacterial gastroenteritis are caused by noroviruses. Very small inocula are required for infection. Thus, although the fecal-oral route is the primary mode of transmission, aerosolization, fomite contact, and person-to-person contact can also result in infection.

Clinical Manifestations

After a 24-h incubation period (range, 12–72 h), pts experience the sudden onset of nausea, vomiting, diarrhea, and/or abdominal cramps with constitutional symptoms (e.g., fever, headache, chills). Stools are loose, watery, and without blood, mucus, or leukocytes. Disease lasts 12–60 h.

Diagnosis

PCR assays have been developed to detect these viruses in stool and other body fluids. Because of poor sensitivity, enzyme immunoassays (EIAs) have limited clinical utility outside of outbreaks.

TREATMENT

Infections with Noroviruses and Related Human Calciviruses

Only supportive measures are required.

■ ROTAVIRUSES

Microbiology and Epidemiology

Rotavirus is a segmented, double-stranded RNA virus that infects nearly all children worldwide by 3–5 years of age; adults can become infected if exposed.

- Reinfections are progressively less severe.
- Large quantities of virus are shed in the stool during the first week of infection, and transmission takes place both via the fecal-oral route and from person to person.
- Disease incidence peaks in the cooler fall and winter months.

7. Vomiting implies an acute infection (e.g., a toxin-mediated illness or food poisoning) but can also be prominent in a variety of systemic illnesses (e.g., malaria) and in intestinal obstruction. 8. Asking pts whether anyone else they know is sick is a more efficient means of identifying a common source than is constructing a list of recently eaten foods. If a common source seems likely, specific foods can be investigated. See text for a discussion of bacterial food poisoning. 9. Current antibiotic therapy or a recent history of treatment suggests *Clostridium difficile* diarrhea. Stop antibiotic treatment if possible and consider tests for *C. difficile* toxins. Antibiotic use may increase the risk of chronic intestinal carriage following salmonellosis. (From Steiner TS, Guerrant RL: Principles and syndromes of enteric infection, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 7th ed, Mandell GL et al [eds]. Philadelphia, Churchill Livingstone, 2010, pp 1335–1351; Guerrant RL, Bobak DA: N Engl J Med 325:327, 1991.)

Clinical Manifestations

After an incubation period of 1–3 days, disease onset is abrupt. Vomiting often precedes diarrhea (loose, watery stools without blood or fecal leukocytes), and about one-third of pts have temperatures $>39^{\circ}\text{C}$ ($>102.2^{\circ}\text{F}$). Symptoms resolve within 3–7 days.

Diagnosis

EIAs or viral RNA detection techniques, such as PCR, can identify rotavirus in stool samples.

TREATMENT**Rotavirus Infections**

Only supportive treatment is needed. Dehydration can be severe, and IV hydration may be needed in pts with frequent vomiting. Antibiotics and antimotility agents should be avoided.

Prevention

Rotavirus vaccines, two of which are available in the United States, are included in the routine vaccination schedule for U.S. infants. Vaccination has led to a >70 – 80% decline in hospital visits due to rotavirus illness. Notably, the efficacy of rotavirus vaccines is lower (50–65%) in low-resource settings.

■ GIARDIASIS**Microbiology and Epidemiology**

Giardia lamblia (also known as *G. intestinalis* or *G. duodenalis*) is a protozoal parasite that inhabits the small intestines of humans and other mammals.

- Cysts are ingested from the environment, excyst in the small intestine, and release flagellated trophozoites that remain in the proximal small intestine. Some trophozoites encyst, with the resulting cysts excreted in feces.
- Transmission occurs via the fecal–oral route, by ingestion of contaminated food and water, or from person to person in settings with poor fecal hygiene (e.g., day-care centers, institutional settings). Infection results from as few as 10 cysts.
- Viable cysts can be eradicated from water by either boiling or filtration. Standard chlorination techniques used to control bacteria do not destroy cysts.
- Young pts, newly exposed pts, and pts with hypogammaglobulinemia are at increased risk—a pattern suggesting a role for humoral immunity in resistance.

Clinical Manifestations

After an incubation period of 5 days to 3 weeks, the manifestations of infection range from asymptomatic carriage (most common) to fulminant diarrhea and malabsorption.

- Prominent early symptoms include diarrhea, abdominal pain, bloating, belching, flatulence, nausea, and vomiting and usually last >1 week. Fever is rare, as is blood or mucus in stool.
- Chronic giardiasis can be continual or episodic; diarrhea may not be prominent, but increased flatulence, sulfurous belching, and weight loss can occur.
- In some cases, disease can be severe, with malabsorption, growth retardation, dehydration, and/or extraintestinal manifestations (e.g., anterior uveitis, arthritis).

Diagnosis

Giardiasis can be diagnosed by parasite antigen detection in feces, by identification of cysts (oval, with four nuclei) or trophozoites (pear-shaped, flattened parasites with two nuclei and four pairs of flagella) in stool specimens, or by nucleic acid amplification tests. Given variability in cyst excretion, multiple samples may need to be examined.

TREATMENT

Giardiasis

- Cure rates with metronidazole (250 mg tid for 5 days) are >90%; tinidazole (2 g PO once) may be more effective. Nitazoxanide (500 mg bid for 3 days) is an alternative agent.
- If symptoms persist, continued infection should be documented before re-treatment, and possible sources of reinfection should be sought. Prolonged therapy with metronidazole (750 mg tid for 21 days) has been successful.

CRYPTOSPORIDIOSIS

Microbiology and Epidemiology

Cryptosporidial infections are caused by *Cryptosporidium hominis* and *C. parvum*.

- Oocysts are ingested and subsequently excyst, enter intestinal cells, and generate oocysts that are excreted in feces. The 50% infectious dose in immunocompetent individuals is ~132 oocysts.
- Person-to-person transmission of infectious oocysts can occur among close contacts and in day-care settings. Waterborne transmission is common. Oocysts are not killed by routine chlorination.

Clinical Manifestations

After an incubation period of ~1 week, pts may remain asymptomatic or develop watery, nonbloody diarrhea, occasionally with abdominal pain, nausea, anorexia, fever, and/or weight loss lasting 1–2 weeks. In immunocompromised hosts (particularly those with CD4⁺ T cell counts <100/μL), diarrhea can be profuse and chronic, resulting in severe dehydration, weight loss, and wasting; the biliary tract can be involved.

Diagnosis

On multiple days, fecal samples should be examined for oocysts (4–5 μm in diameter, smaller than most parasites). Although conventional stool examination for ova and parasites does not detect *Cryptosporidium*, modified acid-fast staining, direct immunofluorescent techniques, and EIAs can facilitate diagnosis.

TREATMENT

Cryptosporidiosis

- Nitazoxanide (500 mg bid for 3 days) is effective for immunocompetent pts but not for HIV-infected pts; improved immune status due to antiretroviral therapy can alleviate symptoms in the latter pts.
- In addition to antiprotozoal agents, supportive measures include replacement of fluid and electrolytes and use of antidiarrheal agents.

CYSTOISOSPORIASIS

Cystoisospora belli (formerly *Isospora belli*) infection is acquired by oocyst ingestion and is most common in tropical and subtropical countries. Acute infection

can begin suddenly with fever, abdominal pain, and watery, nonbloody diarrhea and can last for weeks or months. Eosinophilia may occur. Compromised (e.g., HIV-infected) pts may have chronic disease that resembles cryptosporidiosis. Detection of large oocysts (~25 μm) in stool by modified acid-fast staining confirms the diagnosis.

TREATMENT

Cystoisosporiasis

- Trimethoprim-sulfamethoxazole (TMP-SMX; 160/800 mg bid for 10 days) is effective in immunocompetent pts.
 - Pts with AIDS and GI symptoms that persist after the initial 10-day treatment should receive an additional 3 weeks of TMP-SMX (160/800 mg tid).
 - Pyrimethamine (50–75 mg/d) can be given to pts intolerant of TMP-SMX.
 - Pts with AIDS may need suppressive maintenance therapy (TMP-SMX, 160/800 mg 3 times per week) to prevent relapses.

■ CYCLOSPORIASIS

Cyclospora cayentanensis can be transmitted through water or food (e.g., basil, raspberries). Clinical manifestations include diarrhea, flulike symptoms, flatulence, and burping. Disease can be self-limited or can persist for >1 month. Diagnosis is made by detection of oocysts (spherical, 8–10 μm) in stool; targeted diagnostic studies must be specifically requested.

TREATMENT

Cyclosporiasis

TMP-SMX (160/800 mg bid for 7–10 days) is effective. Pts with AIDS may need suppressive maintenance therapy to prevent relapses.

INFLAMMATORY DIARRHEA

■ SALMONELLOSIS

Microbiology and Pathogenesis

Salmonellae are facultatively anaerobic gram-negative bacilli that cause infection when between 200 and 10^6 organisms are ingested.

- Conditions that reduce gastric acidity or intestinal integrity increase susceptibility to infection.
- Organisms penetrate the small-intestinal mucus layer and traverse the intestinal epithelium through M cells overlying Peyer's patches.
 - *S. Typhi* and *S. Paratyphi* survive within macrophages, then disseminate throughout the body via lymphatics, and ultimately colonize reticuloendothelial tissues.
 - Nontyphoidal salmonellae most commonly cause gastroenteritis, invading the large- and small-intestinal mucosa and resulting in massive PMN infiltration (as opposed to the mononuclear-cell infiltration seen with typhoid fever).

Epidemiology and Clinical Manifestations

Depending on the specific species, salmonellosis results in typhoid fever or gastroenteritis.

- *Typhoid (enteric) fever*: Typhoid fever is a systemic disease characterized by fever and abdominal pain and caused by dissemination of *S. Typhi* or *S. Paratyphi*, for which humans are the only hosts.
 - Disease results from ingestion of food or water contaminated by chronic carriers and is rare in developed nations. Worldwide, there are ~21–27 million cases, with 200,000–600,000 deaths annually.
 - After an incubation period of 5–21 days, prolonged fever (>75% of cases), headache (80%), chills (35–45%), anorexia (55%), and abdominal pain (30–40%) are common. Other signs and symptoms may include sweating, cough, malaise, arthralgias, nausea, vomiting, and diarrhea—or, less often, constipation.
 - Physical findings include *rose spots* (a faint, salmon-colored, blanching, maculopapular rash), hepatosplenomegaly, epistaxis, and relative bradycardia.
 - Intestinal perforation and/or GI hemorrhage can occur in the third and fourth weeks of illness; neurologic manifestations (e.g., meningitis, Guillain-Barré syndrome) occur in 2–40% of pts.
 - Long-term *Salmonella* carriage (i.e., for >1 year) in urine or stool develops in 2–5% of pts.
- *Nontyphoidal salmonellosis (NTS)*: Most commonly caused by *S. Typhimurium* or *S. Enteritidis*, NTS typically presents within 6–48 h of exposure as gastroenteritis (nausea, vomiting, nonbloody diarrhea, abdominal cramping, and fever) that lasts 3–7 days.
 - In the United States, NTS causes ~12 million illnesses annually.
 - Disease is acquired from multiple animal reservoirs. The main mode of transmission is via contaminated food products, such as eggs (*S. Enteritidis*), poultry, undercooked meat, dairy products, manufactured or processed foods, and fresh produce. Infection is also acquired during exposure to pets, especially reptiles.
 - Stool cultures remain positive for 4–5 weeks and—in rare cases of chronic carriage—for >1 year.
 - Bacteremia, usually due to *S. Choleraesuis* and *S. Dublin*, develops in 8% of pts; of these pts, 5–10% develop localized infections (e.g., hepatosplenic abscesses, meningitis, pneumonia, osteomyelitis).
 - Reactive arthritis can follow *Salmonella* gastroenteritis, particularly in persons with the HLA-B27 histocompatibility antigen.

Diagnosis

Positive cultures of blood, stool, or other specimens are required for diagnosis.

TREATMENT

Salmonellosis

- *Typhoid fever*: A fluoroquinolone (e.g., ciprofloxacin, 500 mg PO bid for 5–7 days) is most effective against susceptible organisms.
 - Enteric fever in regions with a high prevalence of reduced ciprofloxacin susceptibility and ciprofloxacin resistance (e.g., India, Nepal, and some locales in Africa) should be empirically treated with ceftriaxone (2 g/d IV for 10–14 days), azithromycin (1 g/d PO for 5 days), or high-dose ciprofloxacin (750 mg PO bid or 400 mg IV q8h for 10–14 days; only for isolates with reduced susceptibility to ciprofloxacin).
 - Dexamethasone may be of benefit in severe cases.
- *NTS*: Antibiotic treatment is not recommended in most cases as it does not shorten the duration of symptoms and is associated with increased rates of relapse, a prolonged carrier state, and adverse drug reactions.

- Antibiotic treatment may be required for infants ≤ 3 months of age; pts > 50 years of age with suspected atherosclerosis; pts with immunosuppression; pts with cardiac, valvular, or endovascular abnormalities; and pts with significant joint disease.
 - Fluoroquinolones or third-generation cephalosporins are given for 3–7 days or until defervescence (if the pt is immunocompetent) or for 1–2 weeks (if the pt is immunocompromised).
 - HIV-infected pts are at high risk for *Salmonella* bacteremia and should receive 4 weeks of oral fluoroquinolone therapy after 1–2 weeks of IV treatment. In cases of relapse, long-term suppression with a fluoroquinolone or TMP-SMX should be considered.
 - Pts with endovascular infections or endocarditis should receive 6 weeks of treatment with a third-generation cephalosporin.
-

■ CAMPYLOBACTERIOSIS

Microbiology

Campylobacters are motile, curved gram-negative rods that are a common bacterial cause of gastroenteritis in the United States. Most cases are caused by *Campylobacter jejuni*.

Epidemiology

Campylobacters are common commensals in the GI tract of many food animals and household pets. In developed countries, ingestion of contaminated poultry accounts for 30–70% of cases. Transmission to humans occurs via contact with or ingestion of raw or undercooked food products or direct contact with infected animals.

Clinical Manifestations

An incubation period of 2–4 days (range, 1–7 days) is followed by a prodrome of fever, headache, myalgia, and/or malaise. Within the next 12–48 h, diarrhea (with stools containing blood in ~10% of cases in adults), cramping abdominal pain, and fever develop.

- Most cases are self-limited, but illness persists for > 1 week in 10–20% of pts and may be confused with inflammatory bowel disease.
- Species other than *C. jejuni* (e.g., *C. fetus*) can cause a similar illness in normal hosts or prolonged relapsing systemic disease without a primary focus in immunocompromised pts.
 - The course may be fulminant, with bacterial seeding of many organs, particularly vascular sites.
 - Fetal death can result from infection in a pregnant pt.
- Three patterns of extraintestinal infection have been noted: (1) transient bacteremia in a normal host with enteritis (benign course, no specific treatment needed); (2) sustained bacteremia or focal infection in a normal host; and (3) sustained bacteremia or focal infection in a compromised host.
- Complications include reactive arthritis (particularly in persons with the HLA-B27 phenotype) and Guillain-Barré syndrome (in which campylobacters are associated with 20–40% of cases).

Diagnosis

The diagnosis is confirmed by cultures of stool, blood, or other specimens on special media and/or with selective techniques.

TREATMENT**Campylobacteriosis**

- Fluid and electrolyte replacement is the mainstay of therapy.
- Use of antimotility agents is not recommended, as they are associated with toxic megacolon.
- Antibiotic treatment (azithromycin, 500 mg PO daily for 3 days or 1000 mg PO given as a single dose) should be reserved for pts with high fever, bloody or severe diarrhea, persistence for >1 week, and worsening of symptoms. Fluoroquinolones are an alternative choice, although resistance to fluoroquinolones is increasing.

SHIGELLOSIS AND INFECTION WITH INTESTINAL PATHOGENIC *E. COLI***Microbiology and Epidemiology**

Shigellae are small, gram-negative, nonmotile bacilli that are very closely related to *E. coli*. The four most common *Shigella* serotypes are *S. dysenteriae* type 1, *S. flexneri*, *S. boydii*, and *S. sonnei* (which is more prevalent in the industrialized world). Humans are the major reservoir, but *Shigella* can be found in other higher primates. Shiga-toxin producing *E. coli* (STEC) and enterohemorrhagic *E. coli* (EHEC) can be found in cows.

- Person-to-person spread via the fecal–oral route is most common for *Shigella* (and is occasionally the route for STEC, EHEC, and Shiga toxin–producing enteroaggregative *E. coli* [ST-EAEC]); ingestion of contaminated food and water is the more common route of transmission of STEC/EHEC/STEAEC (and is occasionally the route for *Shigella*).
- The ability of as few as 100 organisms to cause infection helps explain the high rate of secondary household transmission.
- Shiga toxin and Shiga-like toxins produced by some strains of *E. coli* (including O157:H7) are important factors in disease severity. The toxins target endothelial cells and play a significant role in the microangiopathic complications of *Shigella* and *E. coli* infections, such as hemolytic–uremic syndrome (HUS; i.e., Coombs-negative hemolytic anemia, thrombocytopenia, and acute renal failure) and thrombotic thrombocytopenic purpura.
- An analysis of *Shigella* cases occurring in 1966–1997 revealed an annual incidence of 165 million cases (of which 69% affected children <5 years of age) with 0.5–1.1 million deaths; the mortality rates have decreased since then, but multidrug-resistant strains have emerged.

Clinical Manifestations

After an incubation period of 1–4 days, shigellosis evolves through three phases: watery diarrhea, dysentery (bloody mucopurulent stools), and the postinfectious phase.

- Most episodes resolve in 1 week without treatment; with appropriate treatment, recovery takes place within a few days, with no sequelae.
- Complications are largely intestinal (e.g., toxic megacolon, intestinal perforation, rectal prolapse) or metabolic (e.g., hypoglycemia, hyponatremia). Shiga toxin produced by *S. dysenteriae* type 1 is linked to HUS in developing countries but is rare in industrialized countries, where *E. coli* O157:H7 is a more common cause.

Diagnosis

Shigellosis is diagnosed directly by stool culture. STEC/EHEC infection is diagnosed by simultaneous culture (assaying for *E. coli* strains that do not ferment sorbitol, with subsequent serotyping for O157) and assay for the detection of Shiga toxin (which can rapidly detect non-O157 STEC/EHEC and sorbitol-fermenting strains of O157:H7).

TREATMENT**Shigellosis and Infection with STEC/EHEC/STEAEC**

- In the United States, because of the ready transmissibility of *Shigella*, antibiotics are recommended. Fluoroquinolones (e.g., ciprofloxacin, 500 mg bid) are effective, as are ceftriaxone, azithromycin, pivmecillinam, and some fifth-generation quinolones.
 - *S. dysenteriae* infection should be treated for 5 days and non-*dysenteriae* *Shigella* infection for 3 days.
 - Immunocompromised pts should receive 7–10 days of treatment.
- Antibiotic treatment for STEC/EHEC/ST-EAEC infections should be avoided, since antibiotics may increase the incidence of HUS.
- Rehydration usually is not needed; *Shigella* infection rarely causes significant dehydration. If required, rehydration should be oral, and nutrition should be started as soon as possible. Use of antimotility agents may prolong fever and increase the risk of HUS and toxic megacolon.

YERSINIOSIS**Microbiology and Clinical Manifestations**

Yersinia enterocolitica and *Y. pseudotuberculosis* are nonmotile gram-negative rods that cause enteritis or enterocolitis with self-limited diarrhea that lasts an average of 2 weeks as well as mesenteric adenitis (especially common with *Y. pseudotuberculosis*) and terminal ileitis (especially common with *Y. enterocolitica*), either of which can resemble acute appendicitis. Septicemia can occur in pts with chronic liver disease, malignancy, diabetes mellitus, and other underlying illnesses. Infection has been linked to reactive arthritis in HLA-B27-positive pts.

Diagnosis

Stool culture studies for *Yersinia* must be specifically requested and require the use of special media.

TREATMENT**Yersiniosis**

Antibiotics are not indicated for diarrhea caused by yersiniae; supportive measures suffice.

AMEBIASIS**Microbiology and Epidemiology**

Entamoeba histolytica, the cause of amebiasis, infects ~10% of the world's population and is the second most common cause of death from parasitic disease (after malaria). Infection follows ingestion of cysts from fecally contaminated water, food, or hands. Motile trophozoites are released from cysts in the small

intestine and then cause infection in the large bowel. Trophozoites may be shed in stool (in active dysentery) or encyst. Excreted cysts survive for weeks in a moist environment.

Clinical Manifestations

Most pts harboring *Entamoeba* species are asymptomatic, but some pts develop inflammatory colitis 2–6 weeks after ingestion of amebic cysts.

- Dysentery may develop, with daily passage of 10–12 small stools consisting mostly of blood and mucus. Fewer than 40% of pts have fever.
- Fulminant amebic colitis—characterized by more profuse diarrhea, severe abdominal pain with peritoneal signs, and fever—is more common among children.
- Liver abscess is the most common type of extraintestinal infection and can arise months (usually ≤ 5 months) after exposure to *E. histolytica*. Pts present with RUQ pain, fever, right-sided pleural effusion, and hepatic tenderness and typically do not have active colitis. The abscess can rupture through the diaphragm and metastasize elsewhere (e.g., lung, heart).

Diagnosis

Microscopic examination of three stool samples, often combined with serologic testing, remains the standard diagnostic approach.

- Up to 10% of pts with acute amebic liver abscess may have negative serologies; testing should be repeated in 1 week if clinical suspicion remains high.

TREATMENT

Amebiasis

- Tinidazole (2 g/d PO for 3 days) or metronidazole (750 mg PO or IV tid for 5–10 days) is recommended for amebic colitis and amebic liver abscess.
 - Within 3 days of treatment initiation, >90% of pts respond clinically.
 - Drainage of liver abscesses is rarely needed. Indications for aspiration include the need to rule out pyogenic abscess, a lack of response to treatment in 3–5 days, an imminent threat of liver-abscess rupture, or the need to prevent left-lobe abscess rupture into the pericardium.
- Pts with either colitis or liver abscesses should also receive a luminal agent to ensure eradication of the infection. Paromomycin (500 mg PO tid for 10 days) is the preferred agent; iodoquinol (650 mg PO tid for 20 days) is an alternative.

■ CLOSTRIDIODES DIFFICILE INFECTION (CDI)

Microbiology and Epidemiology

C. difficile is an obligately anaerobic, gram-positive, spore-forming bacillus and causes diarrheal illness that is most commonly acquired in the hospital. The disease is typically acquired in association with antimicrobial treatment; virtually all antibiotics carry a risk of CDI.

- After *C. difficile* colonizes the gut, its spores vegetate, multiply, and secrete toxin A (an enterotoxin) and toxin B (a cytotoxin), causing diarrhea and pseudomembranous colitis. The rate of fecal colonization is often $\geq 20\%$ among adult pts hospitalized for >2 weeks; in contrast, the rate is 1–3% among community residents.
- Spores can persist on environmental surfaces in the hospital for months and on the hands of hospital personnel who do not practice adequate hand hygiene.

- Rates and severity of CDI in the United States, Canada, and Europe have increased markedly since the year 2000. The epidemic NAP1/BI/027 strain accounts for much of the increase and is characterized by production of 16–23 times as much toxin A and toxin B as is documented for control strains, by the presence of a third toxin (binary toxin), and by high-level resistance to fluoroquinolones; however, the incidence of this particular epidemic strain has been decreasing over the past few years, with concomitant decreases in rates of CDI.

Clinical Manifestations

Most commonly, pts develop diarrhea, with stools that are not grossly bloody and are soft to watery, with a characteristic odor. Pts may have up to 20 bowel movements per day. Fever, abdominal pain, and leukocytosis are common.

- Constipation due to an adynamic ileus can occur. Unexplained leukocytosis ($\geq 15,000$ WBCs/ μL) in this setting should prompt evaluation for CDI. These pts are at high risk for complications such as toxic megacolon and sepsis.
- *C. difficile* diarrhea recurs after treatment in ~15–30% of cases.

Diagnosis

CDI is diagnosed in a pt with diarrhea (≥ 3 unformed stools per 24 h for ≥ 2 days) by detection of toxin-producing organism, toxin A, or toxin B in stool or identification of pseudomembranes in the colon.

- Most laboratory tests for toxin (e.g., EIAs) lack sensitivity, but repeat testing is not recommended. PCR assays are rapid, sensitive, and highly specific.
- Testing of asymptomatic pts (including a test of cure for those who have completed therapy) is not recommended.

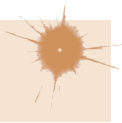
TREATMENT

C. difficile Infection

- **Primary CDI:** When feasible, discontinuation of ongoing antimicrobial treatment is an effective cure in 15–23% of cases. Prompt initiation of specific therapy is recommended.
 - Regardless of disease severity, vancomycin (125 mg qid PO for 10 days) or fidaxomicin (200 mg bid PO for 10 days) is recommended. Metronidazole is recommended only for mild to moderately severe disease when these other agents are not readily accessible.
- **Recurrent CDI:** The first recurrence should be treated the same as the initial episode.
 - For multiple recurrences, there is no standard treatment course. Options include an extended tapered vancomycin regimen (125 mg bid for 1 week, then daily for 1 week, then q2–3d for 2–8 weeks), administration of sequential therapy with vancomycin (125 mg qid for 10 days) followed by rifaximin (400 mg bid for 2 weeks), treatment with fidaxomicin, and fecal microbiota transplantation.
- **Fulminant CDI:** Medical management is complicated by ineffective delivery of oral antibiotics to the intestinal lumen in the setting of ileus. Vancomycin (given PO or via nasogastric tube and by retention enema) combined with IV metronidazole has been used with some success, as has IV tigecycline. Surgical colectomy can be life-saving.

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Sexually Transmitted and Reproductive Tract Infections

**GENERAL PRINCIPLES**

- Worldwide, most adults acquire at least one sexually transmitted infection (STI).
- Three factors determine the initial rate of spread of any STI within a population: rate of sexual exposure of susceptible to infectious people, efficiency of transmission per exposure, and duration of infectivity of those infected.
- STI care and management begin with risk assessment and proceed to clinical assessment, diagnostic testing or screening, syndrome-based treatment to cover the most likely causes, and prevention and control. The “4 C’s” of control are contact tracing, ensuring compliance with treatment, and counseling on risk reduction, including condom promotion and provision.

SPECIFIC SYNDROMES**■ URETHRITIS IN MEN****Microbiology and Epidemiology**

Most cases are caused by either *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. Other causative organisms include *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, HSV, and occasionally anaerobes (especially *Leptotrichia/Sneathia* species) involved in bacterial vaginitis. *Chlamydia* causes 30–40% of nongonococcal urethritis (NGU) cases. *M. genitalium* is the probable cause in many *Chlamydia*-negative cases of NGU.

Clinical Manifestations

Urethritis in men produces urethral discharge, dysuria, or both, usually without frequency of urination.

Diagnosis

Pts present with a mucopurulent urethral discharge that can usually be expressed by milking of the urethra; alternatively, a Gram’s-stained smear of an anterior urethral specimen containing ≥ 2 PMNs/1000 \times field confirms the diagnosis.

- Centrifuged sediment of the day’s first 20–30 mL of voided urine can be examined for inflammatory cells instead.
- *N. gonorrhoeae* can be presumptively identified if intracellular gram-negative diplococci are present in Gram’s-stained samples.
- Early-morning, first-voided urine should be used in “multiplex” nucleic acid amplification tests (NAATs) for *N. gonorrhoeae* and *C. trachomatis*.

TREATMENT**Urethritis in Men**

- Treatment should be given promptly, while test results are pending.
 - Unless these diseases have been excluded, gonorrhea is treated with a single dose of ceftriaxone (250 mg IM) plus azithromycin (1 g PO once), and *Chlamydia* infection is treated with azithromycin (1 g PO once) or doxycycline (100 mg bid for 7 days); the efficacy of azithromycin for treatment of *M. genitalium* is rapidly declining.
 - Sexual partners of the index case should receive the same treatment.

- *For recurrent symptoms:* With re-exposure, both pt and partner are re-treated. Without re-exposure, infection with *T. vaginalis* (with culture or NAATs of a urethral swab and early-morning, first-voided urine) or antibiotic-resistant *M. genitalium* or *Ureaplasma* should be considered; treatment with metronidazole, azithromycin (1 g PO once), or both is recommended, and the azithromycin component is especially important if this drug was not used for the primary episode. Moxifloxacin can be considered for treatment of refractory nongonococcal, nonchlamydial urethritis.

■ EPIDIDYMITIS

Microbiology

In sexually active men <35 years old, epididymitis is caused most frequently by *C. trachomatis* and less commonly by *N. gonorrhoeae*.

- In older men or after urinary tract instrumentation, urinary pathogens are most common.
- In men who practice insertive rectal intercourse, Enterobacteriaceae may be responsible.

Clinical Manifestations

Acute epididymitis—almost always unilateral—produces pain, swelling, and tenderness of the epididymis, with or without symptoms or signs of urethritis. Epididymitis must be differentiated from testicular torsion, tumor, and trauma. If symptoms persist after treatment, a testicular tumor or a chronic granulomatous disease (e.g., tuberculosis) should be considered.

TREATMENT

Epididymitis

- Ceftriaxone (250 mg IM once) followed by doxycycline (100 mg PO bid for 10 days) is effective for epididymitis due to *C. trachomatis* or *N. gonorrhoeae*.
- Oral cephalosporins and fluoroquinolones are no longer recommended because of increasing resistance in *N. gonorrhoeae*.
- If Enterobacteriaceae are suspected as the cause and such organisms are detected in a urine culture, levofloxacin (500 mg PO daily for 10 days) or ofloxacin (300 mg PO bid for 10 days) can be used.

■ URETHRITIS (THE URETHRAL SYNDROME) IN WOMEN

Microbiology and Clinical Manifestations

C. trachomatis, *N. gonorrhoeae*, and occasionally HSV cause symptomatic urethritis—known as the *urethral syndrome* in women—that is characterized by “internal” dysuria (usually without urinary urgency or frequency), pyuria, and an absence of *Escherichia coli* and other uropathogens at counts $\geq 10^2$ /mL in urine.

Diagnosis

Specific tests (e.g., NAATs of vaginal secretions collected with a swab) are used to evaluate for infection with *N. gonorrhoeae* or *C. trachomatis*.

TREATMENT

Urethritis (The Urethral Syndrome) in Women

See “Urethritis in Men,” above.

■ VULVOVAGINAL INFECTIONS

Microbiology

A variety of organisms are associated with vulvovaginal infections, including *N. gonorrhoeae* and *C. trachomatis* (particularly when they cause cervicitis), *T. vaginalis*, *Candida albicans*, *Gardnerella vaginalis*, and HSV.

Clinical Manifestations

Vulvovaginal infections encompass a wide array of specific conditions, each of which has different presenting symptoms.

- Unsolicited reporting of abnormal vaginal discharge suggests trichomoniasis or bacterial vaginosis (BV).
 - *Trichomoniasis* is characterized by vulvar irritation and a profuse white or yellow homogeneous vaginal discharge with a pH that is typically ≥ 5 .
 - *BV* is characterized by vaginal malodor and a slight to moderate increase in white or gray homogeneous vaginal discharge that uniformly coats the vaginal walls and typically has a pH > 4.5 .
 - Vaginal trichomoniasis and BV early in pregnancy are associated with premature onset of labor.
- Vulvar conditions such as genital herpes or vulvovaginal candidiasis can cause vulvar pruritus, burning, irritation, or lesions as well as external dysuria (as urine passes over the inflamed vulva or areas of epithelial disruption) or vulvar dyspareunia.

Diagnosis

Evaluation of vulvovaginal symptoms includes a pelvic examination (with a speculum examination) and diagnostic testing.

- Abnormal vaginal discharge is assessed for pH, a fishy odor after mixing with 10% KOH (BV), evidence on microscopy of motile trichomonads and/or clue cells of BV (vaginal epithelial cells coated with coccobacillary organisms) when the specimen is mixed with saline, or hyphae or pseudohyphae on microscopy when 10% KOH is added (vaginal candidiasis).
- A NAAT for *T. vaginalis* is available.

TREATMENT

Vulvovaginal Infections

- *Vulvovaginal candidiasis*: Miconazole (a single 100-mg vaginal suppository), clotrimazole (100-mg vaginal tablets daily for 3–7 days), or fluconazole (150 mg PO once) are all effective.
- *Trichomoniasis*: Metronidazole (2 g PO once or 500 mg PO bid for 7 days) is effective. Treatment of sexual partners with the same regimen reduces the risk of reinfection and is the standard of care.
- *BV*: Metronidazole (500 mg PO bid for 7 days), 2% clindamycin cream (one full applicator vaginally each night for 7 days), or 0.75% metronidazole gel (one full applicator vaginally daily for 5 days) is effective, but recurrence is common regardless of the regimen used.

■ MUCOPURULENT CERVICITIS

Microbiology

N. gonorrhoeae, *C. trachomatis*, and *M. genitalium* are the primary causes of mucopurulent cervicitis. Of note, NAATs for these pathogens, HSV, and *T. vaginalis* have been negative in nearly half of cases.

Clinical Manifestations

Mucopurulent cervicitis represents the “silent partner” of urethritis in men and results from inflammation of the columnar epithelium and subepithelium of the endocervix.

Diagnosis

Yellow mucopurulent discharge from the cervical os, with ≥ 20 PMNs/1000 \times field on Gram’s stain of cervical mucus, indicates endocervicitis. The presence of intracellular gram-negative diplococci on Gram’s stain of cervical mucus is specific but <50% sensitive for gonorrhea; thus NAATs for *N. gonorrhoeae* and *C. trachomatis* are always indicated.

TREATMENT

Mucopurulent Cervicitis

See “Urethritis in Men,” above.

■ PELVIC INFLAMMATORY DISEASE (PID)

Microbiology

The agents most often implicated in acute PID—infection that ascends from the cervix or vagina to the endometrium and/or fallopian tubes—include the primary causes of endocervicitis (e.g., *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*) and anaerobes associated with BV; other organisms (e.g., *Prevotella* spp., peptostreptococci, *E. coli*, *Haemophilus influenzae*, and group B streptococci) account for 25–33% of cases.

Epidemiology

In 2014, there were 51,000 visits to physicians’ offices for PID in the United States; there are ~70,000–100,000 hospitalizations related to PID annually.

- Risk factors for PID include cervicitis, BV, a history of salpingitis or recent vaginal douching, menstruation, and recent insertion of an intrauterine contraceptive device (IUD).
- Oral contraceptive pills decrease risk.

Clinical Manifestations

The presenting symptoms depend on the extent to which the infection has spread.

- *Endometritis*: Pts present with midline abdominal pain and abnormal vaginal bleeding. Lower-quadrant, adnexal, or cervical motion or abdominal rebound tenderness is less severe in women with endometritis alone than in women who also have salpingitis.
- *Salpingitis*: Symptoms evolve from mucopurulent cervicitis to endometritis and then to bilateral lower abdominal and pelvic pain caused by salpingitis. Nausea, vomiting, and increased abdominal tenderness may occur if peritonitis develops.
- *Perihepatitis (Fitz-Hugh–Curtis syndrome)*: 3–10% of women present with pleuritic upper abdominal pain and tenderness in the RUQ due to perihepatic inflammation. Most cases are due to chlamydial salpingitis.
- *Periappendicitis*: ~5% of pts can have appendiceal serositis without involvement of the intestinal mucosa as a result of gonococcal or chlamydial salpingitis.

Diagnosis

Speculum examination shows evidence of mucopurulent cervicitis in the majority of pts with gonococcal or chlamydial PID; cervical motion tenderness, uterine fundal tenderness, and/or abnormal adnexal tenderness also is usually present. Vaginal or endocervical swab specimens should be obtained for NAATs for *N. gonorrhoeae* and *C. trachomatis*.

TREATMENT

Pelvic Inflammatory Disease

- Empirical treatment for PID should be initiated in sexually active young women and in other women who are at risk for PID and who have pelvic or lower abdominal pain with no other explanation as well as cervical motion, uterine, or adnexal tenderness.
- Hospitalization should be considered when (1) the diagnosis is uncertain and surgical emergencies cannot be excluded, (2) the pt is pregnant, (3) pelvic abscess is suspected, (4) severe illness precludes outpatient management, (5) the pt has HIV infection, (6) the pt is unable to follow or tolerate an outpatient regimen, or (7) the pt has failed to respond to outpatient therapy.
- *Outpatient regimen:* Ceftriaxone (250 mg IM once) plus doxycycline (100 mg PO bid for 14 days) plus metronidazole (500 mg PO bid for 14 days) is effective. Women treated as outpatients should be clinically reevaluated within 72 h.
- *Parenteral regimens:* Parenteral treatment with the two regimens listed below should be continued for ≥ 48 h after clinical improvement. A 14-day course should be completed with doxycycline (100 mg PO bid); if the clindamycin-containing regimen is used, this drug can be given by the oral route (450 mg PO qid).
 - Cefotetan (2 g IV q12h) or cefoxitin (2 g IV q6h) plus doxycycline (100 mg IV/PO q12h)
 - Clindamycin (900 mg IV q8h) plus gentamicin (loading dose of 2.0 mg/kg IV/IM followed by 1.5 mg/kg q8h)
- Male sex partners should be evaluated and treated empirically for gonorrhea and chlamydial infection.

Prognosis

Late sequelae include infertility (11% after one episode of PID, 23% after two, and 54% after three or more); ectopic pregnancy (sevenfold increase in risk); chronic pelvic pain; and recurrent salpingitis.

■ ULCERATIVE GENITAL LESIONS

The most common etiologies for ulcerative genital lesions in the United States are genital herpes, syphilis, and chancroid. See [Table 86-1](#) and the sections on individual pathogens below for specific clinical manifestations. Pts with persistent genital ulcers that do not resolve with syndrome-based antimicrobial therapy should have their HIV serologic status assessed if such testing has not previously been performed. Immediate treatment (before all test results are available) is often appropriate to improve response, reduce transmission, and cover pts who might not return for follow-up visits.

■ PROCTITIS, PROCTOCOLITIS, ENTEROCOLITIS, AND ENTERITIS

Microbiology and Epidemiology

Acquisition of HSV, *N. gonorrhoeae*, or *C. trachomatis* (including lymphogranuloma venereum [LGV] strains of *C. trachomatis*) during receptive anorectal

TABLE 86-1 Clinical Features of Genital Ulcers

FEATURE	SYPHILIS	HERPES	CHANCROID	LYMPHOGRANULOMA VENEREUM	DONOVANOSIS
Incubation period	9–90 days	2–7 days	1–14 days	3 days–6 weeks	1–4 weeks (up to 6 months)
Early primary lesions	Papule	Vesicle	Pustule	Papule, pustule, or vesicle	Papule
No. of lesions	Usually one	Multiple	Usually multiple, may coalesce	Usually one; often not detected, despite lymphadenopathy	Variable
Diameter	5–15 mm	1–2 mm	Variable	2–10 mm	Variable
Edges	Sharply demarcated, elevated, round, or oval	Erythematous	Undermined, ragged, irregular	Elevated, round, or oval	Elevated, irregular
Depth	Superficial or deep	Superficial	Excavated	Superficial or deep	Elevated
Base	Smooth, nonpurulent, relatively nonvascular	Serous, erythematous, nonvascular	Purulent, bleeds easily	Variable, nonvascular	Red and velvety, bleeds readily
Induration	Firm	None	Soft	Occasionally firm	Firm
Pain	Uncommon	Frequently tender	Usually very tender	Variable	Uncommon
Lymphadenopathy	Firm, nontender, bilateral	Firm, tender, often bilateral with initial episode	Tender, may suppurate, loculated, usually unilateral	Tender, may suppurate, loculated, usually unilateral	None; pseudobuboes

Source: From Ballard RM, in Holmes KK et al (eds): *Sexually Transmitted Diseases*, 4th ed. New York, McGraw-Hill, 2008.

intercourse causes most cases of infectious proctitis in women and in men who have sex with men (MSM). Sexually acquired proctocolitis is most often due to *Campylobacter* or *Shigella* spp. In MSM without HIV infection, enteritis is often attributable to *Giardia lamblia*.

Clinical Manifestations

Anorectal pain and mucopurulent, bloody rectal discharge suggest proctitis or proctocolitis. Proctitis is more likely to cause tenesmus and constipation, whereas proctocolitis and enteritis more often cause diarrhea.

- HSV proctitis and LGV proctocolitis can cause severe pain, fever, and systemic manifestations.
- Sacral nerve root radiculopathy, with urinary retention or anal sphincter dysfunction, is associated with primary HSV infection.

Diagnosis

Pts should undergo anoscopy to examine the rectal mucosa and exudates and to obtain specimens for testing for rectal gonorrhea, chlamydial infection, herpes, and syphilis.

TREATMENT

Proctitis, Proctocolitis, Enterocolitis, Enteritis

- Pending test results, pts should receive empirical treatment for gonorrhea and chlamydial infection with ceftriaxone (250 mg IM once) followed by doxycycline (100 mg bid for 7 days); therapy for syphilis or herpes should be given as indicated.
- If LGV proctitis is proven or suspected, doxycycline (100 mg PO bid for 21 days) should be given.

INDIVIDUAL PATHOGENS

■ GONORRHEA

Microbiology

N. gonorrhoeae, the causative agent of gonorrhea, is a gram-negative, nonmotile, non-spore-forming organism that grows singly and in pairs (i.e., as diplococci).

Epidemiology

The ~450,000 cases reported in the United States in 2016 probably represent only half the true number of cases because of underreporting, self-treatment, and non-specific treatment without a laboratory diagnosis.

- More than 70% of reported cases in the United States occur in 15- to 24-year-old women and 20- to 29-year-old men.
- Gonorrhea is transmitted from males to females more efficiently than in the opposite direction, with 50–70% of women acquiring gonorrhea during a single unprotected sexual encounter with an infected man. Roughly two-thirds of all infected men are asymptomatic.
- Drug-resistant strains are widespread. Penicillin, ampicillin, and tetracycline are no longer reliable therapeutic agents, and oral cephalosporins and fluoroquinolones are no longer routinely recommended. In addition, strains highly resistant to ceftriaxone and azithromycin have been isolated in several countries, and combined resistance may contribute to the failure of the currently recommended dual therapy (see below).

Clinical Manifestations

Except in disseminated disease, the sites of infection typically reflect areas involved in sexual contact.

- *Urethritis* and *cervicitis* have an incubation period of 2–7 days and ~10 days, respectively. See above for details.
- *Anorectal gonorrhea* can cause acute proctitis in women (due to the spread of cervical exudate to the rectum) and MSM.
- *Pharyngeal gonorrhea* is usually mild or asymptomatic and results from oral-genital sexual exposure (typically fellatio). Pharyngeal infection almost always coexists with genital infection, resolves spontaneously, and is rarely transmitted to sexual contacts.
- *Ocular gonorrhea* is typically caused by autoinoculation and presents as a markedly swollen eyelid, hyperemia, chemosis, and profuse purulent discharge.
- *Gonorrhea in pregnancy* can have serious consequences for both the mother and the infant.
 - Salpingitis and PID are associated with fetal loss.
 - Third-trimester disease can cause prolonged rupture of membranes, premature delivery, chorioamnionitis, funisitis, and neonatal sepsis.
 - *Ophthalmia neonatorum*, the most common form of gonorrhea among neonates, is preventable by prophylactic ophthalmic ointments (e.g., containing erythromycin or tetracycline), but treatment requires systemic antibiotics.
- *Gonococcal arthritis* results from dissemination of organisms due to gonococcal bacteremia. Pts present during a bacteremic phase (relatively uncommon) or with suppurative arthritis involving one or two joints (most commonly the knees, wrists, ankles, and elbows), with tenosynovitis and skin lesions. Menstruation and complement deficiencies of the membrane attack complex (C5–C9) are risk factors for disseminated disease.

Diagnosis

NAATs, culture, and microscopic examination (for intracellular diplococci) of urogenital samples are used to diagnose gonorrhea; NAAT of urine samples is most sensitive. A single culture of endocervical discharge has a sensitivity of 80–90%.

TREATMENT

Gonorrhea

See [Table 86-2](#).

■ INFECTIONS WITH *CHLAMYDIA TRACHOMATIS*

Microbiology

C. trachomatis organisms are obligate intracellular bacteria that are divided into two biovars: trachoma and LGV. The trachoma biovar causes ocular trachoma and urogenital infections; the LGV biovar causes LGV.

Epidemiology

The World Health Organization (WHO) estimates that >106.4 million cases of *C. trachomatis* infection occur annually worldwide; it is the most prevalent of all bacterial STIs. The estimated 2–3 million cases per year that occur in the United States make *C. trachomatis* infection the most commonly reported infectious disease in this country.

TABLE 86-2 Recommended Treatment for Gonococcal Infections: Adapted from the 2015 Guidelines of the Centers for Disease Control and Prevention

DIAGNOSIS	TREATMENT OF CHOICE ^a
Uncomplicated gonococcal infection of the cervix, urethra, pharynx ^b , or rectum	
First-line regimen	Ceftriaxone (250 mg IM, single dose) plus Azithromycin (1 g PO, single dose)
Alternative regimens ^c	Cefixime (400 mg PO, single dose) or ceftizoxime (500 mg IM, single dose) or cefotaxime (500 mg IM, single dose) or spectinomycin (2 g IM, single dose) ^{d,e} or cefotetan (1 g IM, single dose) plus probenecid (1 g PO, single dose) ^d or cefoxitin (2 g IM, single dose) plus probenecid (1 g PO, single dose) ^d plus Azithromycin (1 g PO, single dose)
Epididymitis	Ceftriaxone (250 mg IM once) followed by doxycycline (100 mg PO bid for 10 days)
Pelvic inflammatory disease	See text on specific syndrome
Gonococcal conjunctivitis in an adult	Ceftriaxone (1 g IM, single dose) ^f
Ophthalmia neonatorum ^g	Ceftriaxone (25–50 mg/kg IV, single dose, not to exceed 125 mg)
Disseminated gonococcal infection ^h	
Initial therapy ⁱ	
Pt tolerant of β -lactam drugs	Ceftriaxone (1 g IM or IV q24h; recommended) or cefotaxime (1 g IV q8h) or ceftizoxime (1 g IV q8h)
Pts allergic to β -lactam drugs	Spectinomycin (2 g IM q12h) ^d
Continuation therapy ^j	Cefixime (400 mg PO bid)
Meningitis or endocarditis	See text for specific recommendations ^j

^aTrue failure of treatment with a recommended regimen is rare and should prompt an evaluation for reinfection, infection with a drug-resistant strain, or an alternative diagnosis.

^bCeftriaxone and azithromycin are the only agents recommended for treatment of pharyngeal infection.

^cSee text for follow-up of persons with infection who are treated with alternative regimens.

^dSpectinomycin, cefotetan, and cefoxitin, which are alternative agents, currently are unavailable or in short supply in the United States.

^eSpectinomycin may be ineffective for the treatment of pharyngeal gonorrhea.

^fPlus lavage of the infected eye with saline solution (once).

^gProphylactic regimens are discussed in the text.

^hHospitalization is indicated if the diagnosis is uncertain, if the pt has frank arthritis with an effusion, or if the pt cannot be relied on to adhere to treatment.

ⁱAll initial regimens should also include azithromycin (1 g PO, single dose) and should be continued for 24–48 h after clinical improvement begins, at which time the switch may be made to an oral agent (e.g., cefixime) if antimicrobial susceptibility can be documented by culture of the causative organism. If no organism is isolated and the diagnosis is secure, then treatment with ceftriaxone should be continued for at least 1 week.

^jHospitalization is indicated to exclude suspected meningitis or endocarditis.

Clinical Manifestations

Of pts with *C. trachomatis* genital infections, 80–90% of women and >50% of men lack symptoms; other pts have very mild symptoms.

- Urethritis, epididymitis, cervicitis, salpingitis, PID, and proctitis are all discussed above.
- Reactive arthritis (conjunctivitis, urethritis or cervicitis, arthritis, and mucocutaneous lesions) occurs in 1–2% of NGU cases, many of which are due to *C. trachomatis*. More than 80% of pts have the HLA-B27 phenotype.
- LGV is an invasive, systemic STI that—in heterosexual individuals—presents most commonly as painful inguinal lymphadenopathy beginning 2–6 weeks after presumed exposure. Progressive periadenitis results in fluctuant, suppurative nodes with development of multiple draining fistulas. Spontaneous resolution occurs after several months. See Table 86-1 for additional clinical details.

Diagnosis

NAATs of urine or urogenital swabs are the diagnostic tests of choice. Serologic testing may be helpful in the diagnosis of LGV and neonatal pneumonia caused by *C. trachomatis*, but it is not useful in diagnosing uncomplicated urogenital infections.

TREATMENT**Infections with *Chlamydia Trachomatis***

- See “Specific Syndromes,” above.
- LGV should be treated with doxycycline (100 mg PO bid) or erythromycin base (500 mg PO qid) for at least 3 weeks.

■ INFECTIONS DUE TO MYCOPLASMAS**Microbiology and Epidemiology**

Mycoplasmas are the smallest free-living organisms known and lack a cell wall. *Mycoplasma hominis*, *M. genitalium*, *Ureaplasma parvum*, and *U. urealyticum* cause urogenital tract disease. These organisms are commonly present in the vagina of asymptomatic women.

Clinical Manifestations

Ureaplasmas are a common cause of *Chlamydia*-negative NGU. *M. hominis* and *M. genitalium* are associated with PID. *M. hominis* is implicated in 5–10% of cases of postpartum or postabortal fever.

Diagnosis

PCR is most commonly used for detection of urogenital mycoplasmas; culture is possible but can be done primarily at reference laboratories. Serologic testing is not helpful.

TREATMENT**Infections Due to Mycoplasmas**

Recommendations for treatment of NGU and PID listed above are appropriate for genital mycoplasmas.

■ SYPHILIS

Microbiology and Epidemiology

Treponema pallidum subspecies *pallidum*—the cause of venereal syphilis—is a thin, spiral organism with a cell body surrounded by a trilaminar cytoplasmic membrane. Humans are the only natural host, and the organism cannot be cultured in vitro.

- Cases are acquired by sexual contact with infectious lesions (chancre, mucous patch, skin rash, condyloma latum); nonsexual acquisition through close personal contact, infection in utero, blood transfusion, and organ transplantation is less common.
- There are ~11 million new infections per year worldwide.
 - In the United States, 31,575 cases were reported in 2000.
 - The reported cases of primary and secondary syphilis combined (which better indicate disease activity) increased from <6000 in 2000 to 23,872 in 2015, primarily affecting MSM, ~50% of whom were co-infected with HIV.
- The transmission rate of syphilis to sexual contacts is high: many exposed individuals already have developed manifestations of syphilis when they are first seen, and ~30% of contacts who are asymptomatic 30 days after exposure will later develop syphilis if not treated. These figures underscore the importance of treating all recently exposed sexual contacts.

Pathogenesis

T. pallidum penetrates intact mucous membranes or microscopic abrasions and, within hours, enters lymphatics and the bloodstream to produce systemic infection and metastatic foci. After a median incubation period of ~21 days, the primary lesion (chancre) appears at the site of inoculation, persists for 4–6 weeks, and then heals spontaneously. Generalized parenchymal, constitutional, mucosal, and cutaneous manifestations of secondary syphilis appear 6–12 weeks later despite high antibody titers, subsiding in 2–6 weeks. After a latent period, one-third of untreated pts eventually develop tertiary disease (syphilitic gummas, cardiovascular disease, neurologic disease).

Clinical Manifestations

Syphilis progresses through three phases with distinct clinical presentations: primary syphilis, secondary syphilis (followed by a period of latent infection), and tertiary syphilis. Syphilis can also be transmitted from mother to fetus.

- *Primary syphilis*: A chancre at the site of inoculation (penis, rectum, or anal canal, mouth, cervix, labia) is characteristic but often goes unnoticed. See Table 86-1 for clinical details. Regional adenopathy can persist long after the chancre heals.
- *Secondary syphilis*: The protean manifestations of the secondary stage usually include mucocutaneous or cutaneous lesions and generalized nontender lymphadenopathy.
 - Skin lesions can be subtle but are often pale red or pink, nonpruritic macules that are widely distributed over the trunk and extremities, including the palms and soles.
 - In moist intertriginous areas, papules can enlarge and erode to produce broad, highly infectious lesions called *condylomata lata*.
 - Superficial mucosal erosions (*mucous patches*) and constitutional symptoms (e.g., sore throat, fever, malaise) can occur.
 - Less common findings include hepatitis, nephropathy, arthritis, and ocular findings (e.g., optic neuritis, anterior uveitis, iritis).

- *Latent syphilis*: Pts without clinical manifestations but with positive syphilis serology have latent disease. *Early latent* syphilis is limited to the first year after infection, whereas *late latent* syphilis is defined as that of ≥ 1 year's (or unknown) duration.
- *Tertiary syphilis*: The classic forms of tertiary syphilis include neurosyphilis, cardiovascular syphilis, and gummas.
 - *Neurosyphilis* represents a continuum, with asymptomatic disease occurring early after infection and potentially progressing to general paresis and tabes dorsalis. Symptomatic disease has three main presentations, all of which are now rare (except in pts with advanced HIV infection). *Meningeal* syphilis presents as headache, nausea, vomiting, neck stiffness, cranial nerve involvement, seizures, and changes in mental status within 1 year of infection. *Meningovascular* syphilis presents up to 10 years after infection as a subacute encephalitic prodrome followed by a gradually progressive vascular syndrome. *Parenchymatous* involvement presents at 20 years for general paresis and 25–30 years for tabes dorsalis. A general mnemonic for paresis is *personality, affect, reflexes* (hyperactive), *eye* (Argyll Robertson pupils, which react to accommodation but not to light), *sensorium* (illusions, delusions, hallucinations), *intellect* (decrease in recent memory and orientation, judgment, calculations, insight), and *speech*. Tabes dorsalis is a demyelination of posterior columns, dorsal roots, and dorsal root ganglia, including ataxia; foot drop; paresthesia; bladder disturbances; impotence; areflexia; and loss of position, deep pain, and temperature sensations.
 - *Cardiovascular syphilis* develops in ~10% of untreated pts 10–40 years after infection. Endarteritis obliterans of the vasa vasorum providing the blood supply to large vessels results in aortitis, aortic regurgitation, saccular aneurysm, and coronary ostial stenosis.
 - *Gummas* are usually solitary lesions showing granulomatous inflammation with central necrosis. Common sites include the skin and skeletal system; however, any organ (including the brain) may be involved.
- *Congenital syphilis*: Syphilis can be transmitted throughout pregnancy, but fetal disease does not become manifest until after the fourth month of gestation. All pregnant women should be tested for syphilis early in pregnancy.

Diagnosis

Serologic tests—both lipoidal (so-called nontreponemal) and treponemal—are the mainstays of diagnosis; changes in antibody titers can also be used to monitor response to therapy.

- Lipoidal serologic tests that measure IgG and IgM antibodies to a cardiolipin-lecithin-cholesterol antigen complex (e.g., rapid plasma reagin [RPR], Venereal Disease Research Laboratory [VDRL]) are recommended for screening or for quantitation of serum antibody. After therapy for early syphilis, a persistent fall in titer by ≥ 4 -fold is considered an adequate response.
- Treponemal tests, including the agglutination assay (e.g., the TPPA test), the fluorescent treponemal antibody-adsorbed (FTA-ABS) test, and treponemal enzyme or chemiluminescence immunoassays (EIAs/CIAs), are used to confirm the results of lipoidal tests and should not be used as screening tests because of high false-positive rates. Results remain positive even after successful treatment.
- LP is recommended for pts with syphilis and neurologic signs or symptoms, an RPR or VDRL titer $\geq 1:32$, active tertiary syphilis, or suspected treatment failure and for HIV-infected pts with a CD4⁺ T cell count $< 350/\mu\text{L}$.
 - CSF exam demonstrates mononuclear pleocytosis (> 5 WBCs/ μL) and increased protein levels (> 45 mg/dL). A positive CSF VDRL test is specific

but not sensitive; an unabsorbed FTA test is sensitive but not specific. A negative unabsorbed FTA test excludes neurosyphilis.

- Pts with syphilis should be evaluated for HIV disease.

TREATMENT

Syphilis

- See [Table 86-3](#) for treatment recommendations.
- The Jarisch-Herxheimer reaction is a dramatic reaction to treatment that is most common with initiation of therapy for primary (~50% of pts) or secondary (~90%) syphilis. The reaction is associated with fever, chills, myalgias,

TABLE 86-3 Recommendations for the Treatment of Syphilis^a

STAGE OF SYPHILIS	PTS WITHOUT PENICILLIN ALLERGY	PTS WITH CONFIRMED PENICILLIN ALLERGY
Primary, secondary, or early latent	CSF normal or not examined: Penicillin G benzathine (single dose of 2.4 mU IM) CSF abnormal: Treat as neurosyphilis.	CSF normal or not examined: Tetracycline HCl (500 mg PO qid) or doxycycline (100 mg PO bid) for 2 weeks CSF abnormal: Treat as neurosyphilis.
Late latent (or latent of unknown duration), cardiovascular, or benign tertiary	CSF normal or not examined: Penicillin G benzathine (2.4 mU IM weekly for 3 weeks) CSF abnormal: Treat as neurosyphilis.	CSF normal and pt not infected with HIV: Tetracycline HCl (500 mg PO qid) or doxycycline (100 mg PO bid) for 4 weeks CSF normal and pt infected with HIV: Desensitize and treat with penicillin if compliance cannot be assured. CSF abnormal: Treat as neurosyphilis.
Neurosyphilis (asymptomatic or symptomatic)	Aqueous crystalline penicillin G (18–24 mU/d IV, given as 3–4 mU q4h or continuous infusion) for 10–14 days or Aqueous procaine penicillin G (2.4 mU/d IM) plus oral probenecid (500 mg qid), both for 10–14 days	Desensitize and treat with penicillin.
Syphilis in pregnancy	According to stage	Desensitize and treat with penicillin.

^aSee text for indications for CSF examination.

Abbreviations: CSF, cerebrospinal fluid; mU, million units.

Source: Adapted from the 2015 Sexually Transmitted Diseases Treatment Guidelines from the Centers for Disease Control and Prevention.

tachycardia, headache, tachypnea, and vasodilation. Symptoms subside within 12–24 h without treatment.

- Response to treatment should be monitored by determination of RPR or VDRL titers at 6 and 12 months in primary and secondary syphilis and at 6, 12, and 24 months in tertiary or latent syphilis.
 - HIV-infected pts should undergo repeat serologic testing at 3, 6, 9, 12, and 24 months, irrespective of the stage of syphilis.
 - Re-treatment should be considered if serologic responses are not adequate (a persistent antibody fall by ≥ 4 -fold) or if clinical signs persist or recur. For these pts, CSF should be examined, with treatment for neurosyphilis if CSF is abnormal and treatment for late latent syphilis if CSF is normal.
 - In treated neurosyphilis, CSF cell counts should be monitored every 6 months until normal. In adequately treated HIV-uninfected pts, an elevated CSF cell count falls to normal in 3–12 months.

■ HERPES SIMPLEX VIRUS GENITAL INFECTIONS

Microbiology and Epidemiology

HSV is a linear, double-strand DNA virus, with two subtypes (HSV-1 and HSV-2).

- Exposure to HSV at mucosal surfaces or abraded skin sites permits viral entry into cells of the epidermis and dermis, viral replication, entry into neuronal cells, and centrifugal spread throughout the body.
- More than 90% of adults have antibodies to HSV-1 by age 40; 15–20% of the U.S. population has antibodies to HSV-2, with a higher prevalence in low-income countries.
- Unrecognized carriage of HSV-2 and frequent asymptomatic reactivations of virus from the genital tract foster the continued spread of HSV disease.
- Genital lesions caused by HSV-1 have lower recurrence rates in the first year (~55%) than those caused by HSV-2 (~90%).

Clinical Manifestations

See Table 86-1 for clinical details. First episodes of genital herpes due to HSV-1 and HSV-2 present similarly and can be associated with fever, headache, malaise, and myalgias. More than 80% of women with primary genital herpes have cervical or urethral involvement. Local symptoms include pain, dysuria, vaginal and urethral discharge, and tender inguinal lymphadenopathy.

Diagnosis

HSV DNA detection by PCR is the most sensitive laboratory technique and is recommended for laboratory confirmation of HSV infection. HSV culture is indicated when antiviral sensitivity testing is required. Staining of scrapings from the base of the lesion with Wright's, Giemsa's (Tzanck preparation), or Papanicolaou's stain to detect giant cells or intranuclear inclusions is well described, but most clinicians are not skilled in these techniques, which furthermore do not differentiate between HSV and VZV.

TREATMENT

HSV Genital Infections

- *First episodes:* Oral acyclovir (400 mg tid), valacyclovir (1 g bid), or famciclovir (250 mg bid) for 7–14 days is effective.

- *Symptomatic recurrent episodes:* Oral acyclovir (800 mg tid for 2 days), valacyclovir (500 mg bid for 3 days), or famciclovir (750 or 1000 mg bid for 1 day, 1500 mg once, or 500 mg stat followed by 250 mg q12h for 3 days) effectively shortens lesion duration.
- *Suppression of recurrent episodes:* Oral acyclovir (400–800 mg bid) or valacyclovir (500 mg qd) is given. Pts with >9 episodes per year should take valacyclovir (1 g qd or 500 mg bid) or famciclovir (250–500 mg bid). Daily valacyclovir appears to be more effective at reducing subclinical shedding than daily famciclovir.

■ CHANCROID

H. ducreyi is the etiologic agent of chancroid, an STI characterized by genital ulceration and inguinal adenitis, and non-sexually transmitted cutaneous ulcers. In addition to being a cause of morbidity in itself, chancroid increases the efficiency of transmission of and the degree of susceptibility to HIV infection. See Table 86-1 for clinical details. Culture of *H. ducreyi* from the lesion confirms the diagnosis; PCR is starting to become available. In the setting of a compatible clinical presentation (including one or more painful genital ulcers) and negative tests for syphilis and HSV infection, a probable diagnosis of chancroid can be made.

TREATMENT

Chancroid

- Regimens recommended by the Centers for Disease Control and Prevention (CDC) include azithromycin (1 g PO once), ciprofloxacin (500 mg PO bid for 3 days), ceftriaxone (250 mg IM once), and erythromycin base (500 mg tid for 1 week).
- Sexual partners within 10 days preceding the pt's onset of symptoms should be identified and treated, regardless of symptom status.

■ DONOVANOSIS

Microbiology and Epidemiology

Also known as *granuloma inguinale*, donovanosis is caused by *K. granulomatis*. The infection is endemic in Papua New Guinea, parts of southern Africa, India, the Caribbean, French Guyana, Brazil, and Aboriginal communities in Australia; few cases are reported in the United States.

Clinical Manifestations

See Table 86-1 for clinical details. Four types of lesions have been described: (1) the classic ulcerogranulomatous lesion that bleeds readily when touched; (2) a hypertrophic or verrucous ulcer with a raised irregular edge; (3) a necrotic, offensive-smelling ulcer causing tissue destruction; and (4) a sclerotic or cicatricial lesion with fibrous and scar tissue. The genitals are affected in 90% of pts and the inguinal region in 10%.

Diagnosis

Diagnosis is often based on identification of typical Donovan bodies (gram-negative intracytoplasmic cysts filled with deeply staining bodies that may have a safety-pin appearance) within large mononuclear cells in smears from lesions or biopsy specimens. PCR is also available.

TREATMENT**Donovanosis**

Pts should be treated with azithromycin (1 g on day 1, then 500 mg qd for 7 days or 1 g weekly for 4 weeks); alternative therapy consists of a 14-day course of doxycycline (100 mg bid), trimethoprim-sulfamethoxazole (960 mg bid), erythromycin (500 mg qid), or tetracycline (500 mg qid). If any of the 14-day treatment regimens are chosen, the pt should be monitored until lesions have healed completely.

■ HUMAN PAPILLOMAVIRUS (HPV) INFECTIONS**Microbiology**

Papillomaviruses are nonenveloped, double-strand DNA viruses. More than 125 HPV types are recognized, and individual types are associated with specific clinical manifestations. For example, HPV types 16 and 18 have been most strongly associated with cervical and anal cancers, causing 70–85% and ~90% of cases, respectively; HPV types 6 and 11 cause genital warts (*condylomata acuminata*).

Epidemiology and Clinical Manifestations

- HPV is transmitted by sexual intercourse, by oral sex, and possibly by touching of a partner's genitalia.
- The interval between initial infection and the diagnosis of HPV-associated cancer may be >20 years, with HIV infection accelerating this progression.
- The physical appearance of warts varies with their anatomic location, ranging from soft, whitish papules on the vulva to raised, keratotic, pigmented plaques on the penis.
- Although subclinical cervical HPV infections are common, pts with cervical cancer present early on with eroded carcinomas that bleed easily; more advanced carcinomas present as ulcerated lesions or as an exophytic lesion.
- Anal cancer typically presents as rectal bleeding and pain or a mass sensation, although 20% of pts are asymptomatic.

Diagnosis

Most visible warts are diagnosed correctly by history and physical examination alone. The primary method used for cervical cancer screening is cytology via Pap smear every 3 years beginning at age 21; for women ≥30 years of age, the testing interval can be lengthened to 5 years if co-testing for HPV DNA is negative. Anal screening is accepted for high-risk groups.

TREATMENT**Human Papillomavirus Infections**

- Many lesions resolve spontaneously. Current treatment is not completely effective, and some agents have significant side effects.
- Provider-administered therapy can include cryotherapy, surgical excision, intralesionally administered IFN, or laser surgery.
- Pt-administered therapy consists of imiquimod (5% or 3.75% cream applied 3 times per week for up to 16 weeks). Podophyllotoxin (0.05% solution or gel or 0.15% cream) and sinecatechins (15% ointment) are occasionally used for external genital warts, but other modalities are more effective and better tolerated.

Prevention

A quadrivalent vaccine (Gardasil, Merck) containing HPV types 6, 11, 16, and 18; a nine-valent vaccine (Gardasil-9, Merck) containing HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and a bivalent vaccine (Cervarix, GlaxoSmithKline) containing HPV types 16 and 18 are available. The CDC recommends vaccine administration to all boys and girls at 11–12 years of age as well as to young men and women 13–26 years of age who have not previously completed the full series.

87

Infections of the Skin, Soft Tissues, Joints, and Bones

**SKIN AND SOFT TISSUE INFECTIONS**

Skin and soft tissue infections are diagnosed principally by a careful history (e.g., temporal progression, travel, animal exposure, bites, trauma, underlying medical conditions) and physical examination (appearance of lesions and distribution). Treatment of common skin infections is summarized in [Table 87-1](#); parenteral treatment is usually given until

TABLE 87-1 Treatment of Common Infections of the Skin

DIAGNOSIS/ CONDITION	PRIMARY TREATMENT	ALTERNATIVE TREATMENT	SEE ALSO CHAP(S).
Animal bite (prophylaxis or early infection) ^a	Amoxicillin–clavulanate (875/125 mg PO bid)	Doxycycline (100 mg PO bid)	29
Animal bite ^a (established infection)	Ampicillin–sulbactam (1.5–3 g IV q6h)	Clindamycin (600–900 mg IV q8h) plus Ciprofloxacin (400 mg IV q12h) or cefoxitin (2 g IV q6h)	29
Bacillary angiomatosis	Erythromycin (500 mg PO qid)	Doxycycline (100 mg PO bid)	94
Herpes simplex (primary genital)	Acyclovir (400 mg PO tid for 10 days)	Famciclovir (250 mg PO tid for 5–10 days) or valacyclovir (1000 mg PO bid for 10 days)	102
Herpes zoster (immunocompetent host >50 years of age)	Acyclovir (800 mg PO 5 times daily for 7–10 days)	Famciclovir (500 mg PO tid for 7–10 days) or valacyclovir (1000 mg PO tid for 7 days)	102
Cellulitis (staphylococcal or streptococcal ^{b,c})	Nafcillin or oxacillin (2 g IV q4–6h)	Cefazolin (1–2 g q8h) or ampicillin/sulbactam (1.5–3 g IV q6h) or erythromycin (0.5–1 g IV q6h) or clindamycin (600–900 mg IV q8h)	89, 90

(Continued)

TABLE 87-1 Treatment of Common Infections of the Skin (Continued)

DIAGNOSIS/ CONDITION	PRIMARY TREATMENT	ALTERNATIVE TREATMENT	SEE ALSO CHAP(S).
MRSA skin infection ^d	Vancomycin (1 g IV q12h)	Linezolid (600 mg IV q12h)	89
Necrotizing fasciitis (group A streptococcal ^b)	Clindamycin (600–900 mg IV q6–8h) plus penicillin G (4 million units IV q4h)	Clindamycin (600–900 mg IV q6–8h) plus a cephalosporin (first- or second-generation)	90
Necrotizing fasciitis (mixed aerobes and anaerobes)	Ampicillin (2 g IV q4h) plus clindamycin (600–900 mg IV q6–8h) plus ciprofloxacin (400 mg IV q6–8h)	Vancomycin (1 g IV q6h) plus metronidazole (500 mg IV q6h) plus ciprofloxacin (400 mg IV q6–8h)	95
Gas gangrene	Clindamycin (600–900 mg IV q6–8h) plus penicillin G (4 million units IV q4–6h)	Clindamycin (600–900 mg IV q6–8h) plus ceftiofur (2 g IV q6h)	95

^a*Pasteurella multocida*, a species commonly associated with both dog and cat bites, is resistant to cephalexin, dicloxacillin, clindamycin, and erythromycin. *Eikenella corrodens*, a bacterium commonly associated with human bites, is resistant to clindamycin, penicillinase-resistant penicillins, and metronidazole but is sensitive to trimethoprim-sulfamethoxazole and fluoroquinolones.

^bThe frequency of erythromycin resistance in group A *Streptococcus* is currently ~5% in the United States but has reached 70–100% in some other countries. Most, but not all, erythromycin-resistant group A streptococci are susceptible to clindamycin. Approximately 90% of *Staphylococcus aureus* strains are sensitive to clindamycin, but resistance—both intrinsic and inducible—is increasing.

^cSevere hospital-acquired *S. aureus* infections or community-acquired *S. aureus* infections that are not responding to the β -lactam antibiotics recommended in this table may be caused by methicillin-resistant strains, requiring a switch to vancomycin, daptomycin, or linezolid.

^dSome strains of methicillin-resistant *S. aureus* (MRSA) remain sensitive to tetracycline and trimethoprim-sulfamethoxazole. Daptomycin (4 mg/kg IV q24h) or tigecycline (100-mg loading dose followed by 50 mg IV q12h) is an alternative treatment for MRSA.

systemic signs and symptoms have improved. Types of skin lesions include the following:

1. *Vesicles*: due to proliferation of organisms, usually viruses, within the epidermis (e.g., VZV, HSV, coxsackievirus, poxviruses, *Rickettsia akari*)
2. *Bullae*: caused by toxin-producing organisms. Different entities affect different skin levels. For example, staphylococcal scalded-skin syndrome and toxic epidermal necrolysis cause cleavage of the stratum corneum and the stratum germinativum, respectively. Bullae are also seen in necrotizing fasciitis, gas gangrene, and *Vibrio vulnificus* infections.
3. *Crusted lesions*: Impetigo caused by either *Streptococcus pyogenes* (impetigo contagiosa) or *Staphylococcus aureus* (bullous impetigo) usually starts with a bullous phase before development of a golden-brown crust. Crusted lesions are also seen in some systemic fungal infections, dermatophytic infections,

and cutaneous mycobacterial infections. It is important to recognize impetigo contagiosa because of its relation to poststreptococcal glomerulonephritis.

4. **Folliculitis:** Localized infection of hair follicles is usually due to *S. aureus*. "Hot-tub folliculitis" is a diffuse condition caused by *Pseudomonas aeruginosa*. Freshwater avian schistosomes cause an allergic reaction after penetrating hair follicles, resulting in "swimmer's itch."
5. **Papular and nodular lesions:** Raised lesions of the skin occur in many different forms and can be caused by *Bartonella henselae* (cat-scratch disease and bacillary angiomatosis), *Treponema pallidum*, human papillomavirus, mycobacteria, and helminths.
6. **Ulcers, with or without eschars:** can be caused by cutaneous anthrax, ulceroglandular tularemia, plague, and mycobacterial infection. Ulcerated lesions on the genitals can be caused by chancroid (painful) or syphilis (painless).
7. **Erysipelas:** abrupt onset of fiery red swelling of the face or extremities, with well-defined indurated margins, intense pain, and rapid progression. *S. pyogenes* is the exclusive cause.

■ CELLULITIS

- **Pathogenesis:** Bacteria gain access to the epidermis through breaks in the skin, whether accidental (e.g., cuts, scratches, burns) or iatrogenic (e.g., surgical incisions, IV catheters). The expanding area of erythema may be due to extracellular toxins and/or the host immune response rather than to increasing bacterial numbers.
- **Microbiology:** Etiologic causes include commensal flora (e.g., *S. aureus*, *S. pyogenes*) or a wide variety of exogenous flora. With the latter, a thorough history and epidemiologic data may help identify the cause.
 - Examples of exogenous bacteria causing cellulitis include the following: *Pasteurella multocida* after a cat or dog bite; *Capnocytophaga canimorsus* after a dog bite; *Eikenella corrodens* after a human bite; *P. aeruginosa* in association with ecthyma gangrenosum in neutropenic pts, a penetrating injury (stepping on a nail), or hot-tub folliculitis; *Aeromonas hydrophila* after a laceration sustained in fresh water; or *Erysipelothrix rhusiopathiae* after contact with domestic swine and fish.
- **Clinical manifestations:** This acute inflammatory condition of the skin is characterized by localized pain, erythema, swelling, and heat.
 - Cellulitis due to *S. aureus* often spreads from a central site of localized infection, such as an abscess or an infected foreign body, and is referred to as *purulent* cellulitis.
 - *S. pyogenes* can cause *nonpurulent* cellulitis, a rapidly spreading, diffuse process that often occurs with fever and lymphangitis.
- **Diagnosis:** If there is drainage, an open wound, or an obvious portal of entry, Gram's staining and culture may identify the etiology. Aspiration or biopsy of the leading edge of the cellulitic tissue yields a diagnosis in only 20% of cases.
- **Treatment:** See Table 87-1.

■ NECROTIZING FASCIITIS

- **Pathogenesis:** Infection, either apparent or inapparent, results from a breach in integrity of the skin or mucous membrane barriers and can be associated with malignancy, a diverticulum, hemorrhoids, or an anal fissure.
 - In the case of infections with no obvious portal of entry, transient bacteremia is thought to seed sites of nonpenetrating trauma (e.g., bruise, muscle strain).
 - Infection spreads to the deep fascia and along fascial planes through venous channels and lymphatics.

- **Microbiology:** Necrotizing fasciitis is caused by *S. pyogenes*, mixed aerobic and anaerobic bacteria, or *Clostridium perfringens*; methicillin-resistant *S. aureus* (MRSA) strains that produce the Panton-Valentine leukocidin have also been reported as an occasional cause.
- **Clinical manifestations:** The timing of cutaneous manifestations (e.g., violaceous bullae; friable, necrotic skin; induration; brawny edema) depends on whether the infection began superficially (rapid onset) or in deeper structures (slower onset).
 - Early in the disease course, severe pain and unexplained fever may be the only findings.
 - Thrombosis of blood vessels in dermal papillae leads to ischemia of peripheral nerves and anesthesia of the affected area.
 - In later stages, pts appear toxic and often develop shock and multiorgan failure.
- **Diagnosis:** Diagnosis is based on clinical presentation. Other findings may include gas detected in deep tissues by imaging studies (particularly with clostridial species but rarely with *S. pyogenes*) and markedly elevated serum CPK levels (in the case of concomitant myositis).
- **Treatment:** Emergent surgical exploration to deep fascia and muscle, with removal of necrotic tissue, is essential. Table 87-1 provides recommendations for adjunctive antibiotic therapy.

■ MYOSITIS/MYONECROSIS

- **Clinical manifestations and microbiology:** Infections involving the muscle have differing manifestations, depending on the etiology.
 - *Myositis:* can be caused by bacteria (clostridia, streptococci), viruses (influenza virus, dengue virus, coxsackievirus), or parasites (*Trichinella*, *Taenia solium*, *Toxoplasma*). This condition usually manifests with myalgias, but pain can be severe in coxsackievirus, *Trichinella*, and bacterial infections.
 - *Pyomyositis:* a localized muscle infection usually due to *S. aureus*, common in tropical areas, and typically with no known portal of entry
 - *Myonecrosis:* can be caused by clostridial species (*C. perfringens*, *C. septicum*, *C. histolyticum*, *C. sordellii*) or by mixed aerobic and anaerobic bacteria. Myonecrosis is usually related to trauma; however, spontaneous gangrene—usually due to *C. septicum*—can occur in pts with neutropenia, GI malignancy, or diverticulosis. Myonecrosis of the uterus, typically due to *C. sordellii*, occurs in women after spontaneous or medically induced abortion and in healthy postpartum women; infection is rapidly and almost uniformly fatal as there are few or no localizing clinical findings.
- **Diagnosis and treatment**
 - Emergent surgical intervention to visualize deep structures, obtain materials for culture and sensitivity testing, remove necrotic tissue, and reduce compartment pressure is both diagnostic and therapeutic.
 - Empirical antibiotic treatment should target likely etiologies—e.g., vancomycin (1 g IV q12h) for pyomyositis and ampicillin/sulbactam (2–3 g IV q6h) for mixed aerobic–anaerobic infections.
 - For treatment of clostridial myonecrosis (gas gangrene), see Table 87-1.

INFECTIOUS ARTHRITIS

- **Pathogenesis:** Joints become infected by hematogenous seeding (the most common route), by spread from a contiguous site of infection, or by direct inoculation (e.g., during trauma or surgery). Acute bacterial infection can rapidly destroy articular cartilage as a result of increased intraarticular pressure and the elicited host immune response.

- **Microbiology:** The predominant etiologic agents differ with the pt's age; *S. aureus* is the most common nongonococcal isolate in adults of all ages.
 - In children <5 years old, *S. aureus*, *S. pyogenes*, and *Kingella kingae* predominate.
 - In young adults, *Neisseria gonorrhoeae* is the most common etiology.
 - In adults, *S. aureus* predominates, but gram-negative bacilli, pneumococci, and β -hemolytic streptococci are involved in one-third of cases in older adults.
 - Other causes of septic arthritis include *Borrelia burgdorferi* (Lyme disease), tuberculosis and other mycobacterial infections, fungal infections (e.g., coccidioidomycosis, histoplasmosis), and viral infections (e.g., rubella, mumps, hepatitis B, parvovirus infection).
- **Epidemiology and clinical manifestations:** The risk factors and presentation differ depending on whether *N. gonorrhoeae* is the cause.
 - **Nongonococcal bacterial arthritis:** Risk is increased in pts with rheumatoid arthritis, diabetes mellitus, glucocorticoid therapy, hemodialysis, malignancy, and IV drug use.
 - In 90% of pts, one joint is involved—most often the knee, which is followed in frequency by the hip, shoulder, wrist, and elbow; IV drug users often have spinal, sacroiliac, or sternoclavicular joint involvement.
 - Pts have moderate to severe pain, effusion, decreased range of motion, and fever.
 - **Gonococcal arthritis:** Women are 2–3 times more likely than men to develop disseminated gonococcal infection (DGI) and arthritis, particularly during menses and during pregnancy (see [Chap. 86](#)).
 - DGI presents as fever, chills, rash, and articular symptoms (migratory arthritis). The cutaneous and articular findings result from an immune reaction to circulating gonococci and immune-complex deposition; thus synovial fluid cultures are consistently negative.
 - In true gonococcal arthritis (which always follows DGI), a single joint (hip, knee, ankle, or wrist) is usually involved.
 - **Prosthetic joint infections:** complicate 1–4% of joint replacements and are usually acquired intra- or perioperatively.
 - Acute presentations are seen in infections caused by *S. aureus*, pyogenic streptococci, and enteric bacilli.
 - Indolent presentations are seen in infections caused by coagulase-negative staphylococci and diphtheroids.
 - **Reactive arthritis:** follows ~1% of cases of nongonococcal urethritis and 2% of enteric infections (e.g., *Yersinia enterocolitica*, *Shigella flexneri*, *Campylobacter jejuni*, *Salmonella* spp.). Only a minority of pts have the other classic findings associated with reactive arthritis, including urethritis, conjunctivitis, uveitis, oral ulcers, and rash.
- **Diagnosis:** If there is concern about joint infection, examination of synovial fluid from the affected joint is essential. There is considerable overlap in the cell counts due to different etiologies, but synovial fluid culture and examination for crystals (to rule out gout and pseudogout) can help narrow the diagnosis.
 - **Normal synovial fluid** contains <180 cells/ μ L (mostly mononuclear). *Acute bacterial infection* of joints results in synovial fluid cell counts averaging 100,000/ μ L (range, 25,000–250,000/ μ L), with >90% PMNs. Synovial fluid in *gonococcal arthritis* contains >50,000 cells/ μ L, but results of Gram's staining are usually negative, and cultures of synovial fluid are positive in <40% of cases. Other mucosal sites should be cultured to diagnose gonorrhea. Pts with septic arthritis due to *mycobacteria* or *fungi* can have 10,000–30,000 cells/

μL in synovial fluid, with 50–70% PMNs. Synovial fluid cell counts in *non-infectious inflammatory arthritides* are typically <30,000–50,000/ μL .

- Gram's staining of synovial fluid should be performed. Injection directly into blood culture bottles can increase the yield of synovial fluid cultures.
- Blood cultures are positive in 50–70% of cases due to *S. aureus* but are less commonly positive with other organisms.
- Plain radiographs show soft tissue swelling, joint space widening, and displacement of tissue planes by distended capsule. Narrowing of the joint space and bony erosions suggest advanced disease.

TREATMENT

Infectious Arthritis

- Drainage of pus and necrotic debris is needed to cure infection and to prevent destruction of cartilage, postinfectious degenerative arthritis, and joint deformity or instability.
- A third-generation cephalosporin (cefotaxime, 1 g IV q8h; or ceftriaxone, 1–2 g IV q24h) provides adequate empirical coverage for most community-acquired infections in adults when smears demonstrate no organisms. Vancomycin (1 g IV q12h) should be used to cover the possibility of MRSA when there are gram-positive cocci on the smear.
 - In IV drug users and other susceptible pts, treatment for gram-negative organisms such as *P. aeruginosa* should be considered.
 - If a pathogen is identified by culture, treatment should be adjusted according to the specific bacterial organism and its antibiotic susceptibility.
- Treatment for *S. aureus* should be given for 4 weeks, that for enteric gram-negative bacilli for 3–4 weeks, and that for pneumococci or streptococci for 2 weeks.
- Treatment for gonococcal arthritis should commence with ceftriaxone (1 g/d) until improvement; depending on the susceptibilities of the isolate, the 7-day course can be completed with an oral fluoroquinolone (e.g., ciprofloxacin, 500 mg bid) or amoxicillin (500 mg tid). Azithromycin (1 g PO) should be given as a single dose to treat chlamydial co-infection.
- Prosthetic joint infections should be treated with surgery and high-dose IV antibiotics for 4–6 weeks. The prosthesis often has to be removed; to avoid joint removal, antibiotic suppression of infection may be tried. A 3- to 6-month course of ciprofloxacin and rifampin has been successful in *S. aureus* prosthetic-joint infections of relatively short duration, although prospective trials confirming the efficacy of this regimen are still needed.

OSTEOMYELITIS

- **Pathogenesis and epidemiology:** Osteomyelitis cases can be classified by pathogenesis, duration of infection, location of infection, and whether prosthetic material is present. Osteomyelitis is typically caused by hematogenous spread, spread from a contiguous site following surgery, and/or secondary infection in the setting of vascular insufficiency or concomitant neuropathy (e.g., in diabetes). The most common primary foci of infection are the urinary tract, skin and soft tissues, intravascular catheterization sites, and the endocardium. Hematogenous osteomyelitis in adults most commonly results in vertebral infection, with 6.5 cases/100,000 at ages >70 years.

- **Microbiology:** Irrespective of the anatomic location involved, *S. aureus* is the most common cause, accounting for ~40–50% of cases.
 - Gram-negative bacilli account for 10–20% of cases.
- **Clinical manifestations:** Pts generally have a febrile illness, with localized pain and tenderness. A history of surgery or trauma in the affected region—even in the remote past—should raise suspicion.
- **Diagnosis**
 - Radiographic studies and occasionally invasive sampling of lesions are needed to confirm the diagnosis.
 - Blood cultures are positive in 30–78% of cases, with lower rates if the pt has previously received antibiotics.
 - CT and especially MRI scans offer increased sensitivity in detecting osteomyelitis.
- **Treatment**
 - **Table 87-2** lists antibiotics for the treatment of osteomyelitis in the absence of implants.
 - The optimal route and duration of therapy remain controversial, but a 6-week course of IV therapy is usually recommended for acute osteomyelitis. If evidence indicates clinical efficacy of an oral antibiotic to which the organism is susceptible and if the pt has normal intestinal function (without vomiting), a transition from IV to PO therapy can be considered.
 - Serial measurements of inflammatory markers (ESR, C-reactive protein) can serve as surrogates for response to treatment in some infections (particularly those due to *S. aureus*).
 - Surgical intervention is usually required in chronic osteomyelitis and cases involving prosthetic implants.

TABLE 87-2 Antibiotic Therapy for Osteomyelitis in Adults Without Implants^a

MICROORGANISM	ANTIMICROBIAL AGENT (DOSE, ^b ROUTE)
<i>Staphylococcus</i> spp.	
Methicillin-susceptible	Nafcillin or oxacillin ^c (2 g IV q6h) followed by Rifampin (300–450 mg PO q12h) plus levofloxacin (750 mg PO q24h or 500 mg PO q12h)
Methicillin-resistant	Vancomycin ^d (15 mg/kg IV q12h) or daptomycin (>6–8 mg/kg IV q24h) followed by Rifampin (300–450 mg PO q12h) plus Levofloxacin (750 mg PO q24h or 500 mg PO q12h) or TMP-SMX ^e (1 double-strength tablet PO q8h) or fusidic acid (500 mg PO q8h)
<i>Streptococcus</i> spp.	Penicillin G ^c (5 million units IV q6h) or ceftriaxone (2 g IV q24h)
Enterobacteriaceae	Ciprofloxacin (750 mg PO q24h)
Quinolone-susceptible	Imipenem (500 mg IV q6h)
Quinolone-resistant ^f	

(Continued)

TABLE 87-2 Antibiotic Therapy for Osteomyelitis in Adults Without Implants^a (Continued)

MICROORGANISM	ANTIMICROBIAL AGENT (DOSE, ^b ROUTE)
<i>Pseudomonas aeruginosa</i>	Cefepime or ceftazidime (2 g IV q8h) plus an aminoglycoside ^g or Piperacillin-tazobactam (4.5 g IV q8h) plus an aminoglycoside ^g for 2–4 weeks followed by Ciprofloxacin ^h (750 mg PO q12h)
Anaerobes	Clindamycin (600 mg IV q6–8h) for 2–4 weeks followed by Clindamycin ⁱ (300 mg PO q6h)

^aUnless otherwise indicated, the total duration of antimicrobial treatment is generally 6 weeks.

^bAll dosages are for adults with normal renal function.

^cWhen the pt has delayed-type penicillin hypersensitivity, cefuroxime (1.5 g IV q6–8h) can be administered. When the pt has immediate-type penicillin hypersensitivity, the penicillin should be replaced by vancomycin (1 g IV q12h).

^dTarget vancomycin trough level: 15–20 µg/mL.

^eTrimethoprim-sulfamethoxazole. A double-strength tablet contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole.

^fIncluding isolates producing extended-spectrum β-lactamase.

^gThe need for addition of an aminoglycoside has not yet been proven. However, this addition may decrease the risk of emergence of resistance to the β-lactam.

^hThe rationale for starting ciprofloxacin treatment only after pretreatment with a β-lactam is the increased risk of emergence of quinolone resistance in the presence of a heavy bacterial load.

ⁱAlternatively, penicillin G (5 million units IV q6h) or ceftriaxone (2 g IV q24h) can be used against gram-positive anaerobes (e.g., *Propionibacterium acnes*), and metronidazole (500 mg IV/PO q8h) can be used against gram-negative anaerobes (e.g., *Bacteroides* spp.).

Source: From Zimmerli W: Vertebral Osteomyelitis. *N Engl J Med* 362:1022, 2010. © Massachusetts Medical Society. Reprinted with permission.

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Pneumococcal Infections

**MICROBIOLOGY**

- *Streptococcus pneumoniae* (the pneumococcus) is a gram-positive coccus that grows in chains, causes α-hemolysis on blood agar, is bile soluble, and is sensitive to optochin.
- Nearly every clinical isolate has a polysaccharide capsule that protects the bacteria from phagocytosis in the absence of type-specific antibody; 98 distinct capsules have been identified.

EPIDEMIOLOGY

- In industrialized countries, children serve as the major vectors of pneumococcal transmission: 20–50% of children <5 years old have asymptomatic nasopharyngeal colonization with *S. pneumoniae* (compared with 5–15% of young and middle-aged adults). Colonization rates for all age groups are even higher in low-income countries.

- Rates of pneumococcal disease vary by season (higher in winter), gender (higher for males), and underlying medical condition (e.g., higher with splenic dysfunction; chronic respiratory, heart, liver, and kidney disease; immunosuppression).
- The introduction and widespread use (in industrialized countries) of pneumococcal conjugate vaccines have led to dramatic changes in the epidemiology of invasive pneumococcal disease; rates have fallen by >75% among infants and children in the United States.

■ PATHOGENESIS

- Nasopharyngeal colonization can persist for many months, resulting in the development of type-specific serum IgG that ultimately leads to pneumococcal clearance from the nasopharynx. Accordingly, pneumococcal disease is usually associated with recent acquisition of a new colonizing serotype.
- Once the nasopharynx has been colonized, the bacteria spread either via the bloodstream to distant sites (e.g., brain, joint, bones) or locally to contiguous areas (e.g., middle ear, lungs).
- Local cytokine production, particularly after intercurrent viral infections, facilitates pneumococcal adherence. Bacterial factors such as peptidoglycan and teichoic acid induce inflammation, result in characteristic pathology, and permit bacterial invasion.

■ CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical manifestations of pneumococcal disease depend on the site of infection and the duration of illness.

Pneumonia

Pneumococcal pneumonia—the most common serious pneumococcal syndrome—is difficult to distinguish from pneumonia of other etiologies on the basis of clinical findings.

- Pts often present with fever, abrupt-onset cough and dyspnea, and sputum production.
 - Pts may also have pleuritic chest pain, shaking chills, or myalgias.
 - Among the elderly, presenting signs and symptoms may be less specific, with confusion and malaise but without fever or cough.
- On physical examination, adults may have tachypnea (>30 breaths/min) and tachycardia, crackles on chest auscultation, and dullness to percussion of the chest in areas of consolidation.
 - In some cases, hypotension, bronchial breathing, a pleural rub, or cyanosis may be present.
 - Upper abdominal pain may be present if the diaphragmatic pleura is involved.
- Pneumococcal pneumonia is generally diagnosed by Gram's staining and culture of sputum.
 - While culture results are awaited, chest x-rays—which classically demonstrate lobar or segmental consolidation—may provide some adjunctive evidence, although they may be normal early in the course of illness or with dehydration.
 - Blood cultures are positive for pneumococci in 5–20% of cases.
 - Leukocytosis (>15,000/ μ L) is common; leukopenia is documented in <10% of cases and is associated with a fatal outcome.
 - A positive pneumococcal urinary antigen test has a high predictive value among adults, in whom the prevalence of nasopharyngeal colonization is low.
 - Co-infection with viral or other bacterial pathogens is common.

- Empyema occurs in <5% of cases and should be considered when a pleural effusion is accompanied by fever and leukocytosis after 4–5 days of appropriate antibiotic therapy. Pleural fluid with frank pus, bacteria, or a pH of ≤ 7.1 indicates empyema and requires aggressive drainage.

Meningitis

S. pneumoniae is among the most common causes of meningitis in both adults and children. Pneumococcal meningitis can present as a primary syndrome or as a complication of other pneumococcal conditions (e.g., otitis media, infected skull fracture, bacteremia). Pneumococcal meningitis is clinically indistinguishable from pyogenic meningitis of other etiologies.

- Pts have fever, headache, neck stiffness, photophobia, and occasionally seizures and confusion.
- On examination, pts have a toxic appearance, altered consciousness, bradycardia, and hypertension (indicative of increased intracranial pressure). Kernig's or Brudzinski's sign or cranial nerve palsies (particularly of the third and sixth cranial nerves) are noted in a small fraction of adult pts.
- Diagnosis of pneumococcal meningitis relies on examination of CSF, which reveals an elevated protein level, an elevated WBC count, and a reduced glucose concentration. The etiologic agent can be specifically identified by culture, antigen testing, or PCR. A blood culture positive for *S. pneumoniae* in conjunction with clinical manifestations of meningitis is also considered confirmatory.

Other Invasive Syndromes

S. pneumoniae can affect virtually any body site and cause invasive syndromes, including bacteremia, osteomyelitis, septic arthritis, endocarditis, pericarditis, and peritonitis. The essential diagnostic approach is collection of fluid from the site of infection by sterile technique and examination by Gram's staining, culture, and—when relevant—capsular antigen assay or PCR. Hemolytic–uremic syndrome can complicate invasive pneumococcal disease.

Noninvasive Syndromes

Sinusitis and otitis media are the two most common noninvasive syndromes caused by *S. pneumoniae*; the latter is the most common pneumococcal syndrome and most often affects young children. See [Chap. 59](#) for more detail.

TREATMENT

Pneumococcal Infections

- Penicillin remains the cornerstone of treatment for pneumococcal disease caused by sensitive isolates, with daily doses ranging from 50,000 U/kg for minor infections to 300,000 U/kg for meningitis. Macrolides and cephalosporins are alternatives for penicillin-allergic pts but otherwise offer no advantage over penicillin.
- Strains resistant to β -lactam drugs are increasing in frequency, and antibiotic recommendations are typically based on the MIC against the isolate, particularly in cases of invasive disease.

PNEMONIA

- *Outpatient treatment:* Amoxicillin (1 g PO q8h) is effective for virtually all cases of pneumococcal pneumonia. Fluoroquinolones (e.g., levofloxacin, 500–750 mg/d; or moxifloxacin, 400 mg/d) are also highly likely to be effective in the United States, although they are much more expensive than amoxicillin. Clindamycin and azithromycin are effective in 90% and 80% of cases, respectively.

- *Inpatient treatment:* For pts with noncritical illness, β -lactam antibiotics are recommended—e.g., penicillin (3–4 mU IV q4h) or ceftriaxone (1 g IV q12–24h). For pts with critical illness, vancomycin may be added, with its use reviewed once susceptibility data are available.
- *Treatment duration:* The optimal duration of treatment is uncertain, but continuation of antibiotics for at least 5 days after the pt becomes afebrile seems prudent.

MENINGITIS

- Because of the increased prevalence of resistant pneumococci, first-line therapy should include vancomycin (1 g IV q12h) plus a third-generation cephalosporin (ceftriaxone, 2 g IV q12h; or cefotaxime, 2 g IV q4h). Rifampin (600 mg/d) can be substituted for the third-generation cephalosporin in pts hypersensitive to β -lactam agents.
- The antibiotic regimen should be adjusted appropriately once susceptibility data are available. If the isolate is resistant to penicillin and cephalosporins, both vancomycin and the cephalosporin should be continued.
- A repeat LP should be considered after 48 h if the organism is not sensitive to penicillin and information on cephalosporin sensitivity is not yet available, if the pt's clinical condition does not improve or deteriorates, or if the pt has received dexamethasone, which may compromise clinical evaluation.
- In adults with community-acquired bacterial meningitis, dexamethasone should be given before or in conjunction with the first dose of antibiotics, as glucocorticoids have been demonstrated to significantly reduce rates of mortality, severe hearing loss, and neurologic sequelae. The data are not clear as to whether this practice is also beneficial in children.

PREVENTION

- All persons ≥ 65 years old and those 2–64 years old who are at increased risk of pneumococcal disease should receive the 23-valent pneumococcal polysaccharide vaccine (PPSV23), which contains capsular polysaccharide from the 23 most prevalent serotypes of *S. pneumoniae*.
 - Persons > 2 years old with continuing increased risk should be revaccinated every 5 years.
 - Persons whose only indication for vaccination is an age of ≥ 65 years do not need to be revaccinated.
- The efficacy of PPSV23 is controversial; it appears to be effective against invasive pneumococcal disease but less effective or ineffective against nonbacteremic pneumococcal pneumonia.
- The duration of protection conferred by PPSV23 is ~ 5 years.
- The poor response of infants and young children to pneumococcal polysaccharide vaccines prompted the development of pneumococcal conjugate vaccines. In the United States, the current recommendation is for infants to be routinely vaccinated with the conjugate vaccine PCV13, which contains the 13 serotypes most associated with disease.
 - Immunocompromised children and adults and all adults ≥ 65 years of age should receive PCV13 prior to receiving PPSV23.
 - Pneumococcal conjugate vaccines are highly effective at providing protection against vaccine-serotype invasive pneumococcal disease, pneumonia, otitis media, nasopharyngeal colonization, and all-cause mortality.
 - In the United States, there has been a $> 90\%$ reduction in vaccine-serotype invasive pneumococcal disease among the whole population, including indirect protection of unvaccinated adults.

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Staphylococcal Infections

**■ MICROBIOLOGY**

Staphylococci are gram-positive cocci that form grapelike clusters on Gram's stain; they are catalase positive (unlike streptococci), nonmotile, aerobic, and facultatively anaerobic. *Staphylococcus aureus*, which is distinguished from other staphylococci by its production of coagulase, is the most virulent species.

■ S. AUREUS INFECTIONS**Epidemiology**

S. aureus is an important cause of community-acquired infections and a leading cause of nosocomial infections.

- *S. aureus* is a component of the normal human flora, most frequently colonizing the anterior nares and oropharynx but also colonizing the skin (particularly damaged skin), vagina, axilla, and perineum. These sites of colonization are reservoirs for future infection.
- Of healthy persons, 20–40% are transiently colonized with *S. aureus*, while ~10% are persistently colonized. The rate is elevated among insulin-dependent diabetic pts, HIV-infected persons, injection drug users, hemodialysis pts, and pts with skin damage.
- Transmission of *S. aureus* most frequently results from direct personal contact, although spread via respiratory secretions has been reported. Most *S. aureus* infections are caused by a strain that is already a component of the pt's own microbiota.
- Methicillin-resistant *S. aureus* (MRSA) is common in hospitals, and its prevalence is increasing dramatically in community settings among individuals without prior medical exposure.
 - In the United States, strain USA300 (defined by pulsed-field gel electrophoresis) causes most community-acquired MRSA (CA-MRSA) infections and can cause severe disease in immunocompetent pts.

Pathogenesis

S. aureus is a pyogenic pathogen known for its capacity to induce abscess formation.

- *Invasive disease*: For invasive *S. aureus* infection to occur, some or all of the following steps are necessary:
 - *Colonization/inoculation*: Bacteria colonize tissue surfaces, particularly the anterior nares, or are inoculated directly into tissue—e.g., as a result of minor abrasions or via IV access catheters.
 - *Invasion*: Bacteria replicate at the site of infection and elaborate enzymes that facilitate survival and local spread. CA-MRSA isolates that produce the Pantan-Valentine leukocidin toxin have been linked to more serious infections.
 - *Evasion of host defense mechanisms*: *S. aureus* possesses an antiphagocytic polysaccharide microcapsule that facilitates evasion of host defenses and plays a role in abscess formation. Organisms can survive intracellularly and then cause recrudescence infections when conditions are suitable.
 - *Metastatic spread*: *S. aureus* can survive in PMNs and may use these cells to spread to and seed other tissue sites.
- *Toxin-mediated disease*: *S. aureus* produces three types of toxin: cytotoxins, pyrogenic toxin superantigens, and exfoliative toxins.

- Antitoxin antibodies are protective against toxin-mediated staphylococcal illness.
- Enterotoxins and toxic shock syndrome toxin 1 (TSST-1) act as “superantigens” or T-cell mitogens and cause the release of large amounts of inflammatory mediators, producing multisystem disease that includes fever, rash, and hypotension.

Diagnosis

S. aureus infections are readily diagnosed by Gram’s stain and microscopic examination of infected tissue.

- Routine cultures of infected material usually yield positive results, and blood cultures are sometimes positive even when infections are localized to extravascular sites.
- PCR assays have been developed for rapid testing and are increasingly being used.

Clinical Syndromes

SKIN AND SOFT TISSUE INFECTIONS *S. aureus* causes a variety of cutaneous infections characterized by pus-containing blisters, many of which can also be caused by group A streptococci and other streptococcal species. Predisposing factors include skin disease (e.g., eczema), skin damage (e.g., minor trauma), injections, and poor personal hygiene.

- Infections can be superficial (e.g., folliculitis, cellulitis, impetigo) or deep and painful (e.g., furuncles, carbuncles, hidradenitis suppurativa).
 - Carbuncles (often located in the lower neck) are more severe and painful than furuncles (boils that extend from hair follicles) and are due to coalesced lesions extending to deeper SC tissue.
 - Mastitis in lactating women can range from superficial cellulitis to abscess.

MUSCULOSKELETAL INFECTIONS See [Chap. 87](#) for additional details.

- *S. aureus* is among the most common causes of *osteomyelitis* arising from either hematogenous dissemination or contiguous spread from a soft tissue site (e.g., diabetic or vascular ulcers).
 - Hematogenous osteomyelitis in adults is often vertebral and occurs in pts with endocarditis, pts undergoing hemodialysis, injection drug users, or diabetics. Intense back pain and fever can occur, but infections may also be clinically occult.
 - *Epidural abscess* is a serious complication that can present as trouble voiding or walking or as radicular pain in addition to symptoms of osteomyelitis; neurologic compromise can develop in the absence of timely treatment, which often requires surgical intervention.
 - Osteomyelitis from contiguous soft-tissue infections is suggested by exposure of bone, a draining fistulous tract, failure to heal, or continued drainage.
- *S. aureus* is the most common cause of *septic arthritis* in native joints of both adults and children. *S. aureus* septic arthritis in adults may result from trauma, surgery, or hematogenous dissemination.
 - The joints most commonly affected are the knees, shoulders, hips, and phalanges.
 - Examination of synovial fluid reveals >50,000 PMNs/ μ L and gram-positive cocci in clusters on Gram’s stain.
- *Pyomyositis*, an infection of skeletal muscles that is seen in tropical climates and in immunocompromised pts (e.g., HIV-infected pts), causes fever, swelling, and pain overlying involved muscle and is usually due to *S. aureus*.

RESPIRATORY TRACT INFECTIONS

- Newborns and infants can develop serious infections characterized by fever, dyspnea, and respiratory failure; pneumatoceles (shaggy, thin-walled cavities), pneumothorax, and empyema are known complications.
- Community-acquired pneumonia usually follows viral infections (e.g., influenza) and manifests as fever, bloody sputum production, and midlung-field pneumatoceles or multiple patchy pulmonary infiltrates.
 - Blood cultures are usually negative.
- Nosocomial pneumonia is common in intubated pts and is indistinguishable from pneumonia of other bacterial etiologies.
 - Pts produce an increased volume of purulent sputum and develop fever, new pulmonary infiltrates, and respiratory distress.

BACTEREMIA AND SEPSIS The incidence of metastatic seeding during bacteremia has been estimated to be as high as 31%, with bones, joints, kidneys, and lungs most commonly infected.

- Diabetes, HIV infection, and renal insufficiency are often seen in association with *S. aureus* bacteremia and increase the risk of complications.

INFECTIVE ENDOCARDITIS See [Chap. 83](#) for additional details.

- *S. aureus* is the leading cause of endocarditis worldwide and accounts for 25–35% of cases.
- The incidence is increasing as a result of injection drug use, hemodialysis, intravascular prosthetic devices, and immunosuppression.
- Mortality rates range from 20% to 40% despite the availability of effective antibiotics.
- The four clinical settings in which *S. aureus* endocarditis is encountered are (1) right-sided endocarditis in association with injection drug use, (2) left-sided native-valve endocarditis, (3) prosthetic-valve endocarditis, and (4) nosocomial endocarditis.

URINARY TRACT INFECTIONS UTIs due to *S. aureus* are uncommon and suggest hematogenous dissemination.

PROSTHETIC DEVICE-RELATED INFECTIONS Compared with coagulase-negative staphylococci (CoNS), *S. aureus* causes more acute disease, with localized and systemic manifestations that tend to be rapidly progressive. Successful treatment usually involves removal of the prosthetic device.

CA-MRSA INFECTIONS While the skin and soft tissues are the most common sites of infection associated with CA-MRSA, 5–10% of these infections are invasive and potentially life threatening (e.g., necrotizing fasciitis, necrotic pneumonia, sepsis, purpura fulminans).

TOXIN-MEDIATED DISEASE Each class of toxin produced by *S. aureus* results in a characteristic syndrome.

- *Food poisoning*: results from inoculation of toxin-producing *S. aureus* into food by colonized food handlers, with subsequent toxin elaboration in growth-promoting foods (e.g., custard, potato salad, processed meat)
 - The heat-stable toxin is not destroyed even if heating kills the bacteria.
 - Because the disease is caused by preformed toxins, its onset is rapid and explosive, occurring within 1–6 h of ingestion of contaminated food.
 - The chief signs and symptoms are nausea and vomiting, but diarrhea, hypotension, and dehydration may occur. Fever is absent.
 - Symptoms resolve within 8–10 h; treatment is entirely supportive.

TABLE 89-1 Case Definition of *Staphylococcus aureus* Toxic Shock Syndrome**Clinical Criteria**

An illness with the following clinical manifestations:

- Fever: temperature $\geq 102.0^{\circ}\text{F}$ ($\geq 38.9^{\circ}\text{C}$)
- Rash: diffuse macular erythroderma
- Desquamation: 1–2 weeks after rash onset
- Hypotension: systolic blood pressure ≤ 90 mmHg for adults or less than the fifth percentile, by age, for children < 16 years old
- Multisystem involvement (≥ 3 of the following organ systems)
 - Gastrointestinal: vomiting or diarrhea at illness onset
 - Muscular: severe myalgia or creatine phosphokinase level at least twice ULN
 - Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
 - Renal: blood urea nitrogen or creatinine level at least twice ULN for laboratory or urinary sediment with pyuria (≥ 5 leukocytes per high-power field) in the absence of urinary tract infection
 - Hepatic: total bilirubin or aminotransferase level at least twice ULN for laboratory
 - Hematologic: platelet count $< 10^5/\mu\text{L}$
 - Central nervous system: disorientation or alterations in consciousness without focal neurologic signs in the absence of fever and hypotension

Laboratory Criteria

Negative results in the following tests, if obtained:

- Blood or cerebrospinal fluid cultures for another pathogen^a
- Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles

Case Classification

Probable: a case that meets the laboratory criteria and in which four of the five clinical criteria are fulfilled

Confirmed: a case that meets the laboratory criteria and in which all five of the clinical criteria are fulfilled, including desquamation (unless the pt dies before desquamation occurs)

^aBlood cultures may be positive for *S. aureus*.

Abbreviation: ULN, upper limit of normal.

Source: Centers for Disease Control and Prevention (<https://www.cdc.gov/nndss/conditions/toxic-shock-syndrome-other-than-streptococcal/case-definition/2011/>).

- *Toxic shock syndrome (TSS)*: results from elaboration of an enterotoxin (many nonmenstrual TSS cases) or TSST-1 (some nonmenstrual cases and $> 90\%$ of menstrual cases)
 - Although the specific toxin may differ, the clinical presentation is similar in menstrual and nonmenstrual cases.
 - Diagnosis is based on a constellation of clinical findings. **Table 89-1** summarizes the case definition for staphylococcal TSS.
 - Menstrual cases occur 2–3 days after menses begin.
 - Illness occurs only in people who lack antibody to the toxin.
- *Staphylococcal scalded-skin syndrome (SSSS)*: most often affects newborns and children. Fragility of the skin, with tender, thick-walled, fluid-filled bullae, can lead to exfoliation of most of the skin surface. *Nikolsky's sign* is positive when gentle pressure on bullae causes rupture of lesions and leaves denuded underlying skin.

Prevention

Hand washing and careful attention to appropriate isolation procedures prevent the spread of *S. aureus* infection. Elimination of nasal carriage (e.g., with mupirocin) and/or colonization of additional body sites (e.g., with chlorhexidine) with *S. aureus* has been successful in high-risk pts (e.g., those in intensive care units).

■ INFECTIONS CAUSED BY COAGULASE-NEGATIVE STAPHYLOCOCCI**Microbiology**

CoNS are generally less virulent than *S. aureus* but are important and common causes of prosthetic-device infections.

- Of CoNS species, *S. epidermidis* most often causes disease. This organism is a normal component of the skin, oropharyngeal, and vaginal flora.
- *S. saprophyticus* is a common cause of UTIs.
- *S. lugdunensis* and *S. schleiferi* are more virulent than other CoNS species and cause serious infections, possibly because they apparently share more virulence determinants with *S. aureus* than do other CoNS species.

Pathogenesis

CoNS are uniquely adapted to cause prosthetic-device infections because they can elaborate an extracellular polysaccharide (glycocalyx or slime) that forms a biofilm on the device surface, protecting bacteria from host defenses as well as from antibiotic treatment while allowing bacterial survival.

Clinical Syndromes

CoNS cause diverse prosthetic device–related infections. Signs of localized infection are usually subtle, disease progression is slow, and systemic findings are limited. Fever and mild leukocytosis may be documented. Infections not associated with prosthetic devices are infrequent, but up to 5% of native-valve endocarditis cases have been due to CoNS in some series. Neutropenic pts and preterm infants are also at risk of CoNS infection, particularly those pts with intravascular devices.

Diagnosis

CoNS are readily detected by standard methods, but distinguishing infection from colonization is often problematic because CoNS are common contaminants of cultures of blood and other sites. Only 10–20% of blood cultures positive for CoNS reflect true bacteremia.

TREATMENT**Staphylococcal Infections**

- Source control (e.g., drainage of suppurative collections, removal of infected prosthetic devices) and rapid institution of antibiotics are essential. The emergence of CA-MRSA has increased the importance of culturing material from all collections to identify the pathogen and determine its antimicrobial susceptibility.
- Antibiotic therapy for *S. aureus* infection is generally prolonged (i.e., 4–6 weeks) for complicated infections, defined as those in which blood cultures remain positive 96 h after initiation of therapy, the infection was acquired in the community, a removable focus of infection is not removed, or the infection is deep-seated. For uncomplicated bacteremias in which shorter therapy (i.e., 2 weeks) is planned, a transesophageal echocardiogram to rule out endocarditis is warranted.
- Antimicrobial therapy for serious staphylococcal infections is summarized in [Table 89-2](#).

TABLE 89-2 Antimicrobial Therapy for Staphylococcal Infections^a

SENSITIVITY/ RESISTANCE OF ISOLATE	DRUG OF CHOICE	ALTERNATIVE(S)	COMMENTS
Parenteral Therapy for Serious Infections			
Sensitive to penicillin	Penicillin G (4 mU q4h)	Nafcillin or oxacillin (2 g q4h), cefazolin (2 g q8h), vancomycin (15–20 mg/kg q8h ^b)	Fewer than 5% of isolates are sensitive to penicillin. The clinical microbiology laboratory must verify that the strain is not a β -lactamase producer.
Sensitive to methicillin	Nafcillin or oxacillin (2 g q4h)	Cefazolin (2 g q8h), vancomycin (15–20 mg/kg q8h ^b)	Pts with a penicillin allergy can be treated with a cephalosporin if the allergy does not involve an anaphylactic or accelerated reaction; desensitization to β -lactams may be indicated in selected cases of serious infection when maximal bactericidal activity is needed (e.g., prosthetic-valve endocarditis ^c). Type A β -lactamase may rapidly hydrolyze cefazolin and reduce its efficacy in endocarditis. Vancomycin is a less effective option than a β -lactam.
Resistant to methicillin	Vancomycin (15–20 mg/kg q8–12h ^b), daptomycin (6–10 mg/kg IV q24h ^{b,d}) for bacteremia, endocarditis, and complicated skin infections	Linezolid (600 mg q12h PO or IV), ceftaroline (600 mg IV q8–12h), telavancin (7.5–10 mg/kg IV q24h ^b), TMP-SMX (5 mg [based on TMP]/kg IV q8–12h) ^f Newer agents include tedizolid (200 mg once daily IV or PO), oritavancin (single dose of 1200 mg), and dalbavancin (single dose of 1500 mg). These drugs are approved only for the treatment of skin and soft tissue infections. ^g	Sensitivity testing is necessary before an alternative drug is selected. The efficacy of adjunctive therapy is not well established in many settings. Linezolid, ceftaroline, and telavancin have in vitro activity against most VISA and VRSA strains. See footnote for treatment of prosthetic-valve endocarditis. ^c

(Continued)

TABLE 89-2 Antimicrobial Therapy for Staphylococcal Infections^a (Continued)

SENSITIVITY/ RESISTANCE OF ISOLATE	DRUG OF CHOICE	ALTERNATIVE(S)	COMMENTS
Resistant to methicillin with intermediate or complete resistance to vancomycin ^e	Daptomycin (6–10 mg/kg q24h ^{b,d}) for bacteremia, endocarditis, and complicated skin infections	Same as for methicillin-resistant strains (check antibiotic susceptibilities) <i>or</i> Ceftaroline (600 mg IV q8–12h) Newer agents include tedizolid (200 mg once daily IV or PO), oritavancin (single dose of 1200 mg), and dalbavancin (single dose of 1500 mg). These drugs are approved only for the treatment of skin and soft tissue infections.	Same as for methicillin-resistant strains; check antibiotic susceptibilities. Ceftaroline is used either alone or in combination with daptomycin.
Not yet known (i.e., empirical therapy)	Vancomycin (15–20 mg/kg q8–12h ^b), daptomycin (6–10 mg/kg q24h ^{b,d}) for bacteremia, endocarditis, and complicated skin infections	—	Empirical therapy is given when the susceptibility of the isolate is not known. Vancomycin with or without a β -lactam is recommended for suspected community- or hospital-acquired <i>Staphylococcus aureus</i> infections because of the increased frequency of methicillin-resistant strains in the community. If isolates with an elevated MIC to vancomycin (≥ 1.5 $\mu\text{g/ml}$) are common in the community, daptomycin may be preferable.
Oral Therapy for Skin and Soft Tissue Infections			
Sensitive to methicillin	Dicloxacillin (500 mg qid), cephalexin (500 mg qid), or cefadroxil (1 g q12h)	Minocycline or doxycycline (100 mg q12h ^b), TMP-SMX (1 or 2 ds tablets bid), clindamycin (300–450 mg tid), linezolid (600 mg PO q12h), tedizolid (200 mg PO q24h)	It is important to know the antibiotic susceptibility of isolates in the specific geographic region. All collections should be drained and drainage should be cultured.

Resistant to methicillin	Clindamycin (300–450 mg tid), TMP-SMX (1 or 2 ds tablets bid), minocycline or doxycycline (100 mg q12h ^b), linezolid (600 mg bid), or tedizolid (200 mg once daily)	Same options as under “Drug of Choice”	It is important to know the antibiotic susceptibility of isolates in the specific geographic region. All collections should be drained and drainage should be cultured.
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^aRecommended dosages are for adults with normal renal and hepatic function.

^bThe dosage must be adjusted for pts with reduced creatinine clearance.

^cFor the treatment of prosthetic-valve endocarditis, the addition of gentamicin (1 mg/kg q8h) and rifampin (300 mg PO q8h) is recommended, with adjustment of the gentamicin dosage if the creatinine clearance rate is reduced.

^dDaptomycin cannot be used for the treatment of pneumonia.

^eVancomycin-resistant *S. aureus* isolates from clinical infections have been reported.

^fTMP-SMX may be less effective than vancomycin.

^gLimited data are available on the efficacy of dalbavancin, oritavancin, and tedizolid for the treatment of invasive infections.

Abbreviations: ds, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole; VISA, vancomycin-intermediate *S. aureus*; VRSA, vancomycin-resistant *S. aureus*.

Source: Data from Liu C et al: Clin Infect Dis 52:285, 2011; Stevens DL et al: Clin Infect Dis 59:148, 2014; Stevens DL et al: Med Lett Drugs Ther 56:39, 2014; and Baddour LM et al: Circulation 132:1435, 2015.

- Penicillinase-resistant β -lactams, such as nafcillin, oxacillin, and cephalosporins, are highly effective against penicillin-resistant strains.
- The incidence of MRSA is high in hospital settings, and strains intermediately or fully resistant to vancomycin have been described. In general, vancomycin is less reliably bactericidal than the β -lactams and should be used only when absolutely indicated. Desensitization to β -lactams remains an option for life-threatening infections.
- Among newer antistaphylococcal agents, ceftaroline is a fifth-generation cephalosporin with bactericidal activity against MRSA; daptomycin is bactericidal but is not effective in pulmonary infections; quinupristin/dalfopristin is typically bactericidal but is only bacteriostatic against isolates resistant to erythromycin or clindamycin; linezolid is bacteriostatic and offers similar bioavailability after oral or parenteral administration; and tigecycline, a broad-spectrum minocycline analogue, is bacteriostatic against MRSA. Telavancin—a lipoglycopeptide derivative of vancomycin—is active against strains with reduced susceptibility to vancomycin (i.e., vancomycin-intermediate *S. aureus*, or VISA), and the long-acting lipoglycopeptides (dalbavancin and oritavancin) can be administered weekly.
- Other alternatives include the quinolones, but resistance to these drugs is increasing, especially among MRSA strains.
- Trimethoprim-sulfamethoxazole (TMP-SMX) and minocycline have been used successfully to treat MRSA infections in cases of vancomycin toxicity or intolerance.
- Combinations of antistaphylococcal agents have been used to enhance bactericidal activity, to optimize empirical therapy (e.g., using a β -lactam plus vancomycin), and, in selected instances (e.g., right-sided endocarditis), to shorten the duration of therapy.

Special considerations for treatment include:

- *Empirical therapy*: Empirical coverage for MRSA is generally indicated.
- *Salvage therapy*: The optimal regimen for treatment of persistent bacteremia (>3 days) despite appropriate therapy is not known, although a combination of different antibiotic classes is often suggested.
- *Uncomplicated skin and soft tissue infections*: Incision and drainage, with or without oral antibiotics, is usually adequate.
- *Native-valve endocarditis*: A β -lactam is recommended for methicillin-sensitive *S. aureus*, and vancomycin (15–20 mg/kg q8–12h) or daptomycin (6–10 mg/kg q24h) is recommended for MRSA. Treatment should continue for 6 weeks.
- *Prosthetic-valve endocarditis*: Surgery is often needed in addition to antibiotics. The combination of a β -lactam drug (or either vancomycin or daptomycin if MRSA is involved) with gentamicin for 2 weeks and rifampin for ≥ 6 weeks is indicated.
- *Hematogenous osteomyelitis or septic arthritis*: A 4-week treatment course is adequate for children, but adults require longer courses. Joint infections require repeated aspiration or arthroscopy to prevent damage from inflammatory cells.
- *Chronic osteomyelitis*: Surgical debridement—in addition to antibiotic therapy—is needed in most cases.
- *Prosthetic-joint infections*: Ciprofloxacin and rifampin have been used successfully in combination, particularly when the prosthesis cannot be removed.

- *TSS*: Supportive therapy and removal of tampons or other packing material or debridement of an infected site are most important. A combination of clindamycin and a semisynthetic penicillin (or vancomycin if the isolate is resistant to methicillin) is often recommended.
 - Clindamycin is recommended because it is a protein synthesis inhibitor and has been shown to decrease toxin synthesis *in vitro*; linezolid also appears to be effective.
 - Anecdotally, IV immunoglobulin is helpful.

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Streptococcal/Enterococcal Infections, Diphtheria, and Infections Caused by Other Corynebacteria and Related Species



STREPTOCOCCAL AND ENTEROCOCCAL INFECTIONS

■ MICROBIOLOGY

Streptococci and enterococci are gram-positive cocci that form chains when grown in liquid media.

- Culture on blood agar reveals three hemolytic patterns:
 - α -Hemolysis results in partial hemolysis that imparts a greenish appearance to agar. This pattern is seen with *S. pneumoniae* and viridans streptococci.
 - β -Hemolysis results in complete hemolysis around a colony. This pattern is seen with streptococci of Lancefield groups A, B, C, and G, which all form large (≥ 0.5 -mm) colonies. Lancefield grouping is based on cell-wall carbohydrate antigens.
 - γ -Hemolysis describes the absence of hemolytic ability. This pattern is typical of enterococci, nonenterococcal group D streptococci, and anaerobic streptococci.
- Streptococci and enterococci colonize the respiratory, GI, and genitourinary tracts as part of the normal flora. Several of these species are also important causes of human diseases.

■ GROUP A STREPTOCOCCUS (GAS)

Epidemiology and Pathogenesis

GAS (*S. pyogenes*) causes suppurative infections and is associated with postinfectious syndromes such as acute rheumatic fever (ARF) and poststreptococcal glomerulonephritis (PSGN).

- Up to 20% of people may have asymptomatic pharyngeal colonization with GAS.
 - Pharyngitis due to GAS is one of the most common bacterial infections of childhood.
 - GAS accounts for 20–40% of all cases of exudative pharyngitis in children >3 years of age.

- The incidence of all GAS infections is ~10-fold higher in low-income than in high-income countries. Worldwide, GAS contributes to ~500,000 deaths per year.
- The major surface protein (M protein) and the hyaluronic acid polysaccharide capsule protect GAS against phagocytic ingestion and killing.
- GAS makes a large number of extracellular products that may contribute to local and systemic toxicity; these include streptolysins S and O, streptokinase, DNases, and the pyrogenic exotoxins that cause the rash of scarlet fever and contribute to the pathogenesis of toxic shock syndrome (TSS) and necrotizing fasciitis.
- Respiratory droplets provide the usual route of transmission, although other mechanisms have been described.

Clinical Manifestations

PHARYNGITIS After an incubation period of 1–4 days, pts develop sore throat, fever, chills, malaise, and GI manifestations.

- Examination may reveal an erythematous and swollen pharyngeal mucosa, purulent exudates over the posterior pharynx and tonsillar pillars, and tender anterior cervical adenopathy.
- Viral pharyngitis is the more likely diagnosis when pts have cough, coryza, hoarseness, conjunctivitis, or mucosal ulcers.
- Throat culture is the gold standard for diagnosis.
 - Latex agglutination or enzyme immunoassay is highly specific (>95%) and can be relied on for a rapid, definitive diagnosis.
 - Given a variable sensitivity of 55–90%, a negative rapid-assay result should be confirmed with a throat culture.

TREATMENT

Gas Pharyngitis

- See [Table 90-1](#) for recommended treatments.
 - The primary goal of treatment is to prevent suppurative complications (e.g., lymphadenitis, abscess, sinusitis, bacteremia, pneumonia) and ARF; therapy does not seem to significantly reduce the duration of symptoms or to prevent PSGN.
 - Follow-up cultures after completion of therapy are not routinely recommended.
- Asymptomatic pharyngeal GAS carriage usually is not treated; however, when the pt is a potential source of infection in others (e.g., health care workers), either a first-generation cephalosporin (e.g., cephalexin, 500 mg PO bid for 10 days) or clindamycin (300 mg PO tid for 10 days) is used. A 10-day course of vancomycin (250 mg PO qid) and rifampin (600 mg PO bid) has eradicated rectal colonization.

SCARLET FEVER Scarlet fever is the designation for GAS infection—usually pharyngitis—associated with a characteristic rash. It is much less common now than in the past, although occasional outbreaks still occur.

- The rash typically appears over the upper trunk in the first 2 days of illness and spreads to the extremities but not to the palms and soles. The skin has a sandpaper feel.

TABLE 90-1 Treatment of Group A Streptococcal Infections

INFECTION	TREATMENT ^a
Pharyngitis	Benzathine penicillin G (1.2 mU IM) or penicillin V (250 mg PO tid or 500 mg PO bid) × 10 days (Children <27 kg: Benzathine penicillin G [600,000 units IM] or penicillin V [250 mg PO bid or tid] × 10 days)
Impetigo	Same as pharyngitis
Erysipelas/cellulitis	Severe: Penicillin G (1–2 mU IV q4h) Mild to moderate: Procaine penicillin (1.2 mU IM bid)
Necrotizing fasciitis/myositis	Surgical debridement plus penicillin G (2–4 mU IV q4h) plus clindamycin ^b (600–900 mg IV q8h)
Pneumonia/empyema	Penicillin G (2–4 mU IV q4h) plus drainage of empyema
Streptococcal toxic shock syndrome	Penicillin G (2–4 mU IV q4h) plus clindamycin ^b (600–900 mg IV q8h) plus IV immunoglobulin ^b (2 g/kg as a single dose)

^aPenicillin allergy: A first-generation cephalosporin, such as cephalexin or cefadroxil, may be substituted for penicillin in cases of penicillin allergy if the nature of the allergy is not an immediate hypersensitivity reaction (anaphylaxis or urticaria) or another potentially life-threatening manifestation (e.g., severe rash and fever). Alternative agents for oral therapy are erythromycin (10 mg/kg PO qid, up to a maximum of 250 mg per dose) and azithromycin (a 5-day course at a dose of 12 mg/kg once daily, up to a maximum of 500 mg/d). Vancomycin is an alternative for parenteral therapy.

^bEfficacy unproven, but recommended by several experts.

- Other findings include circumoral pallor, strawberry tongue (enlarged papillae on a coated tongue), and Pastia's lines (accentuation of rash in skin folds).
- Rash improves in 6–9 days, with desquamation on palms and soles.

SKIN AND SOFT TISSUE INFECTIONS See [Chap. 87](#) for further discussion of clinical manifestations and treatment.

- *Impetigo*: A superficial skin infection, impetigo is most often seen in young children in warmer months or climates and under poor hygienic conditions.
 - Red papular lesions evolve into pustules that ultimately form characteristic honeycomb-like crusts, usually affecting the facial areas around the nose and mouth and the legs. Pts are usually afebrile.
 - GAS impetigo is associated with PSGN but not with ARF.
 - For treatment, see Table 90-1. Given an increasing incidence of impetigo due to *Staphylococcus aureus*, empirical antibiotic therapy should cover GAS and *S. aureus*.
 - Thus dicloxacillin or cephalexin (250 mg PO qid for 10 days) is used.
 - Topical mupirocin ointment is also effective.
- *Cellulitis*: GAS cellulitis develops at anatomic sites where normal lymphatic drainage has been disrupted (e.g., by surgery or prior cellulitis). When skin integrity is breached, organisms may enter at sites distant from the area of cellulitis.
 - GAS may cause rapidly developing postoperative wound infections with a thin exudate.
 - *Erysipelas* is a form of cellulitis characterized by pain, fever, and acute onset of bright red swelling that is sharply demarcated from normal skin.
 - It usually involves the malar facial area or the lower extremities and is caused almost exclusively by β -hemolytic streptococci, usually GAS.
 - The skin often has a *peau d'orange* texture, and blebs or bullae may form after 2 or 3 days.

- For treatment of erysipelas or cellulitis known to be due to GAS, see Table 90-1; empirical treatment should be directed against GAS and *S. aureus*.
- *Necrotizing fasciitis*: See **Chap. 87** for details. GAS causes ~60% of cases of necrotizing fasciitis. For treatment, see Table 90-1.

PNEUMONIA AND EMPYEMA GAS is an occasional cause of pneumonia in previously healthy pts.

- Pts have pleuritic chest pain, fever, chills, and dyspnea; ~50% have accompanying pleural effusions that—unlike the sterile parapneumonic effusions of pneumococcal pneumonia—are almost always infected and should be drained quickly to avoid loculation.
- For treatment, see Table 90-1.

BACTEREMIA In most adult cases of GAS bacteremia, a focus is readily identifiable. Bacteremia occurs occasionally with cellulitis or pneumonia and frequently with necrotizing fasciitis.

- If no focus is immediately evident, a diagnosis of endocarditis, occult abscess, or osteomyelitis should be considered.

TOXIC SHOCK SYNDROME Unlike those with TSS due to *S. aureus*, pts with streptococcal TSS generally lack a rash, have bacteremia, and have an associated soft-tissue infection (cellulitis, necrotizing fasciitis, or myositis).

- **Table 90-2** presents a proposed case definition for streptococcal TSS.
- The mortality rate for streptococcal TSS is $\geq 30\%$, with most deaths due to shock and respiratory failure.
- For treatment, see Table 90-1.

TABLE 90-2 Proposed Case Definition for the Streptococcal Toxic Shock Syndrome^a

- I. Isolation of group A streptococci (*Streptococcus pyogenes*)
 - A. From a normally sterile site
 - B. From a nonsterile site
- II. Clinical signs of severity
 - A. Hypotension *and*
 - B. ≥ 2 of the following signs:
 1. Renal impairment
 2. Coagulopathy
 3. Liver function impairment
 4. Adult respiratory distress syndrome
 5. A generalized erythematous macular rash that may desquamate
 6. Soft tissue necrosis, including necrotizing fasciitis or myositis; or gangrene

^aAn illness fulfilling criteria IA, IIA, and IIB is defined as a *definite* case. An illness fulfilling criteria IB, IIA, and IIB is defined as a *probable* case if no other etiology for the illness is identified.

Source: Modified from Working Group on Severe Streptococcal Infections: JAMA 269:390, 1993.

Prevention

Although household contacts of individuals with invasive GAS infection are at increased risk of infection, the attack rate is low enough that antibiotic prophylaxis is not recommended. However, prophylaxis may be considered in unusually severe cases or for individuals at increased risk for invasive infection.

■ STREPTOCOCCI OF GROUPS C AND G

- Streptococci of groups C and G cause infections similar to those caused by GAS, including cellulitis, bacteremia (particularly in elderly or chronically ill pts), pneumonia, and soft tissue infections.
- Strains that form small colonies (<0.5 mm) on blood agar are generally of the *S. milleri* group (*S. intermedius*, *S. anginosus*); large-colony groups C and G streptococci are now considered a single species (*S. dysgalactiae* subsp. *equisimilis*).
- Treatment is the same as for similar syndromes due to GAS.
 - Although it has not been shown to be superior, the addition of gentamicin (1 mg/kg IV q8h) is recommended by some experts for endocarditis or septic arthritis due to group C or G streptococci because of a poor clinical response to penicillin alone.
 - Joint infections can require repeated aspiration or open drainage for cure.

■ GROUP B STREPTOCOCCUS (GBS)

- GBS is a major cause of meningitis and sepsis in neonates and a common cause of peripartum fever in women.
 - About half of the infants delivered vaginally to mothers colonized with GBS (5–40% of women) become colonized, but only 1–2% develop infection.
 - With maternal colonization, the risk of neonatal GBS infection is high if delivery is preterm or if the mother has an early rupture of membranes (>24 h before delivery), prolonged labor, fever, or chorioamnionitis.
- Widespread prenatal screening for GBS has reduced the incidence of neonatal infection to 0.6 case per 1000 live births; adults now account for a larger proportion of invasive GBS infections than do newborns.

Neonatal Infections

- *Early-onset infection* occurs within the first week of life (median age, 20 h). The infection is acquired within the maternal genital tract during birth.
 - Neonates typically have respiratory distress, lethargy, and hypotension.
 - Bacteremia is noted in ~100% of cases, pneumonia in one-third to one-half, and meningitis in one-third.
- *Late-onset infection* develops in infants >1 week old and generally ≤3 months of age (mean age, 3–4 weeks). The organism is acquired during delivery or during later contact with a source.
 - Meningitis is the most common manifestation.
 - Infants present with lethargy, fever, irritability, poor feeding, and occasionally seizures.

TREATMENT

GBS Infections in Neonates

- Penicillin is the agent of choice for all GBS infections.
 - Empirical therapy for suspected bacterial sepsis consists of ampicillin and gentamicin while cultures are pending.
 - Many physicians continue to give gentamicin until the pt improves clinically.

- *Prevention:* Identification of high-risk mothers and prophylactic administration of ampicillin or penicillin during delivery reduce the risk of neonatal infection.
- Maternal screening for anogenital colonization with GBS at 35–37 weeks of pregnancy is currently recommended.
- Women who have previously given birth to an infant with GBS disease, who have a history of GBS bacteriuria during pregnancy, or who have an unknown culture status but risk factors noted earlier should receive intrapartum prophylaxis (usually 5 mU of penicillin G followed by 2.5 mU q4h until delivery).
 - Cefazolin can be used for pts with a penicillin allergy who are at low risk for anaphylaxis.
 - If the mother is at risk for anaphylaxis and the GBS isolate is known to be susceptible, clindamycin can be used; otherwise, vancomycin is indicated.

Infections in Adults

Most GBS infections in adults are related to pregnancy and parturition. Other GBS infections are seen in the elderly, especially pts with underlying conditions such as diabetes mellitus or cancer.

- Cellulitis and soft-tissue infection, UTI, pneumonia, endocarditis, and septic arthritis are most common.
- Penicillin (12 mU/d for localized infections and 18–24 mU/d for endocarditis or meningitis, in divided doses) is recommended. Vancomycin is an acceptable alternative for penicillin-allergic pts.
- Relapse or recurrent invasive infection occurs in ~4% of cases.

■ NONENTEROCOCCAL GROUP D STREPTOCOCCI

The main nonenterococcal group D streptococci that cause human infections are *S. gallolyticus* and *S. infantarius* (previously classified together as *S. bovis*), each of which has two subspecies.

- These organisms have been associated with GI malignancies and other bowel lesions, which are found in ≥60% of pts presenting with group D streptococcal endocarditis.
- Unlike enterococcal endocarditis, group D streptococcal endocarditis can be adequately treated with penicillin alone.

■ VIRIDANS STREPTOCOCCI

- Many viridans streptococcal species are part of the normal oral flora, residing in close association with the teeth and gingiva. Minor trauma such as flossing or toothbrushing can cause transient bacteremia.
- Viridans streptococci have a predilection to cause endocarditis. Moreover, they are often part of a mixed flora in sinus infections and brain and liver abscesses.
- Bacteremia is common in neutropenic pts, who can develop a sepsis syndrome with high fever and shock. Risk factors in these pts include chemotherapy with high-dose cytosine arabinoside, prior treatment with trimethoprim-sulfamethoxazole (TMP-SMX) or a fluoroquinolone, mucositis, or therapy with antacids or histamine antagonists.
- The *S. milleri* group (including *S. intermedius*, *S. anginosus*, and *S. constellatus*) differs from other viridans streptococci in both hemolytic pattern (i.e., they may be α -, β -, or γ -hemolytic) and clinical syndromes. These organisms commonly cause suppurative infections, especially abscesses of brain and viscera, as well as infections of the oral cavity and respiratory tract such as peritonsillar abscess, empyema, and lung abscess.

- Neutropenic pts should receive vancomycin pending susceptibility testing; other pts may be treated with penicillin.

■ ABIOTROPHIA AND GRANULICATELLA SPECIES (NUTRITIONALLY VARIANT STREPTOCOCCI)

- The organisms formerly known as nutritionally variant streptococci are now classified as *Abiotrophia defectiva* and three species within the genus *Granulicatella*. These fastidious organisms require media that are enriched (e.g., with vitamin B₆) for growth.
- These organisms are more frequently associated with treatment failure and relapse in cases of endocarditis than are viridans streptococci. Thus, gentamicin (1 mg/kg q8h) must be added to the penicillin regimen.

■ ENTEROCOCCI

Microbiology

Enterococci are gram-positive cocci that are observed as single cells, diplococci, or short chains.

- Enterococci share many morphologic and phenotypic characteristics with streptococci and thus were previously classified as the latter.
- Enterococci are generally nonhemolytic when cultured on blood agar plates.
- Enterococci are inherently resistant to a variety of commonly used antibiotics. *Enterococcus faecium* is the most resistant species, with >80% of U.S. isolates resistant to vancomycin (VRE) and >90% resistant to ampicillin. In contrast, resistance to vancomycin and ampicillin in *E. faecalis* isolates is much less common.

Epidemiology

Although ≥ 18 enterococcal species have been isolated from human infections, *E. faecalis* and *E. faecium* cause the overwhelming majority of enterococcal infections.

- Enterococci are the second most common cause of nosocomial infection (after staphylococci), with roughly equal numbers of cases caused by *E. faecalis* and *E. faecium*.
- Colonization with VRE (as opposed to antibiotic-susceptible strains) predisposes to enterococcal infection. Risk factors for VRE colonization include prolonged hospitalization; long antibiotic courses; hospitalization in long-term care facilities, surgical units, and/or ICUs; organ transplantation; renal failure; high APACHE scores; and physical proximity to pts colonized with VRE.

Clinical Manifestations

Enterococci cause UTIs, especially in pts who have undergone instrumentation and in those with chronic prostatitis, bacteremia related to intravascular catheters, bacterial endocarditis of both native and prosthetic valves (usually with a subacute presentation), meningitis (particularly after neurosurgery), soft-tissue infections (particularly involving surgical wounds), and neonatal infections. These organisms can also be a component of mixed intraabdominal infections.

TREATMENT

Enterococcal Infections

- Given low cure rates with β -lactam monotherapy, combination therapy with a cell wall–active agent (a β -lactam or a glycopeptide) plus gentamicin or streptomycin is recommended for serious enterococcal infections. High-level

resistance to aminoglycosides (i.e., MICs of >500 and >2000 µg/mL for gentamicin and streptomycin, respectively) abolishes the synergism otherwise obtained by the addition of an aminoglycoside to a cell wall-active agent. This phenotype must be assessed in isolates from serious infections.

- Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin in the treatment of *E. faecalis* endocarditis, and this combination is now recommended as first-line therapy, particularly in pts at risk for aminoglycoside toxicity.
- For serious infections due to vancomycin- and ampicillin-resistant *E. faecium*:
 - High-dose daptomycin (10–12 mg/kg daily) plus another agent (ampicillin, ceftaroline, or tigecycline) plus potentially an aminoglycoside (if high-level resistance is not present) is recommended.
 - Other options include linezolid (600 mg IV q12h), high-dose ampicillin (if the MIC is ≤64 µg/mL) plus potentially an aminoglycoside, ampicillin plus imipenem (if the ampicillin MIC is ≤32 µg/mL), and quinupristin/dalfopristin (22.5 mg/kg per day in divided doses q8h) plus another active agent (doxycycline with rifampin or a fluoroquinolone). (Quinupristin/dalfopristin is no longer approved by the FDA for endocarditis due to VRE.)

CORYNEBACTERIAL AND RELATED INFECTIONS

■ DIPHTHERIA

Microbiology

Corynebacterium diphtheriae, the causative agent of the nasopharyngeal and skin infection known as diphtheria, is a club-shaped, gram-positive, unencapsulated, nonmotile, nonsporulating rod.

- The bacteria often form clusters of parallel arrays (palisades) in culture, referred to as *Chinese characters*.
- Some strains, including those of *C. ulcerans* and *C. pseudotuberculosis*, produce diphtheria toxin, which can cause myocarditis, polyneuropathy, and other systemic toxicities and is associated with the formation of pseudomembranes in the pharynx during respiratory infection.

Epidemiology and Pathogenesis

As a result of routine immunization, fewer than five cases of diphtheria are diagnosed per year in the United States.

- Low-income countries in Africa and Asia continue to have significant outbreaks; globally, ~7000 cases of diphtheria were reported in 2014, but many more cases likely go unreported.
- *C. diphtheriae* is transmitted by aerosols, primarily during close contact.
- Diphtheria toxin—the primary virulence factor—irreversibly inhibits protein synthesis, thereby causing the death of the cell.

Clinical Manifestations

- *Respiratory diphtheria*: Upper respiratory tract illness due to *C. diphtheriae* typically has a 2- to 5-day incubation period and is diagnosed on the basis of a constellation of sore throat; low-grade fever; and a tonsillar, pharyngeal, or nasal pseudomembrane.
 - Unlike that of GAS pharyngitis, the pseudomembrane of diphtheria is tightly adherent; dislodging the membrane usually causes bleeding.

- Massive swelling of the tonsils and “bull-neck” diphtheria resulting from submandibular and paratracheal edema can develop. This illness is further characterized by foul breath, thick speech, and stridorous breathing.
- Respiratory tract obstruction due to swelling and sloughing of the pseudomembrane can be fatal.
- Neurologic manifestations may appear during the first 2 weeks of illness, beginning with dysphagia and nasal dysarthria and progressing to cranial nerve involvement (e.g., weakness of the tongue, facial numbness, blurred vision due to ciliary paralysis).
 - Several weeks later, generalized sensorimotor polyneuropathy with prominent autonomic dysfunction (including hypotension) may occur.
 - Pts who survive the acute phase gradually improve.
- *Cutaneous diphtheria*: This variable dermatosis is generally characterized by punched-out ulcerative lesions with necrotic sloughing or pseudomembrane formation. Pts typically present to medical care because of nonhealing or enlarging ulcers; the lesions rarely exceed 5 cm in diameter.

Diagnosis

A definitive diagnosis is based on compatible clinical findings and detection of *C. diphtheriae* or toxigenic *C. ulcerans* (by isolation or histologic identification) in local lesions.

- The laboratory should be notified that diphtheria is being considered, and appropriate selective media must be used.
- In the United States, respiratory diphtheria is a notifiable disease; cutaneous diphtheria is not.

TREATMENT

Diphtheria

- Diphtheria antitoxin is the most important component of treatment and should be given as soon as possible. To obtain antitoxin, contact the Emergency Operations Center at the Centers for Disease Control and Prevention (CDC) (770-488-7100) after first contacting the state health department. See <http://www.cdc.gov/diphtheria/dat.html> for further information.
- Antibiotic therapy is administered for 14 days to prevent transmission to contacts. The recommended options are (1) procaine penicillin G (600,000 U IM q12h in adults; 12,500–25,000 U/kg IM q12h in children) until the pt can take oral penicillin V (125–250 mg qid); or (2) erythromycin (500 mg IV q6h in adults; 40–50 mg/kg per day IV in 2–4 divided doses in children) until the pt can take oral erythromycin (500 mg qid).
 - Rifampin and clindamycin are other options for pts who cannot tolerate penicillin or erythromycin.
 - Cultures should document eradication of the organism 1 and 14 days after completion of antibiotic therapy. If the organism is not eradicated after 2 weeks of therapy, an additional 10-day course followed by repeat cultures is recommended.
- Respiratory isolation and close monitoring of cardiac and respiratory functions should be instituted.

Prognosis

The mortality rate for diphtheria is 5–10% but may approach 20% in children <5 years old and adults >40 years of age. Risk factors for death include a long interval between onset of local disease and antitoxin administration; bull-neck diphtheria; myocarditis with ventricular tachycardia; atrial fibrillation; complete heart block; an age of >60 years or <6 months; alcoholism; extensive pseudo-membrane elongation; and laryngeal, tracheal, or bronchial involvement.

Prevention

- DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed) is recommended for primary immunization of children up to age 6 years; Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis) is recommended for children ≥ 7 years old and for adults. All adults should receive a single dose of Tdap if they have not received it previously, regardless of the duration since their last dose of Td (tetanus and diphtheria toxoids).
- Td is recommended for routine booster use in adults at 10-year intervals or for tetanus-prone wounds. When >10 years have elapsed since the last Td dose, adults 19–64 years old should receive a single dose of Tdap.
- Close contacts of pts with respiratory diphtheria should have throat specimens cultured for *C. diphtheriae*, should receive a 7- to 10-day course of oral erythromycin or one dose of benzathine penicillin (1.2 mU for persons ≥ 6 years old; 600,000 U for children <6 years old), and should be vaccinated if their immunization status is uncertain.

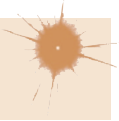
■ OTHER CORYNEBACTERIA AND RELATED ORGANISMS

Nondiphtherial *Corynebacterium* species and related organisms are common components of the normal human flora. Although frequently considered contaminants, these bacteria are associated with invasive disease in immunocompromised hosts.

- *C. ulcerans* infection is a zoonosis that causes diphtheria-like illness and requires similar treatment.
- *C. jeikeium* infects pts with cancer or severe immunodeficiency and can cause severe sepsis, endocarditis, device-related infections, pneumonia, and soft-tissue infections. Treatment consists of removal of the source of infection and administration of vancomycin or linezolid.
- *C. urealyticum* is a cause of sepsis and nosocomial UTI, including *alkaline-encrusted cystitis* (a chronic inflammatory bladder infection associated with deposition of ammonium magnesium phosphate on the surface and walls of ulcerating lesions in the bladder). Vancomycin and linezolid are effective therapeutic agents.
- *Rhodococcus* species appear as spherical to long, curved, clubbed gram-positive rods that are often acid fast. The most common presentation—nodular cavitary pneumonia of the upper lobe (similar to tuberculosis and nocardiosis) in an immunocompromised host—often occurs in conjunction with HIV infection. Vancomycin is the drug of choice, but macrolides, clindamycin, rifampin, and TMP-SMX have also been used to treat these infections.
- *Arcanobacterium haemolyticum* can cause pharyngitis and chronic skin ulcers, often in association with a scarlatiniform rash similar to that caused by GAS. The organism is susceptible to β -lactam agents, macrolides, fluoroquinolones, clindamycin, vancomycin, and doxycycline. Penicillin resistance has been reported.

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Meningococcal and Listerial Infections



MENINGOCOCCAL INFECTIONS

- **Etiology and microbiology:** *Neisseria meningitidis* is a catalase- and oxidase-positive, gram-negative aerobic diplococcus with a polysaccharide capsule that colonizes humans only.
 - Of the 12 capsular groups, only 6—A, B, C, X, Y, and W (formerly W135)—account for the majority of cases of invasive disease.
 - Capsular groups A, W, and X cause recurrent epidemics in sub-Saharan Africa. Serogroup B can cause hyperendemic disease, and capsular groups C and Y cause sporadic disease and small outbreaks.
- **Epidemiology:** Up to 500,000 cases of meningococcal disease occur worldwide each year, with a mortality rate of ~10%.
 - Most commonly, meningococci asymptomatically colonize the nasopharynx; such asymptomatic nasopharyngeal carriage is detected in >25% of healthy adolescents and ~10% of adults.
 - Patterns of meningococcal disease include epidemics, outbreaks (e.g., in colleges, refugee camps), hyperendemic disease, and sporadic or endemic cases.
 - Although most countries have predominantly sporadic cases (0.3–5 cases per 100,000 population), epidemics in sub-Saharan Africa can have rates as high as 1000 cases per 100,000 population.
 - Rates of meningococcal disease are highest among infants, with a second peak in adolescents and young adults (15–25 years of age).
 - Other risk factors for meningococcal disease include complement deficiency (e.g., C5–C9, properdin, factor D), close contact with carriers, exposure to tobacco smoke, and a recent URI caused by a virus or *Mycoplasma* species.
- **Pathogenesis:** Meningococci colonizing the upper respiratory tract invade the bloodstream through the mucosa only rarely, usually within a few days after an invasive strain is acquired.
 - The capsule is an important virulence factor, providing resistance to phagocytosis and helping prevent desiccation during transmission between hosts.
 - Severity of disease is related to the degree of endotoxemia and the magnitude of the inflammatory response.
 - Endothelial injury leads to increased vascular permeability and hypovolemia, resulting in vasoconstriction and ultimately in decreased cardiac output.
 - Intravascular thrombosis caused by activation of procoagulant pathways and downregulation of anticoagulant pathways results in the characteristic purpura fulminans often seen in meningococcemia.
- **Clinical manifestations:** The most common clinical syndromes are meningitis and meningococcal septicemia, with disease usually developing within 4 days of organism acquisition.
 - A nonblanching rash (petechial or purpuric) develops in >80% of cases; early in the illness, the rash is often absent or may be indistinguishable from viral rashes.
 - Meningococcal meningitis alone (without septicemia) accounts for 30–50% of cases.
 - This meningitis is indistinguishable from other forms of bacterial meningitis unless there is an associated petechial or purpuric rash.

- Classic signs of meningitis (e.g., headache, neck stiffness, photophobia) are often absent or difficult to discern in infants and young children.
- Meningococcal septicemia alone accounts for ~20% of cases and initially may present as an influenza-like illness (e.g., fever, headache, myalgias, vomiting, abdominal pain).
 - May progress to shock (e.g., tachycardia, poor peripheral perfusion, oliguria), decreased level of consciousness due to decreased cerebral perfusion, spontaneous hemorrhage (pulmonary, gastric, or cerebral), and ultimately multiorgan failure and death
 - Poor prognostic factors include an absence of meningismus, hypotension, relatively low temperature (<38°C [$<100.4^{\circ}\text{F}$]), leukopenia, and thrombocytopenia.
- Chronic meningococcemia, which is rarely recognized, presents as repeated episodes of petechial rash associated with fever, joint pain, features of arthritis, and splenomegaly that may progress to acute meningococcal septicemia if untreated.
 - This condition is occasionally associated with complement deficiencies or inadequate sulfonamide therapy.
- Postmeningococcal reactive disease is immune complex-mediated and occurs 4–10 days after onset of meningococcal disease.
 - Manifestations can include a maculopapular or vasculitic rash (2% of cases), arthritis ($\leq 8\%$ of cases), iritis (1% of cases), or serositis. These features resolve spontaneously without sequelae.
- Less common clinical manifestations include pneumonia, pyogenic arthritis, osteomyelitis, purulent pericarditis, endophthalmitis, conjunctivitis, or primary peritonitis.
- **Diagnosis:** Although meningococcal infections are often diagnosed on clinical grounds, blood cultures are positive in ~75% of cases and should be performed to confirm the diagnosis and to facilitate public health investigations.
 - In the setting of fever and petechial rash, elevations in the WBC count and inflammatory marker levels suggest meningococcal disease.
 - With antibiotic pretreatment, blood cultures are generally negative; in contrast, PCR analysis of whole-blood samples is effective for several days after initiation of antibiotics and increases the diagnostic yield by $>40\%$.
 - Unless contraindicated on clinical grounds, LP should be performed in cases of suspected meningococcal meningitis.
 - Gram's staining of CSF is ~80% sensitive, and CSF culture is 90% sensitive. Latex agglutination testing of CSF is insensitive and should be avoided.
 - LP should be avoided in pts with meningococcal septicemia, as positioning for the procedure may adversely affect circulatory status.

TREATMENT

Meningococcal Infections

- Initial therapy should focus on urgent clinical issues (e.g., hypovolemic shock, increased intracranial pressure, airway patency) and administration of antibiotics.
- Empirical antibiotic therapy for suspected meningococcal disease consists of a third-generation cephalosporin such as ceftriaxone (75–100 mg/kg per day [maximum, 4 g/d] in one or two divided IV doses) or cefotaxime (200 mg/kg per day [maximum, 8 g/d] in four divided IV doses) to provide coverage both for meningococci and for other, potentially penicillin-resistant organisms that may produce an indistinguishable clinical syndrome.

- Meningococcal meningitis and meningococcal septicemia are conventionally treated for 7 days.
 - A single dose of ceftriaxone has been used successfully in resource-poor settings.
 - Treatment for meningococcal disease at other foci (e.g., pneumonia, arthritis) is usually continued until clinical and laboratory evidence of infection has resolved; cultures usually become sterile within 24 h of initiation of antibiotics.
 - Little evidence supports other adjunctive therapies (e.g., antibody to lipopolysaccharide, recombinant bactericidal/permeability-increasing protein, activated protein C) in relevant pt populations; these therapies are not currently recommended.
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- **Prognosis:** Despite the availability of antibiotics and other intensive medical interventions, ~10% of pts die.
 - Necrosis of purpuric lesions leads to scarring and the potential need for skin grafting in ~10% of cases.
 - 5% of pts have hearing loss, 7% of pts have neurologic complications, and ~25% of pts with serogroup B meningococcal disease have psychological disorders.
 - **Prevention:** Polysaccharide-based and conjugate vaccines exist for primary prevention; secondary cases can be prevented with antibiotic prophylaxis.
 - Meningococcal polysaccharide vaccines are currently formulated as bivalent (capsular groups A and C) or quadrivalent (capsular groups A, C, Y, and W) and provide adults with immunity of 2–10 years' duration. Because the B polysaccharide is the same as a polysaccharide expressed in fetuses and is therefore recognized as self, capsular group B strains have not been targeted by polysaccharide vaccines. Two different vaccines based on subcapsular antigens have been approved for prevention of meningococcal disease due to capsular group B.
 - A variety of meningococcal conjugate vaccines have been developed and have largely superseded plain polysaccharide vaccines. A quadrivalent formulation (capsular groups A, C, Y, and W) is most common in the United States.
 - Close contacts (i.e., household and kissing contacts) of pts with meningococcal disease should receive prophylaxis with ciprofloxacin, ofloxacin, or ceftriaxone to eradicate nasopharyngeal colonization by *N. meningitidis*.
 - Rifampin fails to eradicate carriage in 15–20% of cases, and emerging resistance has been reported.
 - Pts with meningococcal disease who are treated with an antibiotic that does not clear colonization (e.g., penicillin) should also be given a prophylactic agent at the end of therapy.

LISTERIAL INFECTIONS

- **Etiology and microbiology:** *Listeria monocytogenes* is a food-borne pathogen that can cause serious infections, particularly in pregnant women and immunocompromised individuals.
 - The organism is a facultatively anaerobic, nonsporulating, gram-positive rod that demonstrates motility when cultured at low temperatures.
 - After ingestion of food that contains a high bacterial burden, virulence factors expressed by *Listeria* allow internalization into cells, intracellular growth, and cell-to-cell spread.

• Epidemiology

- *Listeria* is commonly found in processed and unprocessed foods such as soft cheeses, delicatessen meats, hot dogs, milk, and cold salads; fresh fruits and vegetables can also transmit the organism.
- There is no human-to-human transmission (other than vertical transmission from mother to fetus) or waterborne infection.

• Clinical manifestations: *Listeria* causes several clinical syndromes, of which meningitis and septicemia are most common.

- **Gastroenteritis:** can develop within 48 h after ingestion of contaminated foods containing a large bacterial inoculum
 - Manifestations include fever, diarrhea, headache, and constitutional symptoms.
 - Listeriosis should be considered in outbreaks of gastroenteritis when cultures for other likely pathogens are negative.
- **Bacteremia:** Pts present with fever, chills, myalgias, and arthralgias. Meningeal symptoms, focal neurologic findings, or mental status changes may suggest the diagnosis.
- **Meningitis:** *Listeria* causes ~5–10% of cases of community-acquired meningitis in adults in the United States, with case–fatality rates of 15–26%.
 - Listerial meningitis differs from meningitis of other bacterial etiologies in that its presentation is often subacute, with meningeal signs and photophobia being less common.
 - The CSF profile usually reveals <1000 WBCs/ μ L, with a less marked neutrophil predominance than in other meningitides. Low glucose levels and a positive Gram's stain are seen in ~30–40% of cases.
- **Meningoencephalitis and focal CNS infection:** *Listeria* can directly invade the brain parenchyma and cause cerebritis or focal abscess.
 - Of CNS infections, ~10% are macroscopic abscesses, which are sometimes misdiagnosed as tumors.
 - Brainstem invasion can cause severe rhombencephalitis, with a prodrome of fever and headache followed by neurologic decline and focal findings. The presentation may be biphasic.
- **Infection in pregnant women and neonates:** Listeriosis in pregnancy is a serious infection that can cause miscarriage and stillbirth.
 - Pregnant women are usually bacteremic and present with a nonspecific febrile illness that includes myalgias/arthralgias, backache, and headache; CNS involvement is uncommon. Infected women usually do well after delivery.
 - Infection develops in 70–90% of fetuses from infected women; almost 50% of infected fetuses die. This risk can be reduced to ~20% with prepartum treatment.
 - Overwhelming listerial fetal infection—*granulomatosis infantiseptica*—is characterized by miliary microabscesses and granulomas, most often in the skin, liver, and spleen.
 - Late-onset neonatal disease develops ~10–30 days after delivery by mothers with asymptomatic infection.
- **Diagnosis:** Timely diagnosis requires that the illness be considered in groups at risk: pregnant women, elderly pts, neonates, immunocompromised pts, and pts with chronic underlying medical conditions (e.g., alcoholism, diabetes).
 - Listeriosis is diagnosed when the organism is cultured from a usually sterile site, such as blood, CSF, or amniotic fluid.
 - Listeriae may be confused with “diphtheroids” or pneumococci in gram-stained CSF or may be gram-variable and confused with *Haemophilus* spp.
 - Serologic tests and PCR assays are not clinically useful at present.

TREATMENT**Listerial Infections**

- Ampicillin (2 g IV q6h) is the drug of choice for the treatment of listerial infections; penicillin is also highly active.
 - Many experts recommend the addition of gentamicin (1.0–1.7 mg/kg IV q8h) for synergy.
 - For penicillin-allergic pts, trimethoprim-sulfamethoxazole (15–20 mg of TMP/kg IV daily in divided doses q6–8h) should be given. Cephalosporins are not effective.
 - Neonates should receive ampicillin and gentamicin, dosed by weight.
 - The duration of therapy depends on the syndrome: 2 weeks for bacteremia, 3 weeks for meningitis, 6–8 weeks for brain abscess/encephalitis, and 4–6 weeks for endocarditis. Early-onset neonatal disease can be severe and requires treatment for >2 weeks.
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- **Prognosis:** With prompt therapy, many pts recover fully.
 - However, permanent neurologic sequelae are common in pts with brain abscess or rhombencephalitis.
 - Of live-born treated neonates in one series, 60% recovered fully, 24% died, and 13% were left with neurologic or other complications.
 - **Prevention:** Pregnant women and other persons at risk for listeriosis should avoid soft cheeses and should avoid or thoroughly reheat ready-to-eat and delicatessen foods, even though the absolute risk posed by these foods is relatively low.

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**Infections Caused by
Haemophilus, *Bordetella*,
Moraxella, and HACEK Group
Organisms****HAEMOPHILUS INFLUENZAE****■ MICROBIOLOGY**

H. influenzae is a small, gram-negative, pleomorphic coccobacillus that grows both aerobically and anaerobically.

- Six major serotypes (designated *a–f*) have been identified on the basis of antigenically distinct polysaccharide capsules.
- Unencapsulated strains are referred to as nontypable (NTHi).

■ EPIDEMIOLOGY

H. influenzae, an exclusively human pathogen, is spread by airborne droplets or through direct contact with secretions or fomites.

- Type b (Hib) strains are most important clinically, causing systemic invasive disease, primarily in infants and children <6 years of age.

- Of the 194 World Health Organization member countries, 99% have introduced Hib conjugate vaccination, but a large number of children worldwide remain unimmunized.
- Both typable and nontypable strains can asymptotically colonize the nasopharynx.

■ PATHOGENESIS

Hib strains cause systemic disease by invasion and systemic spread from the respiratory tract to distant sites (e.g., meninges, bones, joints). In contrast, NTHi strains cause disease by spread from the nasopharynx to contiguous sites (e.g., middle ear, lower respiratory tract).

- The polysaccharide capsule of encapsulated strains is critical for the organism's avoidance of opsonization.
- Levels of maternally derived antibodies to the capsular polysaccharide decline from birth to ~6 months of age and—in the absence of vaccination—remain low until ~2–3 years of age.

■ CLINICAL MANIFESTATIONS

- **Hib infection:** The most serious Hib infections are associated with meningitis or epiglottitis.
 - *Meningitis:* primarily affects children <2 years old and presents similarly to meningitis due to other bacterial pathogens
 - Mortality rates are ~5%.
 - *Morbidity rates are high:* 6% of pts have sensorineural hearing loss; one-fourth have some significant handicap; and one-half have some neurologic sequelae.
 - *Epiglottitis:* occurs in children 2–7 years old and occasionally in adults. It involves cellulitis of the epiglottis and supraglottic tissues that begins with a sore throat and fever and progresses rapidly to dysphagia, drooling, and airway obstruction.
 - *Other infections:* include cellulitis, pneumonia, osteomyelitis, septic arthritis, and bacteremia without an identifiable focus
- **NTHi infection:** NTHi is a common cause of lower respiratory tract disease in adults, particularly those with chronic obstructive pulmonary disease (COPD).
 - *COPD exacerbations:* characterized by increased cough, sputum production, and shortness of breath
 - *Pneumonia:* presents similarly to other bacterial pneumonias, including pneumococcal pneumonia
 - *Other infections:* NTHi is one of the three most common causes of childhood otitis media and is an important cause of sinusitis (in adults and children) and neonatal bacteremia. It is a less common cause of invasive infections in adults.

■ DIAGNOSIS

Recovery of the organism in culture is the most reliable method for diagnosis.

- The presence of gram-negative coccobacilli in gram-stained CSF provides strong evidence for meningitis due to *H. influenzae*.
- Detection of polyribitol ribose phosphate (PRP)—polymers of which form the type b capsule—in CSF allows rapid diagnosis of Hib meningitis before culture results are available.

TREATMENT***H. influenzae* Infections**

- Initial therapy for Hib meningitis consists of a third-generation cephalosporin: ceftriaxone (2 g q12h) or cefotaxime (2 g q4–6h) for adults and ceftriaxone (37.5–50 mg/kg q12h) or cefotaxime (50 mg/kg q6h) for children.
 - Children >2 months of age should receive adjunctive dexamethasone (0.15 mg/kg IV q6h for 2 days) to reduce the incidence of neurologic sequelae.
 - Antibiotic therapy should continue for 7–14 days.
- Antibiotic treatment for invasive infections other than meningitis (e.g., epiglottitis) consists of the same antibiotic but at a dosage different from that given for meningitis—e.g., ceftriaxone (2 g q24h) for adults.
 - Treatment duration depends on the clinical response, but a course lasting 1–2 weeks is generally appropriate.
- Most NTHi infections can be treated with oral antibiotics, such as amoxicillin/clavulanate, extended-spectrum cephalosporins, macrolides (azithromycin or clarithromycin), and fluoroquinolones (in nonpregnant adults).
 - About 20–35% of NTHi strains produce β -lactamase.
 - The incidence of strains with altered penicillin-binding proteins conferring resistance to ampicillin is increasing in Europe and Japan.
 - The incidence of resistance to macrolides is increasing in many regions of the world.

■ PREVENTION

Hib vaccine is recommended for all children worldwide; the immunization series should be started at ~2 months of age.

- Secondary attack rates are high among household contacts of pts with Hib disease. All children and adults (except pregnant women) in households with a case of Hib disease and at least one incompletely immunized contact <4 years of age should receive prophylaxis with oral rifampin.
- A vaccine that combines NTHi and pneumococcal antigens is used in many countries outside the United States and has shown partial efficacy in preventing *H. influenzae* otitis media.

PERTUSSIS**■ MICROBIOLOGY AND PATHOGENESIS**

Bordetella pertussis, the etiologic agent of pertussis, is a fastidious gram-negative pleomorphic aerobic bacillus that attaches to ciliated epithelial cells of the nasopharynx, multiplies locally, and produces a wide array of toxins and biologically active products.

- *B. parapertussis* causes a similar, though typically milder, illness. *B. holmesii* causes up to 20% of pertussis-like syndromes.
- The most important toxin in *B. pertussis* is pertussis toxin, which has ADP-ribosylating activity. The absence of this toxin in *B. parapertussis* may explain the milder illness.

■ EPIDEMIOLOGY

Pertussis is highly communicable. In households, attack rates are 80–100% among unimmunized contacts and 20% among immunized contacts.

- Pertussis remains an important cause of infant morbidity and death in developing countries, with ~63,000 deaths worldwide of children <5 years of age in 2013.
- In the United States, although the incidence of pertussis has decreased by >95% because of universal childhood vaccination, >40,000 cases were reported in 2012, with increasing rates among adolescents and adults.
- Persistent cough of >2 weeks' duration in an adult may be due to *B. pertussis* in 12–30% of cases.
- Severe morbidity and mortality are restricted to infants <6 months of age.

■ CLINICAL MANIFESTATIONS

After an incubation period of 7–10 days, a prolonged coughing illness begins. Symptoms are usually more severe in infants and young children.

- The initial symptoms (the *catarrhal* phase) are similar to those of the common cold (e.g., coryza, lacrimation, mild cough, low-grade fever, malaise) and last 1–2 weeks.
- The *paroxysmal* phase follows and lasts 2–4 weeks. It is characterized by a hallmark cough that occurs in spasmodic fits of 5–10 coughs each. Vomiting or a “whoop” may follow a coughing fit. Apnea and cyanosis can occur during spasms. Most complications occur during this phase.
- During the subsequent *convalescent* phase, coughing episodes resolve gradually over 1–3 months. For 6–12 months, viral infections may induce a recrudescence of paroxysmal cough.
- Disease manifestations are often atypical in adolescents and adults, with paroxysmal cough and the “whoop” being less common. Post-tussive emesis is the best predictor of pertussis as the cause of prolonged cough in adults.
- Lymphocytosis (an absolute lymphocyte count of $>10^5/\mu\text{L}$) suggests pertussis in young children, but is not common among affected adolescents and adults.

■ DIAGNOSIS

- Cultures of nasopharyngeal secretions—the gold standard for diagnosis—remain positive in untreated cases of pertussis for a mean of 3 weeks after illness onset. Given that the diagnosis often is not considered until the pt is in the paroxysmal phase, there is a small window of opportunity for culture-proven diagnosis.
 - Secretions must be inoculated immediately onto selective media.
 - Results become positive by day 5.
- Compared with culture, PCR of nasopharyngeal specimens is more sensitive and yields positive results longer in both treated and untreated pts.
 - Reporting of pseudo-outbreaks of pertussis based on false-positive PCR results indicates the need for greater standardization.
- Although serology can be useful in pts with symptoms lasting >4 weeks, interpretation of results is complicated by late presentation for medical care and prior immunization.

TREATMENT

Pertussis

- Antibiotic therapy does not substantially alter the clinical course unless given early in the catarrhal phase, but is effective at eradicating the organism from the nasopharynx.

- Macrolides (erythromycin, 1–2 g/d for 1–2 weeks; clarithromycin, 250 mg bid for 1 week; or azithromycin, 500-mg load on day 1, then 250 mg/d for 4 days) are the drugs of choice.
- Trimethoprim-sulfamethoxazole (TMP-SMX; one double-strength tablet PO bid for 2 weeks) is recommended for macrolide-intolerant pts.
- Cough suppressants are ineffective and have no role in management of pertussis.
- Respiratory isolation is required for hospitalized pts until antibiotics have been given for 5 days.

■ PREVENTION

- Chemoprophylaxis with macrolides is recommended for household contacts of pts, especially if there are household members at high risk of severe disease (e.g., children <1 year of age, pregnant women); however, there is no evidence demonstrating that this regimen leads to a decrease in the incidence of clinical disease.
- In addition to the regular childhood immunization schedule, adolescents and adults should receive a one-time booster with an acellular vaccine. Some countries, including the United States and the United Kingdom, also recommend vaccination for pregnant women in the third trimester.

MORAXELLA CATARRHALIS

■ MICROBIOLOGY AND EPIDEMIOLOGY

M. catarrhalis is an unencapsulated gram-negative diplococcus. Part of the normal flora of the upper airways, *M. catarrhalis* colonizes 33–100% of infants; the prevalence of colonization decreases steadily with age.

■ CLINICAL MANIFESTATIONS

- *M. catarrhalis* causes 15–20% of cases of acute otitis media in children. Acute otitis media caused by *M. catarrhalis* or NTHi is clinically milder than cases caused by *Streptococcus pneumoniae*, with less fever and a lower frequency of an erythematous, bulging tympanic membrane.
- *M. catarrhalis* accounts for ~20% of cases of acute bacterial sinusitis in children and for a smaller proportion in adults.
- In adults, *M. catarrhalis* is a common cause of exacerbations of COPD, accounting for ~10% of cases.
- *M. catarrhalis* pneumonia is uncommon, generally affecting elderly pts with underlying cardiopulmonary disease.

■ DIAGNOSIS

Invasive procedures are needed to definitively identify the etiology of otitis media or sinusitis and generally are not performed. Isolation of *M. catarrhalis* from sputum samples from pts with COPD is suggestive, but not diagnostic, of *M. catarrhalis* as the cause.

TREATMENT

M. Catarrhalis Infections

- Otitis media in children and exacerbations of COPD in adults are generally managed empirically with antibiotics active against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

- Most strains of *M. catarrhalis* are susceptible to amoxicillin/clavulanate, extended-spectrum cephalosporins, macrolides (e.g., azithromycin, clarithromycin), TMP-SMX, and fluoroquinolones.
- More than 90% of *M. catarrhalis* strains produce a β -lactamase and are resistant to ampicillin. Resistance to macrolides and fluoroquinolones is increasing in Asia.

THE HACEK GROUP

■ MICROBIOLOGY

The HACEK group consists of fastidious, slow-growing, gram-negative bacteria whose growth requires carbon dioxide. Several *Haemophilus* spp., *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, *Aggregatibacter* (formerly *Haemophilus*) *aphrophilus*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae* make up this group. Normal residents of the oral cavity, HACEK bacteria can cause both local oral infections and severe systemic disease, particularly endocarditis.

■ CLINICAL MANIFESTATIONS

- HACEK organisms caused 0.8–6% of cases of infective endocarditis; most of these cases are due to *Aggregatibacter* spp., *Haemophilus* spp., or *C. hominis*.
- Infection typically occurs in pts with underlying valvular disease, often in the setting of a recent dental procedure or nasopharyngeal infection.
- The aortic and mitral valves are most commonly affected. *Aggregatibacter* and *Haemophilus* spp. cause mitral valve vegetations most often, while *C. hominis* is associated with aortic valve vegetations.
- Embolization is common, with 28–71% of pts affected.
- *H. parainfluenzae* is the most common *Haemophilus* species isolated in cases of HACEK endocarditis. Pts usually present within the first 2 months of illness, and 19–50% of pts develop CHF.
- *Aggregatibacter* spp. are the most common cause of HACEK endocarditis and cause prosthetic-valve endocarditis more often than *Haemophilus* spp. *A. actinomycetemcomitans* is isolated from soft-tissue infections in association with *Actinomyces israelii*. Pts with *Aggregatibacter* endocarditis often have periodontal disease or have recently had dental work and are sick for several months before diagnosis.
- *C. hominis* typically causes endocarditis in pts with valvular heart disease or prosthetic valves. Long-standing infection with systemic manifestations usually precedes diagnosis. A second species, *C. valvarum*, has been described in association with endocarditis.
- *E. corrodens* is usually a component of mixed infections and is common in human bite wounds, head and neck soft-tissue infections, endocarditis, and infections in IV drug users.
- *K. kingae* is a common cause of musculoskeletal infections in children <4 years old. Inoculation of clinical specimens (e.g., synovial fluid) into aerobic blood-culture bottles enhances recovery of this organism. Infective endocarditis due to *K. kingae* occurs in older children and adults with preexisting valvular disease.

TREATMENT

HACEK Group Infections

- **Table 92-1** lists antibiotic regimens used to treat endocarditis and other serious infections caused by HACEK organisms.

TABLE 92-1 Treatment of Infections Caused by HACEK Group

ORGANISMS	PREFERRED THERAPY	ALTERNATIVE AGENTS	COMMENTS
<i>Haemophilus</i> spp. <i>Aggregatibacter</i> spp. <i>Cardiobacterium</i> spp. <i>Eikenella corrodens</i> <i>Kingella kingae</i>	Ceftriaxone (2 g/d)	Ampicillin/ sulbactam (3 g of ampicillin q6h) Levofloxacin (750 mg/d)	Ampicillin/sulbactam resistance has been described in <i>Haemophilus</i> and <i>Aggregatibacter</i> spp. Data on use of levofloxacin for endocarditis therapy are limited. Fluoroquinolones are not recommended for treatment of pts <18 years of age. Penicillin (16–18 million units q4h) or ampicillin (2 g q4h) can be used if the organism is susceptible. However, because of the slow growth of HACEK bacteria, antimicrobial testing may be difficult, and β -lactamase production may not be detected.

- Native-valve endocarditis should be treated for 4 weeks and prosthetic-valve endocarditis for 6 weeks.
- Unlike prosthetic-valve endocarditis caused by other gram-negative organisms, that due to HACEK bacteria can often be cured with antibiotics alone (i.e., without surgery).

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Diseases Caused by Gram-Negative Enteric Bacteria and Pseudomonads



GRAM-NEGATIVE ENTERIC BACTERIA

■ GENERAL CONSIDERATIONS

Gram-negative bacilli (GNB) are normal components of the human colonic microbiota and/or a number of environmental habitats and can colonize mucosal and skin surfaces, especially in pts in long-term-care facilities and hospital settings. GNB cause a wide variety of infections involving diverse anatomic sites in both healthy and compromised hosts; extraintestinal infections due to *Escherichia coli*

and, to a lesser degree, *Klebsiella* species are most common. Isolation of GNB from any sterile site almost always implies infection, whereas isolation from nonsterile sites requires clinical correlation. Early appropriate antimicrobial therapy improves outcomes. Given worldwide increases in multidrug-resistant GNB (e.g., due to extended-spectrum β -lactamases [ESBLs] and AmpC β -lactamases), combination empirical antimicrobial therapy pending susceptibility results may be appropriate for critically ill pts.

■ EXTRAINTESTINAL PATHOGENIC *E. COLI* (ExPEC)

In contrast to intestinal pathogenic *E. coli* (see below), ExPEC strains are often found in the intestinal microbiota of healthy individuals but cause disease only when they enter a normally sterile extraintestinal site (e.g., the urinary tract, peritoneal cavity, or lungs). Most ExPEC strains have virulence factor profiles distinct from those of other commensal strains and from those of pathogenic strains that cause intestinal infections.

Clinical Manifestations

The clinical presentation depends in large part on the site of the body infected by ExPEC.

- **UTI:** The urinary tract is the site most frequently infected by ExPEC; see [Chap. 147](#) for more details. *E. coli* causes 80–90% of ~6–8 million episodes of acute uncomplicated UTI in ambulatory premenopausal women.
- **Abdominal and pelvic infection:** The abdomen and pelvis represent the second most common site of infection by ExPEC, which may be isolated in the setting of a polymicrobial infection; see [Chap. 84](#) for more details. Syndromes include peritonitis, intraabdominal abscesses, and cholangitis.
- **Pneumonia:** ExPEC is generally the third or fourth most commonly isolated GNB in hospital-acquired pneumonia and can be a common cause of pneumonia in pts residing in long-term-care facilities; see [Chap. 134](#) for more details.
- **Meningitis:** *E. coli* is one of the two leading causes of neonatal meningitis (the other being group B *Streptococcus*). Strains with the K1 capsular serotype are generally involved.
- **Cellulitis/musculoskeletal infection:** *E. coli* often contributes to infection of decubitus ulcers and diabetic lower-extremity ulcers, cellulitis, and burn-site or surgical-site infections. Hematogenously acquired osteomyelitis, particularly vertebral, is more commonly caused by *E. coli* than is generally appreciated. See [Chap. 87](#) for more details.
- **Bacteremia:** *E. coli* bacteremia can arise from primary infection at any site, but originates most commonly from the urinary tract (50–67% of episodes) and next most commonly from the abdomen (25% of episodes). *E. coli* bacteremia is almost always clinically significant and may be associated with sepsis. Endovascular infections are rare but have been described.

Diagnosis

ExPEC grows readily on standard media under either aerobic or anaerobic conditions. More than 90% of strains ferment lactose and are indole positive.

TREATMENT

Extraintestinal Infections Caused by *E. coli*

- Rates of resistance to ampicillin, first-generation cephalosporins, trimethoprim-sulfamethoxazole (TMP-SMX), and fluoroquinolones are >20%. This resistance

precludes empirical use of these agents for serious infections. ESBLs are increasingly common (8–60%) in *E. coli*.

- Carbapenems, amikacin, piperacillin-tazobactam, ceftazidime-avibactam, and ceftolozane-tazobactam are the most predictably active agents overall, but carbapenemase-producing strains are on the rise.
- It is important to use the most appropriate narrower-spectrum agent whenever possible and to avoid treating colonized but uninfected pts, thus combating the increase in antibiotic resistance.

■ INTESTINAL PATHOGENIC *E. COLI*

Microbiology and Clinical Manifestations

At least five distinct pathotypes of intestinal pathogenic *E. coli* exist; see [Chap. 85](#) for more details. As mentioned above, these strains are rarely encountered as part of the commensal microbiota in healthy individuals.

- *Shiga toxin–producing E. coli (STEC)/enterohemorrhagic E. coli (EHEC)/Shiga toxin–producing enteroaggregative E. coli (ST-EAEC)*: In addition to diarrhea, STEC/EHEC infection results in the hemolytic–uremic syndrome (HUS) in 2–8% of pts, particularly those who are very young or elderly. ST-EAEC results in a higher rate of HUS (~20%), with a higher incidence among adults, especially young women.
 - STEC/EHEC/ST-EAEC is associated with ingestion of contaminated food (e.g., undercooked ground beef, fresh produce) and water; person-to-person transmission (e.g., at day-care centers) is an important route for secondary spread.
 - Disease can be caused by $<10^2$ colony-forming units (CFU) of STEC/EHEC/ST-EAEC.
 - In contrast to the other pathotypes, STEC/EHEC/ST-EAEC (including *E. coli* O157:H7) causes infection more frequently in industrialized countries than in developing countries.
- *Enterotoxigenic E. coli (ETEC)*: These strains are a major cause of endemic diarrhea among children residing in tropical and low-income countries and are the most common agent of traveler’s diarrhea; 10^6 – 10^8 CFU are needed to cause disease.
- *Enteropathogenic E. coli (EPEC)*: EPEC is an important cause of diarrhea among infants in developing countries.
- *Enteroinvasive E. coli (EIEC)*: EIEC, an uncommon cause of diarrhea, produces inflammatory colitis (stools containing mucus, blood, and inflammatory cells) similar to that caused by *Shigella* and primarily affects children and travelers in developing countries; 10^8 – 10^{10} CFU are needed to cause disease.
- *Enteraggregative and diffusely adherent E. coli (EAEC)*: EAEC was initially described in young children in developing countries. More recent studies indicate that EAEC infection requires a large inoculum and may be a common cause of prolonged, watery diarrhea in all age groups in industrialized countries.

Diagnosis

Specific diagnosis is usually unnecessary for management, but detection of STEC/EHEC/ST-EAEC has public health importance. To detect the latter, simultaneous culture (screening for *E. coli* strains that do not ferment sorbitol followed by serotyping for O157) and testing for Shiga toxins or toxin genes is recommended.

TREATMENT**Intestinal Infections Caused by *E. coli***

- See **Chap. 85** for more details. Replacement of water and electrolytes and avoidance of antibiotics in STEC/EHEC/ST-EAEC infection (since antibiotic use may increase the incidence of HUS) are indicated.

■ KLEBSIELLA**Epidemiology**

K. pneumoniae colonizes the colon in 5–35% of healthy individuals and, from a medical standpoint, is the most important *Klebsiella* species. *K. oxytoca* primarily causes infections in long-term care and hospital settings. *K. pneumoniae* subspecies *rhinoscleromatis*, which causes rhinoscleroma, and *K. pneumoniae* subspecies *ozaenae*, which causes chronic atrophic rhinitis, infect pts in tropical climates.

Clinical Manifestations

As in other GNB infections, the clinical presentation depends on the infected anatomic site.

- **Pneumonia:** *Klebsiella* is a common cause of pneumonia among residents of long-term care facilities and hospitalized pts. In Asia and South Africa, community-acquired pneumonia due to hypervirulent strains of *K. pneumoniae* is increasingly common, particularly among younger, healthy pts.
 - The presentation is similar to that of pneumonia caused by other enteric GNB, with purulent sputum production and pulmonary infiltrates on CXR.
 - Infection can progress to pulmonary necrosis, pleural effusion, and empyema.
- **UTI:** *K. pneumoniae* causes 1–2% of cases of uncomplicated cystitis and 5–17% of cases of complicated UTI.
- **Abdominal infections:** *Klebsiella* causes a spectrum of disease similar to that of *E. coli*, but with less frequent occurrence. Hypervirulent strains have become a common cause of monomicrobial community-acquired liver abscess, spontaneous bacterial peritonitis, and splenic abscess.
- **Bacteremia:** Bacteremia can arise from a primary infection at any site; infections of the urinary tract, respiratory tract, and abdomen (especially hepatic abscess) each account for 15–30% of episodes.
- **Other infections:** *Klebsiella* cellulitis or soft-tissue infection most frequently affects devitalized tissue and immunocompromised hosts. *Klebsiella* can also cause endophthalmitis, nosocomial sinusitis, and osteomyelitis.

Diagnosis

Klebsiellae usually ferment lactose, although the *K. pneumoniae* subspecies *rhinoscleromatis* and *ozaenae* are nonfermenters and are indole negative.

TREATMENT***Klebsiella* Infections**

- Klebsiellae are intrinsically resistant to ampicillin and ticarcillin and are inconsistently susceptible to nitrofurantoin.
 - The increase in plasmid-encoded ESBLs has led to increasing resistance to third- and fourth-generation cephalosporins, aminoglycosides, tetracyclines, and TMP-SMX.
 - Fluoroquinolone resistance is increasing, especially among ESBL-containing strains.

- Empirical treatment of serious or health care–associated *Klebsiella* infections with amikacin or carbapenems is prudent; however, carbapenemase-producing strains are increasing in frequency. Optimal therapy for carbapenemase strains is unclear, but tigecycline, the polymyxins (e.g., colistin), and ceftazidime-avibactam (ineffective against metallo-carbapenemases) are used most frequently on the basis of in vitro susceptibility profiles. When resistance to these agents is documented, combination therapy is often used.

■ PROTEUS

Epidemiology

P. mirabilis is part of the normal microbiota in 50% of healthy people and causes 90% of *Proteus* infections. *P. vulgaris* and *P. penneri* are isolated primarily from pts in hospitals and long-term care facilities.

Clinical Manifestations

Most *Proteus* infections arise from the urinary tract. *Proteus* species account for 1–2% of uncomplicated UTIs, 5% of hospital-acquired UTIs, and 10–15% of complicated UTIs (especially those associated with urinary catheters).

- *Proteus* produces high levels of urease that result in alkalization of urine and ultimately in formation of struvite and carbonate-apatite calculi.
- Infections at other sites are uncommon but include pneumonia, abdominal infections, soft-tissue infections, and bacteremia.

Diagnosis

Proteus strains are typically lactose negative, produce H₂S, and exhibit swarming motility on agar plates. *P. mirabilis* and *P. penneri* are indole negative, whereas *P. vulgaris* is indole positive.

TREATMENT

Proteus Infections

- *P. mirabilis* is susceptible to most agents except tetracycline, cefazolin, nitrofurantoin, polymyxins, and tigecycline. Resistance to ampicillin, first-generation cephalosporins, and fluoroquinolones is increasing.
- *P. vulgaris* and *P. penneri* are more resistant; induction of variants with stable derepression of chromosomal AmpC β-lactamase may occur with *P. vulgaris* isolates. Carbapenems, fourth-generation cephalosporins, amikacin, TMP-SMX, and fosfomycin exhibit excellent activity: 90–100% of *Proteus* isolates are susceptible.

■ OTHER GRAM-NEGATIVE ENTERIC PATHOGENS

- *Enterobacter* (e.g., *E. cloacae*, *E. aerogenes*), *Acinetobacter* (e.g., *A. baumannii*), *Serratia* (e.g., *S. marcescens*), and *Citrobacter* (e.g., *C. freundii*, *C. koseri*) usually cause nosocomial infections. Risk factors include immunosuppression, comorbid disease, prior antibiotic use, and ICU stays.
- Infections caused by *Morganella* (e.g., *M. morganii*) and *Providencia* (e.g., *P. stuartii*, *P. rettgeri*) resemble *Proteus* infections in terms of epidemiology, pathogenicity, and clinical manifestations but occur almost exclusively among persons in long-term care facilities and, to a lesser degree, among hospitalized pts.

■ CLINICAL MANIFESTATIONS

These organisms generally cause a spectrum of disease similar to that caused by other GNB, including pneumonia (particularly ventilator-associated), UTI (especially catheter-related), intravascular device-related infection, surgical-site infection, and abdominal infection.

- *Citrobacter*, *Morganella*, and *Providencia* infections are generally associated with UTIs.
- *Acinetobacter* has caused skin and soft-tissue infections in victims of trauma (e.g., soldiers in war zones, victims of natural disasters). *A. baumannii* infections occur frequently among pts admitted to ICUs.

TREATMENT

Infections Caused by Other Gram-Negative Enteric Pathogens

- Significant antibiotic resistance among these organisms makes therapy challenging.
 - Many of these organisms (e.g., *Serratia*, *Providencia*, *Acinetobacter*, *Citrobacter*, *Enterobacter*, *Morganella*) have a derepressible AmpC β -lactamase that results in resistance to third-generation cephalosporins, monobactams, and—in many cases— β -lactam/ β -lactamase inhibitor combinations.
 - *Morganella* and *Providencia* are inherently resistant to the polymyxins and tigecycline.
- Carbapenems and amikacin are most reliably active, and fourth-generation cephalosporins are active provided the organism does not express an ESBL. Susceptibility testing is essential. Some isolates may retain susceptibility only to colistin and polymyxin B.

■ AEROMONAS

Aeromonas organisms (e.g., *A. hydrophila*, *A. caviae*, *A. veronii*, *A. dhakensis*) proliferate in potable water, freshwater, and soil and are a putative cause of gastroenteritis. *Aeromonas* causes bacteremia and sepsis in infants and compromised hosts, especially those with cancer, hepatobiliary disease, trauma, or burns. The organisms can produce skin lesions similar to the ecthyma gangrenosum caused by *Pseudomonas aeruginosa*. *Aeromonas* causes nosocomial infections related to catheters, surgical incisions, and use of leeches.

TREATMENT

Aeromonas Infections

- *Aeromonas* is usually susceptible to fluoroquinolones (e.g., ciprofloxacin, 500 mg PO q12h or 400 mg IV q12h), third- and fourth-generation cephalosporins, carbapenems, and aminoglycosides.
- Susceptibility testing is critical to guide therapy since *Aeromonas* can produce various β -lactamases, including carbapenemases.

P. AERUGINOSA AND RELATED ORGANISMS

The pseudomonads make up a set of gram-negative organisms unable to ferment lactose. This group includes three medically important genera—*Pseudomonas*, *Burkholderia*, and *Stenotrophomonas*—that typically cause opportunistic disease.

■ P. AERUGINOSA

Microbiology

P. aeruginosa is a motile gram-negative rod that commonly produces green or bluish pigment and may have a mucoid appearance (which is particularly common in isolates from pts with cystic fibrosis). *P. aeruginosa* differs from enteric GNB in that it has a positive reaction in the oxidase test and does not ferment lactose.

Epidemiology

Because *P. aeruginosa* is found in most moist environments (e.g., in soil, in tap water, and on countertops), people routinely come into contact with the organism. The many factors that predispose to *P. aeruginosa* infection include disruption of cutaneous or mucosal barriers (e.g., due to burns or trauma), immunosuppression (e.g., due to neutropenia, AIDS, or diabetes), and disruption of the normal bacterial flora (e.g., due to broad-spectrum antibiotic therapy).

- *P. aeruginosa* is no longer a major cause of life-threatening bacteremia among pts with neutropenia or burn injury.
- *P. aeruginosa* bacteremia is currently most common among pts in the ICU.

Clinical Manifestations

P. aeruginosa can infect virtually all sites in the body but has a strong predilection for the lungs.

- **Pneumonia:** *P. aeruginosa* is considered a major cause of ventilator-associated pneumonia, although colonization may be difficult to distinguish from true infection.
 - Clinically, most pts have a slowly progressive infiltrate, although progression is rapid in some cases. Infiltrates may become necrotic.
 - It is unclear whether an invasive procedure (e.g., bronchoalveolar lavage, protected-brush sampling of distal airways) is superior to tracheal aspiration in obtaining samples for culture.
 - Chronic respiratory infection with *P. aeruginosa* is associated with underlying or predisposing conditions (e.g., cystic fibrosis, bronchiectasis).
- **Bacteremia:** The presentation of *P. aeruginosa* bacteremia resembles that of sepsis in general but may be more severe, with attributable mortality rates of 28–44%.
 - Pathognomonic skin lesions (*ecthyma gangrenosum*) that at first are painful, reddish, and maculopapular and later become black and necrotic may develop in pts with marked neutropenia or HIV infection.
 - Endovascular infections occur mostly in IV drug users and pts with prosthetic valves.
- **Bone and joint infections:** *P. aeruginosa* is an infrequent cause of bone and joint infections.
 - Injection drug use (associated with sternoclavicular joint infections and vertebral osteomyelitis) and UTIs in the elderly (associated with vertebral osteomyelitis) are risk factors.
 - *Pseudomonas* osteomyelitis of the foot most often follows puncture wounds through sneakers and most commonly affects children.
- **CNS infections:** CNS infections due to *P. aeruginosa* are relatively rare and are almost always secondary to a surgical procedure or head trauma.
- **Eye infections:** Keratitis and corneal ulcers can occur, usually resulting from trauma or surface injury by contact lenses. These infections are rapidly progressing entities that demand immediate therapeutic intervention. *P. aeruginosa* endophthalmitis secondary to bacteremia is a fulminant disease with severe pain, chemosis, decreased visual acuity, anterior uveitis, vitreous involvement, and panophthalmitis.

- **Ear infections:** In addition to mild swimmer's ear, *Pseudomonas* ear infections can result in malignant otitis externa, a life-threatening infection that presents as severe ear pain and decreased hearing.
 - Pts may develop cranial-nerve palsies or cavernous venous sinus thrombosis.
 - Most ear infections due to *P. aeruginosa* occur in elderly diabetic pts.
- **UTIs:** UTIs due to *P. aeruginosa* usually result from a foreign body in the urinary tract, an obstruction in the genitourinary system, or urinary tract instrumentation or surgery.
- **Skin and soft tissue infections:** *P. aeruginosa* can cause a variety of dermatitides, including pyoderma gangrenosum in neutropenic pts, folliculitis, and other papular or vesicular lesions. Multiple outbreaks have been linked to whirlpools, spas, and swimming pools.
- **Infections in pts with fever and neutropenia:** *P. aeruginosa* is always targeted in empirical treatment of these pts, given high rates of infection in the past and high associated mortality rates.
- **Infections in pts with AIDS:** *P. aeruginosa* infections in pts with AIDS can be fatal even though the clinical presentation is not particularly severe.
 - Pneumonia is the most common type of infection, with a high frequency of cavitory disease.
 - Since the advent of antiretroviral therapy, *P. aeruginosa* infection has declined in incidence among these pts but still occurs.

TREATMENT

P. aeruginosa Infections

- See [Table 93-1](#) for antibiotic options and schedules.
- Several observational studies indicate that a single modern antipseudomonal β -lactam agent to which the isolate is sensitive is as efficacious as combination therapy. However, if—in the local environment—the susceptibility rate to first-line agents is <80%, empirical combination therapy should be administered until isolate-specific susceptibility data are available.

■ BACTERIA RELATED TO PSEUDOMONAS SPECIES

Stenotrophomonas maltophilia

S. maltophilia is an opportunistic pathogen. Most infections occur in the setting of prior broad-spectrum antimicrobial therapy that has eradicated the normal flora in immunocompromised pts.

- *S. maltophilia* causes pneumonia, especially ventilator-associated pneumonia, with or without bacteremia.
- Central venous line infection (most often in cancer pts) and ecthyma gangrenosum in neutropenic pts have been described.

Burkholderia cepacia

This organism can colonize airways during broad-spectrum antimicrobial treatment and is a cause of ventilator-associated pneumonia, catheter-associated infection, and wound infection.

- *B. cepacia* is recognized as an antibiotic-resistant nosocomial pathogen in ICU pts.
- *B. cepacia* can cause a rapidly fatal syndrome of respiratory distress and septicemia (the “*cepacia* syndrome”) in pts with cystic fibrosis.

TABLE 93-1 Antibiotic Treatment of Infections Due to *Pseudomonas aeruginosa* and Related Species

INFECTION	ANTIBIOTICS AND DOSAGES	OTHER CONSIDERATIONS
<p>Bacteremia</p> <p>Nonneutropenic host</p> <p>Neutropenic host</p>	<p>Ceftazidime (2 g q8h IV) or cefepime (2 g q8h IV) or piperacillin/tazobactam (3.375 g q4h IV) or imipenem (500 mg q6h IV) or meropenem (1 g q8h IV) or doripenem (500 mg q8h IV)</p> <p>Optional:</p> <p>Amikacin (7.5 mg/kg q12h or 15 mg/kg q24h IV)</p> <p>Cefepime (2 g q8h IV) or all the other agents above (except doripenem) in the above dosages</p>	<p>Add an aminoglycoside for pts in shock and in regions or hospitals where rates of resistance to the primary β-lactam agents are high. Tobramycin may be used instead of amikacin (susceptibility permitting). The duration of therapy is 7 days for nonneutropenic pts. Neutropenic pts should be treated until no longer neutropenic.</p>
Endocarditis	Antibiotic regimens as for bacteremia for 6–8 weeks	Resistance during therapy is common. Surgery is required for relapse.
Pneumonia	Drugs and dosages as for bacteremia, except that the available carbapenems should not be the sole primary drugs because of high rates of resistance during therapy	IDSA guidelines recommend the addition of an aminoglycoside or ciprofloxacin. The duration of therapy is 7 days.
Bone infection, malignant otitis externa	Cefepime or ceftazidime at the same dosages as for bacteremia; aminoglycosides not a necessary component of therapy; ciprofloxacin (500–750 mg q12h PO) may be used	Duration of therapy varies with the drug used (e.g., 6 weeks for a β -lactam agent; at least 3 months for oral therapy except in puncture-wound osteomyelitis, for which the duration should be 2–4 weeks).
Central nervous system infection	Ceftazidime or cefepime (2 g q8h IV) or meropenem (1 g q8h IV)	Abscesses or other closed-space infections may require drainage. The duration of therapy is ≥ 2 weeks.
Eye infection Keratitis/ulcer	Topical therapy with tobramycin/ciprofloxacin/levofloxacin eyedrops	Use maximal strengths available or compounded by pharmacy. Therapy should be administered for 2 weeks or until the resolution of eye lesions, whichever is shorter.

(Continued)

TABLE 93-1 Antibiotic Treatment of Infections Due to *Pseudomonas aeruginosa* and Related Species (Continued)

INFECTION	ANTIBIOTICS AND DOSAGES	OTHER CONSIDERATIONS
Endophthalmitis	Ceftazidime or cefepime as for central nervous system infection plus Topical therapy	
Urinary tract infection	Ciprofloxacin (500 mg q12h PO) or levofloxacin (750 mg q24h) or any aminoglycoside (total daily dose given once daily)	Relapse may occur if an obstruction or a foreign body is present. The duration of therapy for complicated UTI is 7–10 days (up to 2 weeks for pyelonephritis).
Multidrug-resistant <i>P. aeruginosa</i> infection	Ceftazidime/avibactam (2.5 g q8h, infused over 2 h) or ceftolozane/tazobactam (1.5 g q8h) or colistin (100 mg q12h IV for the shortest possible period to obtain a clinical response)	Higher doses of ceftolozane/tazobactam may be required for pneumonias. The colistin doses used have varied. Dosage adjustment for colistin is required in renal failure. Inhaled colistin may be added for pneumonia (100 mg q12h).
<i>Burkholderia cepacia</i> infection	Meropenem (1 g q8h IV) or TMP-SMX (1600/320 mg q12h IV) for 14 days	Resistance to both agents is increasing. Do not use them in combination because of possible antagonism.
Melioidosis (<i>B. pseudomallei</i>), glanders (<i>B. mallei</i>)	Ceftazidime (2 g q6h) or meropenem (1 g q8h) or imipenem (500 mg q6h) for 2 weeks followed by TMP-SMX (1600/320 mg q12h PO) for 3 months	
<i>Stenotrophomonas maltophilia</i> infection	TMP-SMX (1600/320 mg q12h IV) plus ticarcillin/clavulanate (3.1 g q4h IV) for 14 days	Resistance to all agents is increasing. Levofloxacin or tigecycline may be alternatives, but there is little published clinical experience with these agents.

Abbreviations: IDSA, Infectious Diseases Society of America; TMP-SMX, trimethoprim-sulfamethoxazole.

TREATMENT

S. maltophilia and *B. cepacia* Infections

- Intrinsic resistance to many antibiotics limits treatment. See Table 93-1 for recommended antibiotic regimens.

Miscellaneous Organisms

Melioidosis is endemic to Southeast Asia and northern Australia and is caused by *B. pseudomallei*. Glanders is associated with close contact with horses or other equines and is caused by *B. mallei*. These diseases present as acute or chronic pulmonary or extrapulmonary suppurative illnesses or as acute septicemia. Treatment recommendations are shown in Table 93-1.

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Infections Caused by Miscellaneous Gram-Negative Bacilli



BRUCELLOSIS

■ MICROBIOLOGY

Brucellae are small, gram-negative, unencapsulated, nonsporulating, nonmotile rods or coccobacilli that can persist intracellularly. The genus *Brucella* includes four major clinically relevant species: *B. melitensis* (acquired by humans most commonly from sheep, goats, and camels), *B. suis* (from swine), *B. abortus* (from cattle or buffalo), and *B. canis* (from dogs).

■ EPIDEMIOLOGY

Brucellosis is transmitted via ingestion, inhalation, or mucosal or percutaneous exposure; the disease in humans is usually associated with exposure to infected animals or their products in either occupational settings (e.g., slaughterhouse work, farming) or domestic settings (e.g., consumption of contaminated foods, especially dairy products). The global prevalence of brucellosis is unknown because of difficulties in diagnosis and inadequacies in reporting systems.

■ CLINICAL MANIFESTATIONS

Regardless of the specific infecting species, brucellosis often presents with one of three patterns: a febrile illness similar to but less severe than typhoid fever; fever and acute monoarthritis, typically of the hip or knee, in a young child (septic arthritis); or long-lasting fever, misery, and low-back or hip pain in an older man (vertebral osteomyelitis).

- An incubation period of 1 week to several months is followed by the development of undulating fever; sweats; increasing apathy and fatigue; and nonspecific symptoms such as anorexia, headache, myalgias, and chills.
- *Brucella* infection can cause lymphadenopathy, hepatosplenomegaly, epididymo-orchitis, neurologic involvement, and focal abscess.
- Given the persistent fever and similar symptoms, tuberculosis is the most important differential diagnosis (Table 94-1).

■ DIAGNOSIS

Laboratory personnel must be alerted to the potential diagnosis to ensure that they take precautions to prevent occupational exposure.

- The organism is successfully cultured in 50–70% of cases. Cultures using the BACTEC system usually become positive in 7–10 days and can be deemed negative at 3 weeks.
- PCR analysis of blood or tissue samples is more sensitive, faster, and safer than culture.

TABLE 94-1 Radiology of the Spine: Differentiation of Brucellosis from Tuberculosis

	BRUCELOSIS	TUBERCULOSIS
Site	Lumbar and others	Dorsolumbar
Vertebrae	Multiple or contiguous	Contiguous
Diskitis	Late	Early
Body	Intact until late	Morphology lost early
Canal compression	Rare	Common
Epiphysitis	Anterosuperior (Pom's sign)	General: upper and lower disk regions, central, subperiosteal
Osteophyte	Anterolateral (parrot beak)	Unusual
Deformity	Wedging uncommon	Anterior wedge, gibbus
Recovery	Sclerosis, whole-body	Variable
Paravertebral abscess	Small, well-localized	Common and discrete loss, transverse process
Psoas abscess	Rare	More likely

- Agglutination assays for IgM are positive early in infection. Single titers of $\geq 1:160$ and $\geq 1:320$ are diagnostic in nonendemic and endemic areas, respectively.

TREATMENT

Brucellosis

- The recommended regimen is streptomycin at a dosage of 0.75–1 g/d IM (or gentamicin at 5–6 mg/kg qd) for 14–21 days plus doxycycline at 100 mg bid for 6 weeks.
 - Rifampin (600–900 mg/d) plus doxycycline (100 mg bid) for 6 weeks constitute an alternative regimen (the current World Health Organization [WHO] recommendation).
 - Significant neurologic disease requires at least 3–6 months of treatment, with ceftriaxone supplementation of a standard regimen.
 - Endocarditis requires a four-drug regimen (an aminoglycoside, rifampin, a tetracycline, and ceftriaxone or a fluoroquinolone) for at least 6 weeks.
 - Relapse rates range from 5% to >20% and depend on the specific antibiotic regimen used; pts should be monitored for at least 2 years.

TULAREMIA

■ MICROBIOLOGY AND EPIDEMIOLOGY

Tularemia is the only disease caused by *Francisella tularensis*, a small, gram-negative, aerobic bacillus that is a potential agent of bioterrorism.

- Humans are infected incidentally through various exposure routes (i.e., via the skin, mouth, lungs, or eyes) by the bite of an insect (e.g., tick, deerfly), handling of infected wildlife (e.g., while hunting or skinning), consumption of undercooked infected meat, drinking of contaminated water, or inhalation of contaminated aerosols.
 - As few as ≤ 25 inhaled organisms can result in infection.

- A disproportionate number of U.S. cases occur in Arkansas, Kansas, Oklahoma, and Missouri.

■ CLINICAL MANIFESTATIONS

After an incubation period of 3–7 days, tularemia generally starts with an acute onset of fever, chills, headache, fatigue, arthralgias, and myalgias. The *ulceroglandular/glandular* forms of tularemia are most common, but several other syndromes involving systemic manifestations can occur.

- *Ulceroglandular/glandular tularemia*: The hallmark of ulceroglandular tularemia is a small papule that evolves into an ulcer and is accompanied by painful regional lymphadenopathy.
 - Skin manifestations (e.g., erythema nodosum, papular/maculopapular rash) occur in 30% of cases.
 - Glandular tularemia presents with similar lymphadenopathy but lacks the ulcer.
 - If either syndrome is untreated for >2 weeks, the lymph nodes may suppurate.
- *Oropharyngeal and oculoglandular tularemia*: *Oropharyngeal* infection presents as fever, sore throat, marked cervical adenopathy (typically unilateral), and pharyngitis (which may be exudative or accompanied by a small ulcer). *Oculoglandular* tularemia is rare and results from touching of the conjunctival sac with contaminated fingers or possibly by exposure to infectious aerosols. Pts present with fever, unilateral conjunctivitis with mucopurulent discharge, eyelid swelling, and ulcers or pustules on the palpebral conjunctivae. Pts may have tender lymphadenopathy in the preauricular, submandibular, or cervical regions.
- *Pneumonic tularemia*: Primary pneumonic tularemia, the most severe form of the disease, is acquired via inhalation of *F. tularensis*. Pneumonic tularemia can also develop as a secondary complication of other clinical forms of tularemia.
 - Pts present with signs and symptoms similar to those of pneumonia of other etiologies (e.g., dry paroxysmal cough, dyspnea, pleuritic or retrosternal pain, CXR with lobar or multilobar infiltrates).
 - Exudative pleural effusions occur in 20–30% of cases.
- *Typhoidal tularemia*: This designation originally categorized pts with systemic infections where the portal of entry was unclear, particularly before the recognition of ingestion and inhalation as routes of exposure to *F. tularensis*. This term is outdated and rarely used.

■ DIAGNOSIS

The diagnosis of tularemia requires a culture yielding *F. tularensis* or a rise in antibody titer between paired acute- and convalescent-phase sera.

- Serology is useful for diagnosing all clinical presentations of tularemia. However, it is of limited utility in acute illness, given that detectable antibody titers are not present for ~10 days after illness onset.
- Clinical specimens for culture must be collected before antibiotic treatment. The sample type (e.g., respiratory secretions, pleural fluid, swabs of lesions, lymph node biopsies) depends on the disease presentation, although blood can be used in all clinical forms. The laboratory must be notified that tularemia is being considered as a diagnosis so that the exposure risk to laboratory staff is minimized.
- PCR and direct fluorescence assays are *F. tularensis*-specific assays that can be used to aid diagnosis.

TREATMENT**Tularemia**

- Streptomycin (1 g IM bid for 10 days), doxycycline (100 mg PO bid for 14 days), and tetracycline (500 mg PO qid for 14 days) are the only FDA-approved drugs for treatment of tularemia.
- Aminoglycosides are recommended for severe cases, with gentamicin (either 1.5–2 mg/kg for 1 dose followed by 1–1.7 mg/kg IV or IM q8h or 5–7 mg/kg IV q24h for 10–14 days, depending on the nature and severity of infection) often used as an acceptable alternative to streptomycin.
- The Infectious Diseases Society of America's guidelines for treatment of skin and soft-tissue infections due to *F. tularensis* recommend treatment with levofloxacin (500 mg PO daily) or ciprofloxacin (750 mg PO bid) for ≥14 days for mild to moderate cases.
- Doxycycline (100 mg PO bid) or ciprofloxacin (500 mg PO bid) for 14 days can be used as postexposure prophylaxis in the event that *F. tularensis* is used as a biological weapon.

PLAGUE**■ EPIDEMIOLOGY**

Yersinia pestis causes plague, a systemic zoonosis that primarily affects small rodents in rural areas of Africa (where 96% of all human cases worldwide occur), Asia, and the Americas. As the rodent population succumbs to disease, fleas (the arthropod vector) search for a new host and can transmit the bacteria to humans.

- In addition to fleabites, direct contact with infected tissues or airborne droplets can cause human infections. Given the possibility of airborne transmission, *Y. pestis* is a potential agent of bioterrorism.
- A mean of seven cases per year occur in the United States, most of them near the "Four Corners" (the junction point of New Mexico, Arizona, Colorado, and Utah) and further west in California, southern Oregon, and western Nevada.

■ CLINICAL MANIFESTATIONS

Worldwide, bubonic plague accounts for 80–95% of all plague cases, with primary septicemic plague occurring in 10–20% of cases and primary pulmonary plague in only a small minority of cases.

- *Bubonic plague*: After an incubation period of 2–6 days, the onset of bubonic plague is sudden and is characterized by fever (>38°C), malaise, myalgia, dizziness, and increasing pain due to progressive lymphadenitis in the regional lymph nodes near the fleabite or other inoculation site.
 - The tender, swollen lymph node (bubo) has a boggy consistency with an underlying hard core when palpated.
 - With treatment, fever resolves within 2–5 days, although buboes may remain enlarged for >1 week and can become fluctuant; without treatment, infection can disseminate and cause serious illness (e.g., secondary pneumonic plague, meningitis).
- *Primary septicemic plague*: Pts present with gram-negative septicemia not preceded by lymphadenopathy. Persons >40 years old are at greater risk, although this form of the disease can occur in all age groups. Diabetes and hemochromatosis are additional risk factors.

- **Pneumonic plague:** After a short incubation period averaging a few hours to 3 days, pts experience a sudden onset of fever, nonspecific signs and symptoms (e.g., headache, myalgias, vomiting), and respiratory manifestations (e.g., cough, chest pain, sputum production with hemoptysis).
 - Pneumonitis that is initially segmental can progress to lobar pneumonia and then to bilateral lung involvement.
 - The mortality rate is nearly 100% without treatment and is still >50% with effective treatment.

■ DIAGNOSIS

The WHO recommends an initial presumptive diagnosis followed by confirmation in a reference laboratory.

- The appropriate specimens for diagnosis of bubonic, pneumonic, and septicemic plague are bubo aspirate (after injection of 1 mL of normal saline), bronchoalveolar lavage fluid or sputum, and blood, respectively. Gram's, Wayson, or Wright-Giemsa staining of these samples may reveal bipolar gram-negative rods.
- Given the potential risk to laboratory workers, culture of *Y. pestis* should be performed only at reference laboratories, which use direct immunofluorescence, PCR, and/or specific bacteriophage lysis as confirmatory tests for identification. The optimal growth temperature is 25–29°C.
- In the absence of other positive diagnostic testing, a serologic diagnosis can be made.

TREATMENT

Plague

- Streptomycin (1 g IM q12h) or gentamicin (5 mg/kg IV q24h) is the drug of choice. Levofloxacin (500 mg PO/IV q24h), doxycycline (200 mg/d PO/IV in 1 or 2 doses), and chloramphenicol (25 mg/kg PO/IV q6h) are alternative agents. Antibiotics should be given for 10–14 days (or as a course continued until 2 days after fever subsides).
- For pts who are hospitalized with pneumonic plague or in whom this disease is suspected, respiratory droplet precautions should be implemented until treatment has been given for at least 48 h.

PROPHYLAXIS

Postexposure antimicrobial prophylaxis lasting 7 days is recommended after household, hospital, or other close (<2 m) contact with persons with untreated pneumonic plague. Doxycycline (200 mg/d PO/IV in 1 or 2 doses), levofloxacin (500 mg PO q24h), ciprofloxacin (500 mg PO q12h), and trimethoprim-sulfamethoxazole (320 mg of the trimethoprim component PO q12h) are effective agents for prophylaxis.

BARTONELLA INFECTIONS

- *Bartonella* species are fastidious, facultative intracellular, gram-negative bacteria that cause an array of infectious disease syndromes in humans.
- Most *Bartonella* species have successfully adapted to survival in specific domestic or wild mammals, creating a reservoir for human infection. The exceptions are *B. bacilliformis* and *B. quintana*, which are not zoonotic.
- Clinical presentation generally depends on both the infecting *Bartonella* species and the immune status of the infected individual.
- Therapy for syndromes caused by *Bartonella* is summarized in [Table 94-2](#).

TABLE 94-2 Antimicrobial Therapy for Disease Caused by *Bartonella* Species in Adults

DISEASE	ANTIMICROBIAL THERAPY
Typical cat-scratch disease	Not routinely indicated; for pts with extensive lymphadenopathy, consider azithromycin (500 mg PO on day 1, then 250 mg PO once a day for 4 days)
Cat-scratch disease neuroretinitis	Value of systemic antibiotics is controversial, particularly when visual acuity is not significantly compromised. For more severe cases, doxycycline (100 mg PO bid) plus rifampin (300 mg PO bid) for 4–6 weeks is given. Consider adding systemic glucocorticoids.
Other atypical cat-scratch disease manifestations ^a	As per neuroretinitis. Treatment duration should be individualized.
Trench fever or chronic bacteremia with <i>B. quintana</i>	Gentamicin (3 mg/kg IV once a day for 14 days) plus doxycycline (200 mg PO once a day or 100 mg PO bid for 6 weeks)
Suspected <i>Bartonella</i> endocarditis	Gentamicin ^b (1 mg/kg IV q8h for ≥14 days) plus doxycycline (100 mg PO/IV bid for 6 weeks ^c) plus ceftriaxone (2 g IV once a day for 6 weeks)
Confirmed <i>Bartonella</i> endocarditis	As for suspected <i>Bartonella</i> endocarditis minus ceftriaxone
Bacillary angiomatosis	Erythromycin ^d (500 mg PO qid for 3 months) or Doxycycline (100 mg PO bid for 3 months)
Bacillary peliosis	Erythromycin ^d (500 mg PO qid for 4 months) or Doxycycline (100 mg PO bid for 4 months)
Carrion's disease	
Oroya fever	Chloramphenicol (500 mg PO/IV qid for 14 days) plus another antibiotic (β-lactam preferred) or Ciprofloxacin (500 mg PO bid for 10 days)
Verruga peruana	Rifampin (10 mg/kg PO once a day, to a maximum of 600 mg, for 14 days) or Streptomycin (15–20 mg/kg IM once a day for 10 days)

^aData on treatment efficacy for encephalitis and hepatosplenic cat-scratch disease are lacking. Therapy similar to that given for neuroretinitis is reasonable.

^bSome experts recommend gentamicin at 3 mg/kg IV once a day. If gentamicin is contraindicated, rifampin (300 mg PO bid) can be added to doxycycline for documented *Bartonella* endocarditis.

^cSome experts recommend extending oral doxycycline therapy for 3–6 months.

^dOther macrolides are probably effective and may be substituted for erythromycin or doxycycline.

Source: Rolain JM et al: Antimicrob Agents Chemother 48:1921, 2004. Amended with permission from American Society of Microbiology.

CAT-SCRATCH DISEASE (CSD)

■ MICROBIOLOGY AND EPIDEMIOLOGY

B. henselae is the principal etiologic agent of CSD, although other *Bartonella* species may rarely be involved. Consistent with the disease's name, contact with apparently healthy cats (being scratched, bitten, or licked), and especially with

kittens, is the primary source of infection. Adults are affected nearly as frequently as children. In the United States, the estimated incidence is ~4–10 cases per 100,000 population.

■ CLINICAL MANIFESTATIONS

Of pts with CSD, 85–90% have typical disease consisting of a localized lesion (papule, vesicle, or nodule) at the site of inoculation with subsequent painful regional lymphadenopathy ≥ 1 –3 weeks after cat contact.

- Axillary and epitrochlear nodes are most commonly involved and suppurate in 10–15% of cases.
- Low-grade fever, malaise, and anorexia develop in ~50% of pts.
- Atypical disease involves extranodal manifestations (e.g., fever of unknown origin, ophthalmologic manifestations, neurologic involvement, osteomyelitis) and occurs in 10–15% of pts.
- In immunocompetent pts, the disease resolves spontaneously without treatment, although its resolution takes weeks or months. Some ophthalmologic manifestations may result in moderate or severe vision loss.

■ DIAGNOSIS

Serologic testing is most commonly used but is variably sensitive and specific. It is noteworthy that seroconversion may take a few weeks. *Bartonella* species are difficult to culture, but PCR analysis of lymph node tissue, pus, or the primary inoculation lesion is highly sensitive and specific.

BACILLARY ANGIOMATOSIS AND PELIOSIS

Bacillary angiomatosis is caused by *B. henselae* and *B. quintana*, while peliosis is caused only by the former species. These diseases occur most often in HIV-infected pts with CD4+ T cell counts of $< 100/\mu\text{L}$.

- Pts with bacillary angiomatosis present with one or more painless skin lesions that may be tan, red, or purple in color. SC masses or nodules, ulcerated plaques, and verrucous growths also occur. Painful osseous lesions, primarily in the long bones, may develop and appear as lytic lesions on radiography.
- Peliosis is an angioproliferative disorder characterized by blood-filled cystic structures that affects primarily the liver but also the spleen and lymph nodes. Hypodense hepatic areas are usually evident on imaging.
- Both diseases are diagnosed on histologic grounds. Blood cultures may be positive.

TRENCH FEVER

- Trench fever (*5-day fever*) is caused by *B. quintana*, which is spread by the human body louse to its only animal reservoir: humans.
- Much less common today than in the trenches of World War I, the disease now primarily affects homeless people.
- After a usual incubation period of 15–25 days, disease classically ranges from a mild febrile illness to a recurrent or protracted and debilitating disease. Fever is often periodic, with episodes of 4–5 days separated by ~5-day afebrile periods.
- Diagnosis requires identification of *B. quintana* in blood cultures.
- Untreated, the disease usually lasts 4–6 weeks. Death is rare.

BARTONELLA ENDOCARDITIS

Bartonella species (typically *B. quintana* or *B. henselae*) are an important cause of culture-negative endocarditis. The disease's manifestations are similar to those of subacute endocarditis of any etiology (Chap. 83). Even if incubated

for prolonged periods (up to 6 weeks), blood cultures are positive in only ~25% of cases. Serologic or PCR testing for *Bartonella* in cardiac valve tissue can help establish the diagnosis in pts with negative blood cultures.

CARRIÓN'S DISEASE (OROYA FEVER AND VERRUGA PERUANA)

Carrión's disease is a biphasic disease caused by *B. bacilliformis*, which is transmitted by a sandfly vector found in the Andes valleys of Peru, Ecuador, and Colombia.

- *Oroya fever* is the initial, bacteremic, systemic form, and *verruca peruana* is its late-onset, eruptive manifestation.
- Oroya fever may present as a nonspecific bacteremic febrile illness without anemia or as acute, severe hemolytic anemia with hepatomegaly and jaundice of rapid onset.
 - In *verruca peruana*, red, hemangioma-like, cutaneous vascular lesions of various sizes appear either weeks to months after systemic illness or with no previous suggestive history. The lesions persist for months up to 1 year.
- In systemic illness, Giemsa-stained blood films may show typical intraerythrocytic bacilli, and blood and bone marrow cultures are positive. Serologic assays may be helpful. Biopsy may be required to confirm the diagnosis of *verruca peruana*.

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Anaerobic Infections

DEFINITIONS

- *Obligate anaerobes*: killed in the presence of $\geq 0.5\%$ oxygen
- *Aerotolerant organisms*: can tolerate the presence of oxygen but cannot use it for growth
- *Facultative anaerobes*: can grow in the presence or absence of oxygen

TETANUS

■ MICROBIOLOGY, EPIDEMIOLOGY, AND PATHOGENESIS

Tetanus is characterized by increased muscle tone and spasms caused by tetanospasmin ("tetanus toxin"), a toxin produced by *Clostridium tetani*.

- *C. tetani* is a spore-forming, anaerobic gram-positive rod that is ubiquitous in soil and whose spores are highly resilient.
- Tetanus is a rare disease in the developed world: 26 cases were reported in the United States in 2013. Most cases occur in incompletely vaccinated or unvaccinated individuals.
- After spores contaminate wounds (typically puncture wounds or, in the case of neonates, the umbilical stump) and reach a suitable anaerobic environment (e.g., devitalized tissue), organisms proliferate and release toxin.
 - The toxin blocks release of inhibitory neurotransmitters (glycine and γ -aminobutyric acid) in presynaptic terminals, and rigidity results from an increased resting firing rate of the α -motor neurons.
 - A toxin dose as low as 2.5 ng/kg can be fatal.

■ CLINICAL MANIFESTATIONS

C. tetani can cause a usually mild local disease confined to the muscles near the wound or a more severe generalized disease (e.g., neonatal disease).

- If the cranial nerves are involved in localized cephalic tetanus, the pt may aspirate or develop airway obstruction due to pharyngeal or laryngeal muscle spasm. This situation is associated with a poor prognosis.
- The early signs and symptoms of generalized tetanus often include trismus (lockjaw), muscle pain and stiffness, back pain, and difficulty swallowing. As the disease progresses, painful muscle spasms develop and can sometimes be strong enough to cause crush fractures.
 - Without ventilatory support, respiratory failure is the most common cause of death in tetanus.
 - Autonomic disturbance (e.g., labile blood pressure; GI stasis; increased tracheal secretions; acute, high-output renal failure) is maximal during the second week of severe tetanus, and death due to cardiovascular events becomes the major risk.

■ DIAGNOSIS

The diagnosis is made on clinical grounds. Culture of *C. tetani* from a wound provides supportive evidence.

TREATMENT

Tetanus

- The mainstays of early treatment are the elimination of ongoing toxin production and the neutralization of circulating toxin.
 - The entry wound should be identified, cleaned, and debrided of necrotic material in order to remove anaerobic foci of infection and prevent further toxin production.
 - Metronidazole (400 mg rectally or 500 mg IV q6h for 7 days) is the preferred antibiotic. Penicillin (100,000–200,000 IU/kg qd) is an alternative but theoretically may increase spasms.
 - Antitoxin should be given as early as possible.
 - Standard treatment consists of a single IM dose of tetanus immune globulin (TIG; 3000–5000 IU) or equine antitoxin (10,000–20,000 IU). However, there is evidence that intrathecal TIG (50–1500 IU) inhibits disease progression and leads to a better outcome than IM-administered TIG. TIG is preferred as it is less likely to cause an anaphylactoid reaction.
- Monitoring and supportive care in a calm, quiet environment are important because light and noise can trigger spasms.
 - Spasms are controlled by heavy sedation with benzodiazepines, chlorpromazine, and/or phenobarbital; magnesium sulfate can also be used as a muscle relaxant. The doses required to control spasms also cause respiratory depression; thus, it is difficult to control spasms adequately in settings without mechanical ventilation.
 - Cardiovascular instability in severe tetanus is notoriously difficult to treat; increased sedation (e.g., with magnesium sulfate, fentanyl, or morphine) or administration of short-acting agents that work specifically on the cardiovascular system (e.g., esmolol, calcium antagonists, inotropes) may be required.
- Recovery from tetanus may take 4–6 weeks. Because natural disease does not induce immunity, recovering pts should be immunized.

■ PREVENTION

Vaccination effectively prevents disease.

- “Catch-up” vaccination schedules recommend a three-dose primary course followed by two further doses for unimmunized adolescents. For persons who have received a complete primary course in childhood but no further boosters, two doses at least 4 weeks apart are recommended.
- Individuals sustaining tetanus-prone wounds should be immunized if their vaccination status is incomplete or unknown or if their last booster was given >10 years earlier. Pts sustaining wounds not classified as clean or minor should also undergo passive immunization with TIG.

■ PROGNOSIS

A shorter incubation period (time from wound to first symptom) or onset period (time from first symptom to first generalized spasm) is associated with worse outcome.

BOTULISM

■ MICROBIOLOGY, EPIDEMIOLOGY, AND PATHOGENESIS

Botulism is a paralytic disease caused by neurotoxins elaborated by *Clostridium botulinum*, an anaerobic spore-forming gram-positive bacterium, as well as a few other toxigenic *Clostridium* spp.

- Botulism is caused by the toxin’s inhibition of acetylcholine release at the neuromuscular junction through an enzymatic mechanism.
 - *C. botulinum* toxin types A, B, E, and (rarely) F cause human disease, with toxin type A causing the most severe syndrome.
 - Toxin type E is associated with foods of aquatic origin.
- Transmission is usually due to consumption of foods contaminated with botulinum toxin, but contamination of wounds with spores also can result in disease.
 - Most U.S. food-borne cases (average, 20 cases per year) are associated with home-canned food.
 - Infant botulism results from toxigenic clostridial colonization of the intestine of children <1 year of age and is the most common form of the disease in the United States, with ~80–100 cases reported annually.
- Toxin is heat-labile, and spores are heat-resistant; these properties underscore the importance of properly heating foods.
- Botulinum toxin is among the most toxic substances known and thus is of concern as a potential weapon of bioterrorism.

■ CLINICAL MANIFESTATIONS

Botulism occurs naturally as four syndromes: (1) food-borne illness; (2) wound infection; (3) infant botulism; and (4) adult intestinal toxemia, which is similar to infant botulism. The disease manifests as bilateral cranial-nerve palsies (diplopia, dysarthria, dysphonia, ptosis, facial paralysis, and/or impaired gag reflex) that may progress to respiratory compromise, bilateral descending flaccid paralysis of voluntary muscles, and even death. Constipation due to paralytic ileus is often noted, and fever is usually absent.

- *Food-borne botulism* occurs 8–36 h (or up to 10 days, depending on the dose) after ingestion of food contaminated with toxin and ranges in severity from mild to fatal (within 24 h). Nausea, vomiting, and abdominal pain may precede or follow the onset of paralysis.

- *Wound botulism* occurs when spores contaminate wounds and germinate, with an incubation period of 4–17 days.
- In *infant botulism* and *adult intestinal toxemia*, spores germinate in the intestine and produce toxin, which is absorbed and causes illness. This form in infants has been associated with contaminated honey; thus, honey should not be fed to children <12 months of age. Adult pts typically have some anatomic or functional bowel abnormality or have a bowel microbiota disrupted by recent antibiotic use.

■ DIAGNOSIS

The clinical symptoms suggest the diagnosis. The definitive test is the demonstration of the toxin in clinical specimens (serum, stool, gastric aspirates, wound material) and food samples.

- This test may yield a negative result even if the pt has botulism, particularly if specimens are collected >7 days after symptom onset; additional tests (e.g., culture of stool or wound material for toxigenic clostridia) may be necessary.
- The temporal occurrence of two or more cases with botulism-compatible symptoms is essentially pathognomonic, as other botulism-like illnesses do not typically occur in clusters.

TREATMENT

Botulism

- The mainstays of treatment are meticulous supportive care and immediate administration of botulinum antitoxin—the only specific treatment.
 - Adults are given an equine antitoxin available through the CDC (770-488-7100); infant botulism is treated with a human-origin antitoxin (licensed as BabyBIG®) available through the California Department of Public Health (510-231-7600).
 - In wound botulism, suspect wounds and abscesses should be cleaned, debrided, and drained promptly, and antimicrobial therapy (e.g., with a penicillin) should be guided by clinical judgment, as its clinical efficacy has not been established and may result in increased circulating toxin from lysis of bacteria.

■ PROGNOSIS

Botulinum antitoxin limits progression of illness by neutralizing free toxin without affecting paralysis that is already present. Toxin binding is irreversible, but nerve terminals do regenerate.

OTHER CLOSTRIDIAL INFECTIONS

■ MICROBIOLOGY AND PATHOGENESIS

Clostridia are pleomorphic, gram-positive, spore-forming organisms. Most species are obligate anaerobes; some (e.g., *C. septicum*, *C. tertium*) can grow—but not sporulate—in air.

- In humans, clostridia reside in the GI and female genital tracts and on the oral mucosa.
- Clostridial species produce more protein toxins than any other bacterial genus; the *C. perfringens* epsilon toxin is among the most lethal and is considered a potential agent of bioterrorism.

■ EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Life-threatening clostridial infections range from intoxications (e.g., food poisoning, tetanus) to necrotizing enteritis/colitis, bacteremia, myonecrosis, and toxic shock syndrome (TSS).

- *Clostridial wound contamination*: Of open traumatic wounds, 30–80% are contaminated with clostridial species. Diagnosis and treatment of clostridial infection should be based on clinical signs and symptoms, given that clostridia are isolated with equal frequency from both suppurative and well-healing wounds.
- *Polymicrobial infections involving clostridia*: Clostridial species can be involved in infection throughout the body; 66% of intraabdominal infections related to compromised mucosal integrity involve clostridia (most commonly *C. ramosum*, *C. perfringens*, and *C. bifermentans*).
- *Enteric clostridial infections*: Disease ranges from food-borne illnesses and antibiotic-associated colitis (**Chap. 85**) to extensive necrosis of the intestine (e.g., *enteritis necroticans* and *necrotizing enterocolitis*, which are due to toxigenic *C. perfringens* type C and type A, respectively).
- *Clostridial bacteremia*: *C. perfringens* causes 79% of clostridial bacteremias; when associated with myonecrosis, clostridial bacteremia has a grave prognosis.
 - *C. septicum* is also commonly associated with bacteremia (<5% of cases). More than 50% of pts with *C. septicum* bacteremia have a GI anomaly or an underlying malignancy. Neutropenia (of any origin) is also associated with *C. septicum* bacteremia.
 - Pts with clostridial bacteremia—particularly that due to *C. septicum*—require immediate treatment, as infection can metastasize and cause spontaneous myonecrosis.
- *Clostridial skin and soft-tissue infections*: Necrotizing clostridial soft-tissue infections are rapidly progressive and are characterized by marked tissue destruction, gas in the tissues, and shock. Most pts develop severe pain, crepitus, brawny induration with rapid progression to skin sloughing, violaceous bullae, and marked tachycardia.
 - *C. perfringens myonecrosis (gas gangrene)* is accompanied by bacteremia, hypotension, and multiorgan failure and is invariably fatal if untreated.
 - If due to trauma, gas gangrene has an incubation period of 6 h to <4 days. Disease initially presents as excruciating pain at the affected site and the development of a foul-smelling wound containing a thin serosanguineous discharge and gas bubbles.
 - Spontaneous gas gangrene results from hematogenous seeding of normal muscle with toxigenic clostridia from a GI source. Confusion, extreme pain in the absence of trauma, and fever should heighten suspicion.
 - *TSS*: Endometrial clostridial infection (particularly with *C. sordellii*) is usually related to pregnancy or gynecologic procedures and proceeds rapidly to TSS and death.
 - Systemic manifestations, including edema, effusions, profound leukocytosis (50,000–200,000/ μ L), and hemoconcentration (Hct of 75–80%), are followed by the rapid onset of hypotension and multiple-organ failure.
 - Fever is usually absent.
 - Other clostridial skin and soft-tissue infections include crepitant cellulitis (involving SC or retroperitoneal tissues in diabetic pts), cellulitis and abscess formation due to *C. histolyticum*, and endophthalmitis due to *C. sordellii* or *C. perfringens*.

■ DIAGNOSIS

Isolation of clostridia from clinical sites does not in itself indicate severe disease. Clinical findings and presentation must also be taken into account.

TREATMENT

Other Clostridial Infections

- **Table 95-1** lists treatment regimens for clostridial infections.

MIXED ANAEROBIC INFECTIONS

■ MICROBIOLOGY, EPIDEMIOLOGY, AND PATHOGENESIS

Nonsporulating anaerobic bacteria are important components of the normal microbiota of mucosal surfaces of the mouth, lower GI tract, skin, and female genital tract and contribute to physiologic, metabolic, and immunologic functions of the host.

TABLE 95-1 Treatment of Clostridial Infections

CONDITION	ANTIBIOTIC TREATMENT	PENICILLIN ALLERGY	ADJUNCTIVE TREATMENT/NOTE
Wound contamination	None	—	Treatment should be based on clinical signs and symptoms as listed below and not solely on bacteriologic findings.
Polymicrobial anaerobic infections involving clostridia (e.g., abdominal wall, gynecologic)	Ampicillin (2 g IV q4h) plus Clindamycin (600–900 mg IV q6–8h) plus Ciprofloxacin (400 mg IV q6–8 h)	Vancomycin (1 g IV q12h) plus Metronidazole (500 mg IV q6h) plus Ciprofloxacin (400 mg IV q6–8h)	Empirical therapy should be initiated. Therapy should be based on Gram's stain and culture results and on sensitivity data when available. Add gram-negative coverage if indicated (see text).
Clostridial sepsis	Penicillin (3–4 mU IV q4–6h) plus Clindamycin (600–900 mg IV q6–8h)	Clindamycin alone or Metronidazole (as above) or Vancomycin (as above)	Transient bacteremia without signs of systemic toxicity may be clinically insignificant.
Gas gangrene ^a	Penicillin G (4 mU IV q4–6 h) plus Clindamycin (600–900 mg IV q6–8h)	Cefoxitin (2 g IV q6h) plus Clindamycin (600–900 mg IV q6–8h)	Emergent surgical exploration and thorough debridement are extremely important. Hyperbaric oxygen therapy may be considered after surgery and antibiotic initiation.

^a*C. tertium* is resistant to penicillin, cephalosporins, and clindamycin. Appropriate antibiotic therapy for *C. tertium* infection is vancomycin (1 g q12h IV) or metronidazole (500 mg q8h IV).

- Most clinically relevant anaerobes are relatively aerotolerant.
 - Clinically relevant anaerobes include gram-positive cocci (e.g., *Peptostreptococcus* spp.), gram-positive rods (e.g., spore-forming clostridia and *Propionibacterium acnes*), and gram-negative bacilli (e.g., the *Bacteroides fragilis* group in the intestines, *Fusobacterium* spp. in the oral cavity and GI tract, *Prevotella* spp. in the oral cavity and female genital tract, and *Porphyromonas* spp. in the oral microbiota).
- Infections caused by anaerobes are typically polymicrobial (including at least one anaerobic organism and sometimes involving facultative bacteria) and occur when organisms penetrate a previously sterile site that has a reduced oxidation–reduction potential—e.g., from tissue ischemia, trauma, surgery, perforated viscus, shock, or aspiration. Bacterial synergy, bacterial virulence factors, and mechanisms of abscess formation are factors involved in the pathogenesis of anaerobic infections.
- Anaerobes account for 0.6–0.8% of all cases of bacteremia, with *Bacteroides* spp. isolated in ~60% of these cases.

■ CLINICAL MANIFESTATIONS

The clinical presentation of anaerobic infections depends, in part, on the anatomic location affected.

- *Mouth, head, and neck infections:* Odontogenic infections (e.g., dental caries, periodontal disease, gingivitis) are common, can spread locally, and may be life-threatening.
 - Acute necrotizing ulcerative gingivitis (trench mouth, Vincent’s stomatitis) is associated with bleeding tender gums, foul breath, and ulceration with yellowish-white or gray “pseudomembranes.”
 - Noma (*cancrum oris*) is a gangrenous infection that destroys the soft and hard tissues related to the oral cavity. Noma occurs most frequently in 1- to 4-year-old children with malnutrition or systemic disease, particularly those in sub-Saharan Africa.
 - Peritonsillar abscess (quinsy) is the most common peripharyngeal infection and occurs as a complication of acute tonsillitis, with adolescents most commonly affected. Pts present with sore throat, dysphagia, peritonsillar swelling, muffled voice, and uvular deviation to the contralateral side.
 - Chronic sinusitis and otitis (Chap. 59) are commonly due to anaerobes.
 - Complications of anaerobic mouth, head, and neck infections include Lemierre’s syndrome, osteomyelitis, CNS infections (e.g., brain abscess, epidural abscess, subdural empyema), mediastinitis, pleuropulmonary infections, and hematogenous dissemination.
 - Lemierre’s syndrome, which is typically due to *Fusobacterium necrophorum*, is an acute oropharyngeal infection with secondary septic thrombophlebitis of the internal jugular vein and frequent septic emboli, most commonly to the lung.
 - Pleuropulmonary infections include aspiration pneumonia (which is difficult to distinguish from chemical pneumonitis due to aspiration of alveolar irritants, such as gastric juices), lung abscesses, and empyema. Antibiotic therapy is not indicated for aspiration pneumonia unless bacterial superinfection occurs. Anaerobic lung abscesses usually arise from a dental source.
- *Intraabdominal infections:* See Chap. 84.
- *Pelvic infections:* See Chap. 86 for details. Anaerobes, typically in combination with coliforms, are isolated from most women with genital tract infections that are not caused by a sexually transmitted pathogen (e.g., pelvic inflammatory disease, pelvic abscess, endometritis, tubo-ovarian abscess, postoperative or postpartum infections). The major anaerobic pathogens are the *B. fragilis*

group and *Prevotella* spp. (*bivia*, *disiens*), but many other anaerobes have also been implicated.

- **Skin and soft-tissue infections:** See [Chap. 87](#) for details. Skin or soft-tissue injury due to trauma, ischemia, or surgery creates a suitable environment for anaerobic infections. The most common locations for anaerobic cellulitis include the neck, trunk, groin, and legs.
- **Bone and joint infections:** Actinomycosis is the leading cause of anaerobic bone infections worldwide, particularly of the mandible. Anaerobic arthritis is uncommon, typically involves a single isolate, and often results from hematogenous spread; *P. acnes*, peptostreptococci, and *B. fragilis* are among the most common anaerobic causes of septic arthritis.

Diagnosis

The three critical steps in successfully culturing anaerobic bacteria from clinical samples are (1) proper specimen collection, with avoidance of contamination by the normal microbiota; (2) rapid specimen transport to the microbiology laboratory in anaerobic transport media; and (3) proper specimen handling. A foul odor is often indicative of an anaerobic infection.

TREATMENT

Mixed Anaerobic Infections

- Appropriate treatment requires antibiotic administration ([Table 95-2](#)), surgical resection or debridement of devitalized tissues, and drainage of any large abscess.
 - Given that most infections involving anaerobes also include aerobic bacteria, therapeutic regimens should include agents active against both classes of organisms.
 - Infections above the diaphragm usually reflect the orodental microbiota, which includes many organisms that produce β -lactamase. Accordingly, the recommended regimens include clindamycin, a β -lactam/ β -lactamase inhibitor combination, or metronidazole in combination with a drug active against microaerophilic and aerobic streptococci (e.g., penicillin).

TABLE 95-2 Antimicrobial Therapy That Is Typically Active Against Commonly Encountered Anaerobes

ANTIBIOTIC(S)	CAVEATS
Metronidazole	This drug is clinically unreliable against gram-positive non-spore-forming anaerobes (e.g., <i>Actinomyces</i> spp., <i>Propionibacterium</i> spp., <i>Peptostreptococcus</i> spp.).
β -Lactam/ β -lactamase inhibitor combinations (ampicillin-sulbactam, ticarcillin-clavulanic acid, piperacillin-tazobactam)	Rates of resistance are increasing in some gram-negative anaerobes. The newer cephalosporin/ β -lactamase combinations have limited anaerobic activity.
Clindamycin	Rates of resistance are increasing in <i>Bacteroides</i> spp.
Carbapenems (meropenem, imipenem, ertapenem, doripenem)	Rates of resistance are currently very low (<5%), although some carbapenemase-producing strains have been identified.
Chloramphenicol	Some clinical failures have been noted, even when the isolate is found to be susceptible by in vitro testing.

- Infections below the diaphragm must be treated with agents active against *Bacteroides* spp., such as ceftiofloxacin, moxifloxacin, a β -lactam/ β -lactamase inhibitor combination, or a carbapenem. Treatment should also cover the aerobic gram-negative microbiota, including enterococci (e.g., ampicillin or vancomycin) when indicated.
- Pts with anaerobic infections that fail to respond to treatment or that relapse should be reassessed, with consideration of additional surgical drainage or debridement. Superinfection with resistant gram-negative facultative or aerobic bacteria should also be considered.

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Nocardiosis, Actinomycosis, and Whipple's Disease



NOCARDIOSIS

■ MICROBIOLOGY

Nocardiae are branching, beaded, gram-positive filaments that usually give positive results with modified acid-fast stains. These saprophytic aerobic actinomycetes are common in soil.

- Nine species or species complexes are most commonly associated with human disease.
- Speciation of nocardiae is precluded in most clinical laboratories, although improvements in mass spectrometry-based techniques may change this limitation in high-resource countries.
- *Nocardia brasiliensis* is most often associated with localized skin lesions.

■ EPIDEMIOLOGY

Nocardiosis occurs worldwide and has an incidence of ~0.375 cases per 100,000 persons in Western countries. The risk of disease is greater than usual among persons who have deficient cell-mediated immunity—e.g., that associated with lymphoma, transplantation, glucocorticoid therapy, HIV infection with <250 CD4+ T cells/ μ L, or immunomodulating drugs such as tumor necrosis factor inhibitors.

■ PATHOGENESIS

Pneumonia and disseminated disease follow inhalation of fragmented bacterial mycelia.

- Nocardiosis causes abscesses with neutrophilic infiltration and necrosis.
- Organisms have multiple mechanisms for surviving within phagocytes.

■ CLINICAL MANIFESTATIONS

- *Respiratory tract disease*: Pneumonia is usually subacute, presenting over days to weeks, but can be acute in immunocompromised pts.
 - A prominent cough productive of small amounts of thick purulent sputum, fever, anorexia, weight loss, and malaise are common; dyspnea, hemoptysis, and pleuritic chest pain are less common.
 - CXR may demonstrate single or multiple nodular infiltrates of varying sizes that tend to cavitate. Empyema is noted in one-quarter of cases.
 - Extrapulmonary disease is documented in $>50\%$ of cases.
- *Extrapulmonary disease*: In 20% of cases of disseminated disease, lung disease is absent.

- Nocardial dissemination manifests as subacute abscesses in the brain (most commonly), skin, kidney, bone, eye, and/or muscle.
- Brain abscesses are usually supratentorial, are often multiloculated, can be single or multiple, and tend to burrow into ventricles or extend into the subarachnoid space.
- Meningitis is uncommon, and nocardiae are difficult to recover from CSF.
- *Disease following transcutaneous inoculation*: usually presents as cellulitis, lymphocutaneous disease, or actinomycetoma
 - *Cellulitis* presents 1–3 weeks after a break in the skin (often with contamination by soil).
 - The firm, tender, erythematous, warm, and nonfluctuant lesions may involve underlying structures, but dissemination is rare.
 - *N. brasiliensis* and species in the *N. otitidiscaviarum* complex are most common in cellulitis.
 - *Lymphocutaneous* disease resembles sporotrichosis and presents as a pyodermtous nodule at the inoculation site, with central ulceration and purulent or honey-colored discharge.
 - SC nodules often appear along lymphatics that drain the primary lesion.
 - *Actinomycetoma* progresses from a nodular swelling at the site of local trauma (typically on the feet or hands, although other sites can be affected) to fistula formation; dissemination is rare.
 - The discharge is serous or purulent and can contain granules consisting of masses of mycelia.
 - Lesions, which spread slowly along fascial planes to involve adjacent skin and SC tissue and bone, can cause extensive deformity after months or years.
- *Eye disease*: Endophthalmitis can occur after eye surgery or during disseminated disease.

■ DIAGNOSIS

- Sputum or pus should be examined microscopically and by culture for the presence of nocardiae. In pts with nocardial pneumonia, sputum smears are often negative, and bronchoscopy may be needed to obtain adequate specimens.
 - Cultures take 2–4 weeks to yield the organism. To maximize the likelihood of isolation, the laboratory should be alerted if nocardiosis is being considered.
 - Sputum cultures positive for nocardiae should be assumed to reflect disease in immunocompromised hosts, but may represent colonization in immunocompetent pts.
- Discharge from lesions suspected to constitute an actinomycetoma should be examined for granules, the appearance of which can help differentiate this diagnosis from eumycetoma (cases involving fungi) and botryomycosis (cases involving cocci or bacilli).
 - Granules from actinomycetomas consist of fine filaments (0.5–1 μm wide) radiating from a central core.
 - In contrast, granules from eumycetomas have broader filaments (2–5 μm wide) encased in a matrix, and those from botryomycosis consist of loose masses of bacteria.
- Brain imaging should be considered in pts with pulmonary or disseminated disease.

TREATMENT

Nocardiosis

- Trimethoprim-sulfamethoxazole (TMP-SMX; 10–20 mg of TMP/kg per day and 50–100 mg of SMX/kg per day in two divided doses initially, with

later reduction to 5 and 25 mg/kg, respectively) is the drug of choice for most pts.

- Susceptibility testing, particularly in severe cases or cases failing to improve, can guide alternative treatments and should be performed at reference labs.
- Alternative oral agents that are often effective include minocycline, linezolid (whose use for >2–3 weeks is often complicated by side effects), amoxicillin/clavulanic acid (except for strains in the *N. nova* complex), and fluoroquinolones (with moxifloxacin and gemifloxacin the most active).
- Effective parenteral agents include amikacin, ceftriaxone, cefotaxime, and imipenem.
- Pts with severe disease are initially treated with a combination of TMP-SMX, amikacin, and either ceftriaxone or imipenem. After definite clinical improvement, the regimen can usually be simplified to a single oral agent.
- Surgical management of nocardial infections is similar to that of other bacterial diseases.
 - Brain abscesses that are large or unresponsive to antibiotic treatment should be aspirated.
 - Medical therapy is generally sufficient for actinomycetomas.
- Relapse is common.
 - Long courses of therapy are required (Table 96-1).
 - Pts should be followed for at least 6 months after therapy completion.

ACTINOMYCOSIS

■ MICROBIOLOGY

Actinomycosis is caused by anaerobic or microaerophilic bacteria, primarily of the genus *Actinomyces* (e.g., *A. israelii*, *A. naeslundii*, *A. odontolyticus*), that colonize

TABLE 96-1 Treatment Duration for Nocardiosis

DISEASE	DURATION
Pulmonary or systemic	
Intact host defenses	6–12 months
Deficient host defenses	12 months ^a
CNS disease	12 months ^b
Cellulitis, lymphocutaneous syndrome	2 months
Osteomyelitis, arthritis, laryngitis, sinusitis	4 months
Actinomycetoma	6–12 months after clinical cure
Keratitis	Topical: until apparent cure Systemic: until 2–4 months after apparent cure

^aIn some pts with AIDS and CD4+ T lymphocyte counts of <200/μL or with chronic granulomatous disease, therapy for pulmonary or systemic disease must be continued indefinitely.

^bIf all apparent CNS disease has been excised, the duration of therapy may be reduced to 6 months.

the mouth, colon, and vagina. Most infections are polymicrobial, but the role of other species in the pathogenesis of the disease is unclear.

■ EPIDEMIOLOGY

Actinomycosis is associated with poor dental hygiene, prolonged use of intrauterine contraceptive devices (IUCDs), and treatment with immunosuppressing drugs (e.g., anti-tumor necrosis factor α agents, glucocorticoids, bisphosphonates).

■ PATHOGENESIS

After disruption of the mucosal barrier, resident *Actinomyces* can infect locally and spread contiguously in a slow progressive manner, ignoring tissue planes. The hallmark of actinomycosis is the development of single or multiple indurated lesions with fibrotic walls often described as “wooden.” Central necrosis of lesions with neutrophils and sulfur granules is virtually diagnostic of the disease.

■ CLINICAL MANIFESTATIONS

- *Oral-cervicofacial disease*: Infection starts as a soft-tissue swelling, abscess, mass, or ulcerative lesion, often at the angle of the jaw, with occasional contiguous extension to the cranium, cervical spine, or thorax. Pain, fever, and leukocytosis are variable. Radiation therapy and particularly bisphosphonate treatment are associated with actinomycosis of the maxilla and mandible.
- *Thoracic disease*: The pulmonary parenchyma and/or pleural space is usually involved. Chest pain, fever, and weight loss are common.
 - Radiographic studies demonstrate a mass lesion or pneumonia. Cavitory disease may occur, and >50% of pts have pleural thickening, effusion, or empyema.
 - Lesions cross fissures or pleura and may involve the mediastinum, contiguous bone, or the chest wall (*empyema necessitatis*). In the absence of these findings, the disease is often mistaken for a neoplasm or for pneumonia.
- *Abdominal disease*: The diagnosis is challenging given that abdominal disease may not present clinically until months or years after the initial event (e.g., appendicitis, diverticulitis, bowel surgery) and that any abdominal organ or region can be involved.
 - The disease usually presents as an abscess, mass, or lesion fixed to underlying tissue and is often mistaken for cancer.
 - Sinus tracts to the abdominal wall, perianal region, or other organs may develop and mimic inflammatory bowel disease. Recurrent disease or a wound or fistula that fails to heal suggests actinomycosis.
- *Pelvic disease*: Pelvic actinomycosis is often associated with IUCDs that have been in place for >1 year; other foreign bodies (e.g., surgical mesh) have also been implicated. The presentation is indolent.
 - Pts have fever, weight loss, abdominal pain, and abnormal vaginal bleeding or discharge. Endometritis progresses to pelvic masses or tubo-ovarian abscess.
 - When there are no symptoms and *Actinomyces*-like organisms are identified on Papanicolaou-stained specimens, the pt should undergo close follow-up but the IUCD does not have to be removed. Symptomatic pts should probably have their IUCD removed and—if advanced disease is excluded—receive a 14-day course of empirical antibiotics for possible early endometritis.
- *Miscellaneous sites*: Actinomycosis can involve musculoskeletal tissue, soft tissue, or (rarely) the CNS. Hematogenous dissemination, most commonly to the lungs and liver, can occur.

■ DIAGNOSIS

Actinomycosis should be considered when a chronic progressive process with mass-like features crosses tissue boundaries, a sinus tract develops, and/or the pt has evidence of a refractory or relapsing infection despite short courses of antibiotics.

- Aspirations, biopsies, or surgical excision may be required to obtain material for diagnosis.
- Microscopic identification of sulfur granules (an in vivo matrix of bacteria, calcium phosphate, and host material) in pus or tissues helps establish the diagnosis; however, additional histopathologic and microbiologic studies are required to distinguish actinomycosis from mycetoma and botryomycosis, in both of which sulfur granules develop.
- Anaerobic cultures usually require 5–7 days to become positive but may take 2–4 weeks; even a single antibiotic dose can affect the yield of cultures.

TREATMENT

Actinomycosis

- For serious infection and bulky disease, IV therapy for 2–6 weeks (usually with penicillin, 18–24 million units IV daily) followed by oral therapy for 6–12 months (e.g., with penicillin or ampicillin) is suggested.
 - Less extensive disease, particularly that involving the oral–cervicofacial region, may be cured with a shorter course.
 - If treatment is extended beyond the point of resolution of measurable disease (as quantified by CT or MRI), relapse is minimized.
- Suitable alternative agents include the tetracyclines (e.g., doxycycline or minocycline, 100 mg PO/IV q12h), ceftriaxone, or carbapenems.

WHIPPLE'S DISEASE

■ MICROBIOLOGY AND EPIDEMIOLOGY

Whipple's disease is a chronic multiorgan infection caused by *Tropheryma whipplei*, a weakly staining gram-positive bacillus. Humans are the only known host. Seroprevalence studies indicate that ~50% of people in Western Europe and ~75% of those in rural Senegal have been exposed to *T. whipplei*, and the disease prevalence is estimated at 1–3 cases per 1 million population. The route of transmission is unclear but probably involves fecal–oral spread and possibly involves droplet and/or airborne transmission.

■ CLINICAL MANIFESTATIONS

Exposure to *T. whipplei* typically results in asymptomatic carriage but can lead to acute disease or chronic infection (Whipple's disease).

- *Acute infection*: Acquisition of *T. whipplei* can result in fever, acute gastroenteritis, and/or pneumonia.
- *Chronic infection*: "Classic" Whipple's disease typically begins with oligo- or polyarthralgias/seronegative arthritis. GI signs and symptoms (diarrhea, weight loss, abdominal pain) due to involvement of the duodenum and/or jejunum begin, on average, 6–8 years later. Other organ systems (e.g., the CNS and the cardiac, pulmonary, and lymphatic systems) are variably involved.

■ DIAGNOSIS

The key to diagnosis is considering *T. whipplei* infection. PCR-based testing of tissue specimens rather than body fluids generally has a higher diagnostic yield. Histologic examination of intestinal biopsy samples remains an important diagnostic procedure, although it is less sensitive than PCR. Serology is of little value in diagnosing active infection.

TREATMENT**Whipple's Disease**

Although the optimal regimen and duration are not known (and likely depend on the site of infection), ceftriaxone (2 g IV q24h) or meropenem (1 g IV q8h) for 2 weeks followed by TMP-SMX (160/800 mg PO bid) for 3–12 months appears to be efficacious. For CNS or cardiac infection, ceftriaxone (2 g IV q12h) or meropenem (2 g IV q8h) for 2–4 weeks followed by oral doxycycline or minocycline plus hydroxychloroquine or chloroquine for ≥ 1 year seems prudent.

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Tuberculosis and Other Mycobacterial Infections**TUBERCULOSIS****■ MICROBIOLOGY**

Tuberculosis (TB) is caused by organisms of the *Mycobacterium tuberculosis* complex, which includes *M. tuberculosis*, the most common and important agent of human mycobacterial disease, and *M. bovis*, which (like several other mycobacterial species) is acquired via ingestion of unpasteurized milk. *M. tuberculosis* is a thin aerobic bacillus that is neutral on Gram's staining but that, once stained, is acid-fast; i.e., it cannot be decolorized by acid alcohol because of the cell wall's high content of mycolic acids and other lipids.

■ EPIDEMIOLOGY

An estimated 10.4 million new cases of TB occurred worldwide in 2016, with ~1.7 million TB-related deaths—almost entirely in low-income countries. Globally, TB rates are stable or falling.

- In the United States, TB primarily affects HIV-infected adults, immigrants, the elderly, and disadvantaged/marginalized populations.
- Isolates of *M. tuberculosis* that are multidrug-resistant (MDR; resistant to at least isoniazid and rifampin) and extensively drug-resistant (XDR; resistant to isoniazid, rifampin, and fluoroquinolones and to amikacin, kanamycin, or capreomycin) are increasing in frequency; ~500,000 cases of MDR-TB may have emerged in 2016, of which ~9.5% were probably XDR.
- Disease from a pt with pulmonary TB is spread by droplet nuclei that are aerosolized by coughing, sneezing, or speaking.
 - Droplets $< 5\text{--}10\ \mu\text{m}$ in diameter may be suspended in air for several hours.
 - Transmission is determined by the intimacy and duration of contact with a pt with TB, the degree of infectiousness of the pt, and the shared environment.
 - Pts with cavitary or laryngeal disease are most infectious, with as many as $10^5\text{--}10^7$ acid-fast bacilli (AFB)/mL of sputum.
- Risk factors for development of active disease after *M. tuberculosis* infection include recent acquisition (i.e., within the preceding 18 months), comorbidity (e.g., HIV disease, diabetes, silicosis, immunosuppression, gastrectomy), malnutrition, tobacco smoking, and presence of fibrotic lesions.

■ PATHOGENESIS

AFB that reach alveoli are ingested by macrophages. The bacilli impair phagosome maturation, multiply, lyse the macrophages, and spread to regional lymph

nodes, from which they may disseminate throughout the body. These initial stages of infection are generally asymptomatic and induce cellular and humoral immunity.

- About 2–4 weeks after infection, a tissue-damaging response resulting from delayed-type hypersensitivity (the basis for tuberculin skin testing [TST]) destroys nonactivated macrophages that contain multiplying bacilli, and a macrophage-activating response activates cells capable of killing AFB. A granuloma forms at the site of the primary lesion and at sites of dissemination. The lesions can then either heal by fibrosis or undergo further evolution. Despite “healing,” viable bacilli can remain dormant within macrophages or in necrotic material for years.
- Cell-mediated immunity confers partial protection against TB. Cytokines secreted by alveolar macrophages contribute to disease manifestations, granuloma formation, and mycobacterial killing.

■ CLINICAL MANIFESTATIONS

TB is classified as pulmonary, extrapulmonary, or both. Extrapulmonary TB may occur in 10–40% of pts, with even higher rates among HIV-infected pts.

Pulmonary TB Primary disease may cause no or mild signs and symptoms (fever and occasional pleuritic chest pain) in contrast to the prolonged disease course that is common in postprimary or adult-type disease.

- Primary disease is frequently located in the middle and lower lobes. The primary lesion usually heals spontaneously, and a calcified nodule (Ghon focus) remains.
 - Transient hilar and paratracheal lymphadenopathy is common.
 - In immunosuppressed pts and children, primary disease may progress rapidly to significant clinical disease, with cavitation, pleural effusions, and hematogenous dissemination (miliary disease).
- Adult-type disease presents initially with nonspecific and insidious signs and symptoms, such as diurnal fever, night sweats, weight loss, anorexia, malaise, and weakness.
 - As the disease progresses, pts develop cough and purulent sputum production, often with blood streaking. Extensive cavitation may develop, with occasional massive hemoptysis following erosion of a vessel located in the wall of a cavity.
 - Disease is usually localized to the apical and posterior segments of the upper lobes and the superior segments of the lower lobes.

Extrapulmonary TB Any site in the body can be involved, but the most commonly affected sites are (in descending order of frequency) the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum, and pericardium. Up to two-thirds of HIV-infected pts with TB have extrapulmonary disease.

- *Lymphadenitis* occurs in 35% of extrapulmonary TB cases, especially among children and HIV-infected pts. Painless swelling of cervical and supraclavicular nodes (scrofula) is typical.
 - Nodes are discrete early on but can develop into a matted nontender mass with a fistulous tract.
 - Fine-needle aspiration or surgical-excision biopsy of the node is required for diagnosis. Cultures are positive in 70–80% of cases.
- *Pleural involvement* is common (~20% of extrapulmonary cases) and results from a hypersensitivity response to mycobacterial antigens or contiguous spread of parenchymal inflammation.

- Pleural fluid is straw-colored and exudative, with protein levels >50% of those in serum, normal to low glucose levels, a usual pH of ~7.3 (occasionally <7.2), and pleocytosis (500–6000 cells/ μ L). The pleural concentration of adenosine deaminase, if low, virtually excludes TB.
- Pleural biopsy is often required for diagnosis, with up to 80% of biopsy cultures and 75% of PCR tests positive. Direct smears, cultures, and PCR of pleural fluid are less sensitive.
- Empyema is an uncommon complication of pulmonary TB and results from rupture of a cavity with many bacilli into the pleural space. In these cases, direct smears and cultures are often positive, and surgical drainage is usually required in addition to chemotherapy.
- In *genitourinary disease*, local symptoms predominate (e.g., urinary frequency, dysuria, hematuria, abdominal or flank pain), and up to 75% of pts have a CXR demonstrating previous or concomitant pulmonary disease. Disease is occasionally identified only after severe destructive lesions of the kidneys have developed.
 - In 90% of cases, urinalysis shows pyuria and hematuria with negative bacterial cultures.
 - Mycobacterial culture of three morning urine specimens is diagnostic in 90% of cases.
- Weight-bearing joints (spine, hips, and knees) are the most common sites of *skeletal disease*.
 - Spinal TB (Pott's disease) often involves two or more adjacent vertebral bodies; in adults, lower thoracic/upper lumbar vertebrae are usually affected. Disease spreads to adjacent vertebral bodies, later affecting the intervertebral disk and causing collapse of vertebral bodies in advanced disease (kyphosis, gibbus). Paravertebral cold abscesses may form.
- *Meningitis* occurs most often in young children and HIV-seropositive pts. Disease typically evolves over 1–2 weeks and often involves paresis of cranial nerves (particularly of ocular nerves). The ultimate evolution is toward coma, with hydrocephalus and intracranial hypertension.
 - CSF can have a high lymphocyte count, an elevated protein level, and a low glucose concentration. Cultures are positive in 80% of cases. PCR is ~80% sensitive and is the preferred initial diagnostic option.
 - Neurologic sequelae are seen in ~25% of treated pts; adjunctive glucocorticoids enhance survival among pts >14 years of age but do not reduce the frequency of neurologic sequelae.
- *Gastrointestinal disease* can affect any portion of the GI tract (with the terminal ileum and cecum most commonly involved), causing abdominal pain, obstruction, hematochezia, and often a palpable mass. TB peritonitis can follow spread of the organism from ruptured lymph nodes and intraabdominal organs; peritoneal biopsy is usually required for diagnosis.
- *Pericarditis* is characterized by an acute or subacute onset of fever, dull retrosternal pain, and sometimes a friction rub. Effusion is common. Chronic constrictive pericarditis is a potentially fatal complication, even in treated pts. Adjunctive glucocorticoids remain controversial; no conclusive data demonstrate a benefit.
- *Miliary disease* arises from hematogenous spread of *M. tuberculosis* throughout the body. Symptoms are nonspecific, and small (1- to 2-mm) granulomas may develop in many organs. Hepatomegaly, splenomegaly, lymphadenopathy, and choroidal tubercles of the eye may occur.

HIV-Associated TB The manifestations of TB vary with the stage of HIV infection. When cell-mediated immunity is only partly compromised, pulmonary TB presents as typical upper-lobe cavitory disease. In late HIV infection, a primary

TB-like pattern may be evident, with diffuse interstitial or miliary infiltrates, little or no cavitation, and intrathoracic lymphadenopathy.

- Extrapulmonary disease occurs frequently; common forms include lymphadenitis, meningitis, pleuritis, pericarditis, mycobacteremia, and disseminated disease.
- Immune reconstitution inflammatory syndrome (IRIS), which may occur 1–3 months after initiation of antiretroviral therapy, may exacerbate the signs and symptoms of TB.

■ DIAGNOSIS

The key to diagnosis is a high index of suspicion.

- AFB microscopy of diagnostic specimens—i.e., light microscopy of specimens stained with Ziehl-Neelsen basic fuchsin dyes or fluorescence microscopy of samples stained with auramine–rhodamine—can provide a presumptive diagnosis. In suspected pulmonary TB, two or three sputum samples should be examined.
- Definitive diagnosis requires growth of *M. tuberculosis* in culture or identification of the organism's DNA in clinical samples.
 - Liquid media and speciation by molecular methods have decreased the time required for diagnostic confirmation to 2–3 weeks (from 4 to 8 weeks).
 - Nucleic acid amplification is useful not only for rapid confirmation of TB in AFB-positive specimens but also for diagnosis of AFB-negative pulmonary and extrapulmonary TB.
- Drug susceptibility can be assessed via indirect testing on solid media (which takes ≥ 8 weeks), direct testing in liquid media (which takes ~ 3 weeks), or PCR (which can provide results within hours).
- TST is of limited value in active disease because of low sensitivity and specificity but is the most widely used screening test for latent TB infection.
- Interferon γ release assays (IGRAs) measure the release of interferon γ by T cells after stimulation with TB-specific antigens and are more specific for *M. tuberculosis* than is TST.
 - In low-incidence settings, IGRAs may be more sensitive than TST.
 - In high TB- and/or HIV-burden settings, the performance of IGRAs has varied greatly, and cost considerations may currently limit wider use.

TREATMENT

Tuberculosis

DRUGS

First-Line Agents

- *Rifampin*: Rifampin is the most important and potent antituberculous agent. The standard dosage in adults is 600 mg/d.
 - The drug distributes well throughout body tissues, including inflamed meninges. It turns body fluids (e.g., urine, saliva, tears) red-orange and is excreted through bile and the enterohepatic circulation.
 - Rifampin is usually well tolerated; adverse events are infrequent and generally mild.
 - Of note, rifampin is a potent inducer of the hepatic cytochrome P450 system and decreases the half-life of many other drugs.

- **Isoniazid:** Isoniazid is a critical drug for active and latent TB disease. The usual adult dosage is 300 mg/d or 900 mg twice per week.
 - Isoniazid is distributed well throughout the body and infected tissues, including CSF and body cavities.
 - The most important toxicities are hepatotoxicity and peripheral neuropathy.
 - Isoniazid-associated hepatitis is idiosyncratic. Its frequency increases with age and alcohol use and in the postpartum period.
 - Because peripheral neuropathy can result from interference with pyridoxine metabolism, pyridoxine (25–50 mg/d) should be given to pts with other risk factors for neuropathy, such as diabetes, alcohol abuse, or malnutrition.
- **Ethambutol:** The least potent first-line agent, ethambutol is synergistic with the other drugs in the standard first-line regimen. Ethambutol is usually given at a dosage of 15 mg/kg daily.
 - The drug is distributed throughout the body but reaches only low levels in CSF.
 - This agent can cause dose-dependent optic neuritis, producing central scotoma and impairing both visual acuity and the ability to see green.
- **Pyrazinamide:** The usual dosage is 15–30 mg/kg daily (maximum, 2 g/d). The drug distributes well throughout the body, including the CSF.
 - Hyperuricemia that can be managed conservatively is common.
 - Clinical gout is rare.

Other Effective Agents

- **Streptomycin:** The usual adult dose is 0.75–1.0 g IM daily or 5 times per week. Streptomycin causes ototoxicity (primarily vestibulotoxicity) but is less nephrotoxic than other aminoglycosides.
- **Rifabutin:** Rifabutin has fewer drug interactions than rifampin and is recommended in place of rifampin for HIV-infected pts who are taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors. Rifabutin reaches tissue concentrations 5–10 times higher than those in plasma and has a much longer half-life than rifampin. The most common adverse effects are gastrointestinal, although rifabutin is better tolerated by adult TB pts with rifampin-related adverse effects.
- **Rifapentine:** Rifapentine is similar to rifampin but can be given once or twice weekly. This drug is not approved for treatment in HIV-infected pts because of elevated rates of relapse.

Second-Line Agents

- **Fluoroquinolones:** Levofloxacin, gatifloxacin (no longer marketed in the United States because of its severe toxicity), and moxifloxacin have solid, broad antimycobacterial activity. Ciprofloxacin and ofloxacin are no longer recommended for treatment of TB because of poor efficacy.
- Other agents (e.g., capreomycin, clofazimine, linezolid, carbapenems, bedaquiline) are used uncommonly but may be needed in disease caused by resistant strains of *M. tuberculosis*.

REGIMENS

See [Table 97-1](#).

TABLE 97-1 Recommended Antituberculosis Treatment Regimens

INDICATION	INITIAL PHASE		CONTINUATION PHASE	
	DURATION, MONTHS	DRUGS	DURATION, MONTHS	DRUGS
New smear- or culture-positive cases	2	HRZE ^{a,b}	4	HR ^{a,c}
New culture-negative cases	2	HRZE ^a	4	HR ^{a,d}
Pregnancy	2	HRE ^e	7	HR
Relapses and treatment default ^f	← Tailored according to rapid drug susceptibility testing →			
Failures ^f	← Tailored according to rapid drug susceptibility testing →			
Resistance (or intolerance) to H	Throughout (6)	RZEQ		
Resistance (or intolerance) to R	← See text →			
MDR-TB (resistance to at least H + R)	← See text →			
XDR-TB	← See Table 173-4 →			
Intolerance to Z	2	HRE	7	HR

^aAll drugs should be given daily. Recommended daily dosages for adults: isoniazid, 5 mg/kg, max 300 mg; rifampin, 10 mg/kg, max 600 mg; pyrazinamide, 25 mg/kg, max 2 g; and ethambutol, 15 mg/kg.

^bStreptomycin was used in the past in place of ethambutol but is no longer considered a first-line drug.

^cA clinical trial showed that HIV-negative pts with noncavitary pulmonary tuberculosis who have negative sputum AFB smears after the initial phase of treatment can be given once-weekly rifapentine/isoniazid in the continuation phase. However, this regimen is rarely used.

^dThe American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America suggest that a 2-month continuation phase could be used in HIV-seronegative pts with sputum smear-negative and culture-negative TB.

^eThe 6-month regimen with pyrazinamide can probably be used safely during pregnancy and is recommended by the WHO and the International Union against Tuberculosis and Lung Disease. If pyrazinamide is not included in the initial treatment regimen, the minimal duration of therapy is 9 months.

^fThe availability of rapid molecular methods to identify drug resistance allows initiation of a proper regimen at the start of treatment.

Abbreviations: E, ethambutol; H, isoniazid; MDR-TB, multidrug-resistant tuberculosis; Q, a quinolone antibiotic; R, rifampin; WHO, World Health Organization; XDR-TB, extensively drug-resistant tuberculosis; Z, pyrazinamide.

- During the intensive (bactericidal) phase, the majority of tubercle bacilli are killed, symptoms resolve, and usually the pt becomes noninfectious. The continuation phase is required to eliminate persisting mycobacteria and prevent relapse.
 - Nonadherence to the regimen is the most important impediment to cure. Directly observed treatment (especially during the initial 2 months) and fixed drug-combination products should be used if possible.
 - Bacteriologic evaluation is the preferred method of monitoring response to treatment.
 - Virtually all pts should have negative sputum cultures after 3 months of treatment. If the culture remains positive, treatment failure and drug resistance should be suspected.
 - With extrapulmonary TB, bacteriologic monitoring may not be feasible. In these cases, the response to treatment must be assessed clinically and radiographically.
 - Drug resistance may be either primary (i.e., present in a strain prior to therapy) or acquired (i.e., arising during treatment because of an inadequate regimen or noncompliance).
 - Treatment regimens for MDR- and XDR-TB should be chosen in consultation with experts. The WHO recommends a regimen of a fluoroquinolone (levofloxacin or moxifloxacin), bedaquiline, linezolid, clofazimine, and cycloserine or terizidone for 18–20 months. Some pts may be eligible for a shorter (9- to 12-month) regimen of a standardized 7-drug combination, but current data suggest that this shorter regimen may be more likely to be followed by treatment failure or relapse.
 - Close monitoring for drug toxicity should take place during treatment and should include baseline LFTs and monthly questioning about possible hepatitis symptoms. High-risk pts (e.g., older pts, pts who use alcohol daily) should have LFT values monitored during treatment.
 - For pts with symptomatic hepatitis and those with marked (five- to sixfold) elevations in serum levels of aspartate aminotransferase, treatment should be stopped and drugs reintroduced one at a time after liver function has returned to normal.
 - Three important considerations are relevant to TB treatment in HIV-infected pts: an increased frequency of paradoxical reactions, interactions between antiretroviral agents and rifamycins, and development of rifampin mono-resistance with widely spaced intermittent treatments.
-

■ PREVENTION

- *Vaccination*: An attenuated strain of *M. bovis*, bacille Calmette-Guérin (BCG), protects infants and young children from serious forms of TB (e.g., meningitis and miliary disease) and is recommended for routine use in countries with high TB prevalence.
- *Treatment of latent infection*: Candidates for chemoprophylaxis are identified by TST or IGRA. Positive skin tests are determined by reaction size and risk group (Table 97-2). Drug treatment should be considered for pts with evidence of latent infection (Table 97-3). Isoniazid should not be given to persons with active liver disease.

TABLE 97-2 Tuberculin Reaction Size and Treatment of Latent *Mycobacterium tuberculosis* Infection

RISK GROUP	TUBERCULIN REACTION SIZE, mm
HIV-infected persons	≥5
Recent contacts of a pt with TB	≥5 ^a
Organ transplant recipients	≥5
Persons with fibrotic lesions consistent with old TB on chest radiography	≥5
Persons who are immunosuppressed—e.g., due to the use of glucocorticoids or tumor necrosis factor α inhibitors	≥5
Persons with high-risk medical conditions ^b	≥5
Recent immigrants (≤5 years) from high-prevalence countries	≥10
Injection drug users	≥10
Mycobacteriology laboratory personnel; residents and employees of high-risk congregate settings ^c	≥10
Children <5 years of age; children and adolescents exposed to adults in high-risk categories	≥10
Low-risk persons ^d	≥15

^aTuberculin-negative contacts, especially children, should receive prophylaxis for 2–3 months after contact ends and should then undergo repeat tuberculin skin testing (TST). Those whose results remain negative should discontinue prophylaxis. HIV-infected contacts should receive a full course of treatment regardless of TST results.

^bThese conditions include silicosis and end-stage renal disease managed by hemodialysis.

^cThese settings include correctional facilities, nursing homes, homeless shelters, and hospitals and other health care facilities.

^dExcept for employment purposes where longitudinal TST screening is anticipated, TST is not indicated for these low-risk persons. A decision to treat should be based on individual risk/benefit considerations.

Source: Adapted from Centers for Disease Control and Prevention: TB elimination—treatment options for latent tuberculosis infection (2011). Available at <http://www.cdc.gov/tb/publications/factsheets/testing/skintestresults.pdf>.

LEPROSY

■ MICROBIOLOGY AND EPIDEMIOLOGY

Leprosy is a nonfatal chronic infectious disease caused by *M. leprae*, an obligate intracellular bacterial species indistinguishable microscopically from other mycobacteria. The organism is confined to humans, armadillos (in some locales), and sphagnum moss.

- *M. leprae* cannot yet be cultured in vitro. The organism has a doubling time in mice of 2 weeks (compared with 20 min for *Escherichia coli* and 1 day for *M. tuberculosis*).
- Leprosy, which is associated with poverty and rural residence, is a disease of the developing world; its global prevalence is difficult to assess and is variously estimated at 0.6–8 million.
 - More than 80% of the world's cases occur in a few countries: India, China, Myanmar, Indonesia, Nepal, Brazil, Nigeria, and Madagascar.
 - In the United States, ~4000 people have leprosy and 100–200 new cases are reported annually.
- The route of transmission is uncertain but may be via nasal droplets, contact with infected soil, or amoeba insect vectors.

TABLE 97-3 Recommended Regimens and Drug Dosages for Treatment of Latent *Mycobacterium tuberculosis* Infection^a

REGIMEN	DOSE	ADVERSE EVENTS
Isoniazid alone for 6 or 9 months	Adults: 5 mg/kg (max, 300 mg) per day Children: 10 mg/kg per day	Drug-induced liver injury, nausea, vomiting, abdominal pain, skin rash, peripheral neuropathy, dizziness, drowsiness, seizure
Rifampin alone for 3–4 months	Adults: 10 mg/kg per day Children: 10 mg/kg (max: <45 kg, 450 mg; >45 kg, 600 mg) per day	Flu-like syndrome, skin rash, drug-induced liver injury, anorexia, nausea, abdominal pain, neutropenia, thrombocytopenia, renal reactions (e.g., acute tubular necrosis and interstitial nephritis)
Isoniazid plus rifampin for 3–4 months	As above	As above
Rifapentine plus isoniazid for 3 months	Adults and children: Isoniazid: 15 mg/kg (900 mg) weekly Rifapentine: 15–30 mg/kg (900 mg) weekly	Hypersensitivity reactions, petechial skin rash, drug-induced liver injury Anorexia, nausea, abdominal pain Hypotensive reactions

^aSee text for full description of evidence on and limitations of these regimens.

Source: World Health Organization.

■ CLINICAL MANIFESTATIONS

The spectrum from polar tuberculoid to polar lepromatous disease is associated with an evolution from asymmetric localized macules and plaques to nodular and indurated symmetric generalized skin manifestations, an increasing bacterial load, and loss of *M. leprae*-specific cellular immunity. Prognosis, complications, and intensity of antimicrobial therapy depend on where a pt presents on the clinical spectrum. The incubation period ranges from 2 to 40 years but is usually 5–7 years.

Tuberculoid (TT) Leprosy At the less severe end of the disease spectrum, TT leprosy results in symptoms confined to the skin and peripheral nerves.

- One or several hypopigmented macules or plaques with sharp margins that are hypesthetic and have lost sweat glands and hair follicles are present. AFB are few or absent.
- There is asymmetric enlargement of one or several peripheral nerves—most often the ulnar, posterior auricular, peroneal, and posterior tibial nerves—associated with hypesthesia and myopathy.

Lepromatous (LL) Leprosy Pts develop symmetrically distributed skin nodules, raised plaques, and diffuse dermal infiltration that can cause leonine facies, loss of eyebrows and lashes, pendulous earlobes, and dry scaling.

- Numerous bacilli are present in skin (up to 10^9 /g), nerves, and all organs except the lungs and CNS.
- Nerve enlargement and damage are usually symmetric and are due to bacillary invasion.

■ COMPLICATIONS

- *Reactional states*: These common, immunologically mediated inflammatory states cause considerable morbidity. *Erythema nodosum leprosum*—characterized by painful erythematous papules that resolve spontaneously in ~1 week—occurs in ~50% of pts near the LL end of the disease spectrum within 2 years of initiation of therapy.
- *Extremities*: Neuropathy results in insensitivity and affects fine touch, pain, and heat receptors. The loss of distal digits in leprosy is a consequence of insensitivity, trauma, secondary infection, and—in lepromatous pts—a poorly understood and sometimes profound osteolytic process.
- *Eyes*: Owing to cranial nerve palsies, lagophthalmos and corneal insensitivity may complicate leprosy, resulting in trauma, secondary infection, and (without treatment) corneal ulcerations and opacities. Leprosy is a major cause of blindness in low-income countries.
- *Nerve abscesses*: Pts with leprosy can develop abscesses of nerves (most commonly the ulnar) and require urgent surgical decompression to prevent irreversible sequelae.

■ DIAGNOSIS

In TT leprosy, the advancing edge of a skin lesion should be biopsied. In LL leprosy, biopsy of even normal-appearing skin often yields positive results. Serology, skin testing, and PCR of the skin offer little diagnostic assistance.

TREATMENT

Leprosy

DRUGS

- Rifampin (600 mg daily or monthly) is the only agent bactericidal against *M. leprae*. See the preceding section on *M. tuberculosis* for more details on rifampin. Relapse rates are >10% and most commonly occur after >10 years.
- Monotherapy with dapsone (50–100 mg/d) results in a resistance-related relapse rate of only 2.5%.
 - A decrease in hemoglobin levels of ~1 g/dL is a common adverse effect; the *sulfone syndrome* (high fever, anemia, exfoliative dermatitis, and a mononucleosis-type blood picture) occurs rarely.
 - G6PD deficiency must be ruled out before therapy to avoid hemolytic anemia.
- Clofazimine (50–100 mg/d, 100 mg 3 times per week, or 300 mg monthly) is a phenazine iminoquinone dye that is weakly active against *M. leprae*. Adverse effects include red-black skin discoloration.

REGIMENS

The conventional approach to treatment of leprosy was originally based on recommendations made by the World Health Organization in 1982 (with some modifications made since then), but many experts think a more intensive regimen is warranted.

- *Tuberculoid disease*: In adults, tuberculoid leprosy is treated with dapsone (100 mg/d) and rifampin (600 mg monthly, supervised) for 6 months. A more intensive regimen consists of treatment with dapsone (100 mg/d) for 5 years.
- *Lepromatous disease*: In adults, lepromatous leprosy is treated with dapsone (100 mg/d) plus clofazimine (50 mg/d)—unsupervised—in addition to rifampin (600 mg monthly) plus clofazimine (300 mg monthly)—supervised—for

1–2 years. A more intensive regimen consists of treatment with rifampin (600 mg/d) for 3 years plus dapsone (100 mg/d) indefinitely.

- Relapse can occur years later; prolonged follow-up is needed.
- **Reactional states**
 - Lesions at risk for ulceration or in cosmetically important areas can be treated with glucocorticoids (40–60 mg/d for at least 3 months).
 - If erythema nodosum leprosum is present and persists despite two short courses of steroids (40–60 mg/d for 1–2 weeks), thalidomide (100–300 mg nightly) should be given. Because of thalidomide's teratogenicity, its use is strictly regulated.

INFECTIONS WITH NONTUBERCULOUS MYCOBACTERIA (NTM)

Mycobacteria other than those of the *M. tuberculosis* complex and *M. leprae* are referred to as *nontuberculous* or *atypical* mycobacteria and are ubiquitous in soil and water.

■ MICROBIOLOGY

NTM are broadly differentiated into rapidly and slowly growing forms (<7 days and ≥7 days, respectively). *M. abscessus*, *M. fortuitum*, and *M. chelonae* are examples of rapid growers; species such as *M. avium* and *M. intracellulare* (the *M. avium* complex, or MAC), *M. kansasii*, *M. ulcerans*, and *M. marinum* are slow growers.

■ EPIDEMIOLOGY

Most NTM cause disease in humans only rarely unless some aspect of host defense is impaired (as in bronchiectasis) or breached (as by inoculation—e.g., during liposuction or trauma). The bulk of NTM disease in North America is due to *M. kansasii*, MAC organisms, and *M. abscessus*.

■ CLINICAL MANIFESTATIONS

Although there are many NTM species, the clinical presentations they cause can be broadly categorized by the organ system(s) affected.

- *Disseminated disease* is now quite rare; even pts with advanced HIV infection do not often develop disseminated NTM infection, given improved treatment of HIV infection and effective antimycobacterial prophylaxis.
 - Organisms typically spread from the bowel to the bone marrow and bloodstream, but disease is indolent, and it can take weeks or months for the pt to present for medical attention with malaise, fever, weight loss, organomegaly, and lymphadenopathy.
 - A child with involvement of two or more organ systems and no iatrogenic cause should be evaluated for defects in the interferon γ /interleukin 12 pathway.
- *Pulmonary disease* represents the most common NTM infection in industrialized countries. MAC organisms are most commonly involved in North America. Pts present with months or years of throat clearing, nagging cough, and slowly progressive fatigue. *M. kansasii* can cause a TB-like syndrome, with hemoptysis, chest pain, and cavitary lung disease.
- Isolated *cervical lymphadenopathy* is the most common NTM infection among young children in North America and is most frequently caused by MAC organisms. The nodes are typically firm and painless and develop in the absence of systemic symptoms.

- *Skin and soft-tissue disease* usually requires a break in the skin for introduction of the organism. Different NTM species are associated with specific exposures.
 - *M. fortuitum* is linked to pedicure bath–associated infections, particularly if skin abrasion (e.g., during leg shaving) has immediately preceded the pedicure.
 - Rapidly growing NTM are associated with outbreaks of infection acquired via skin contamination from surgical instruments (especially in cosmetic surgery), injections, and other procedures. These infections are typically accompanied by painful, erythematous, draining SC nodules, usually without associated fever or systemic symptoms.
 - *M. marinum* can be acquired from fish tanks, swimming pools, barnacles, and fish scales. Pts typically develop papules or ulcers (“fish-tank granuloma”) that can progress to tendonitis and tender nodules on the arm in a pattern similar to that caused by *Sporothrix schenckii*. Lesions appear days or weeks after acquisition of the organism.
 - *M. ulcerans* is a waterborne organism found primarily in tropical areas, especially in Africa. Skin lesions are typically painless, clean ulcers that slough and can cause osteomyelitis.

■ DIAGNOSIS

Similar to *M. tuberculosis*, NTM can be detected on acid-fast or fluorochrome smears of clinical samples and can be cultured on mycobacterial medium. Isolation of NTM from a clinical specimen may reflect colonization and requires an assessment of the organism’s clinical significance.

- Isolation of NTM from blood specimens is clear evidence of disease; many NTM species require special media and will not grow in standard blood culture medium.
- The American Thoracic Society has published guidelines for the diagnosis of pulmonary NTM disease that require the growth of NTM from two of three sputum samples, a positive bronchoalveolar lavage sample, or a pulmonary parenchyma biopsy sample with granulomatous inflammation or mycobacteria found on section and NTM in culture. Although these guidelines are specific to MAC, *M. abscessus*, and *M. kansasii*, they probably apply to other NTM as well.
- The only antibiotic susceptibility assessment indicated is testing of MAC organisms for susceptibility to clarithromycin and of *M. kansasii* for susceptibility to rifampin.

TREATMENT

Infections with NTM

Since NTM disease evolves over a long period, it is rarely necessary to begin treatment on an emergency basis before identifying the infecting species.

- MAC infection requires multidrug therapy with a macrolide (clarithromycin or azithromycin), ethambutol, and a rifamycin (rifampin or rifabutin). Therapy is prolonged, generally continuing for 12 months after culture conversion; typically, a course lasts for at least 18 months.
- *M. kansasii* lung disease is similar to TB in many ways and is also effectively treated with isoniazid (300 mg/d), rifampin (600 mg/d), and ethambutol (15 mg/kg per day). Treatment should continue until cultures have been negative for at least 1 year.

- Extrapulmonary disease due to rapidly growing NTM is often treated successfully with a macrolide and another drug (with the choice based on in vitro susceptibility). Pulmonary disease due to *M. abscessus* is difficult to cure and often requires repeated courses that include a macrolide along with an IV-administered agent such as amikacin, a carbapenem, ceftoxitin, or tigecycline.
- *M. marinum* infection is effectively treated with any combination of a macrolide, ethambutol, and a rifamycin for 1–2 months after clinical resolution of isolated soft-tissue disease; tendon and bone involvement may require longer courses in light of clinical evolution.
- Treatment of infections caused by other NTM is less well defined, but macrolides and aminoglycosides are usually effective, with other agents added as indicated.

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Lyme Disease and Other Nonsyphilitic Spirochetal Infections



LYME BORRELIOSIS

■ MICROBIOLOGY AND EPIDEMIOLOGY

Borrelia burgdorferi, the causative agent of Lyme disease, is a fastidious micro-aerophilic spirochete. The human infection Lyme borreliosis is caused primarily by three pathogenic genospecies: *B. burgdorferi sensu stricto* (hereafter referred to as *B. burgdorferi*), *Borrelia garinii*, and *Borrelia afzelii*.

- *B. burgdorferi* is the sole cause of Lyme borreliosis in the United States; all three genospecies are found in Europe, and the latter two species occur in Asia.
- Lyme disease is the most common vector-borne illness in the United States, with ~300,000 cases each year.
 - *Ixodes* ticks transmit the disease.
 - *I. scapularis*, which also transmits babesiosis and anaplasmosis, is found in northeastern and midwestern states; *I. pacificus* is found in western states.
- The white-footed mouse is the preferred host for larval and nymphal *I. scapularis*. Adult ticks prefer the white-tailed deer as host.
- Nymphal ticks transmit the disease to humans during the early summer months after feeding for ≥ 24 h.

■ CLINICAL MANIFESTATIONS

Lyme disease usually begins with *erythema migrans* (EM; stage 1, localized infection) before disseminating (stage 2) or causing persistent infection (stage 3).

- *Stage 1 (localized infection)*: After an incubation period of 3–32 days, EM develops at the site of the tick bite (commonly the thigh, groin, or axilla) in 80% of pts.
 - The classic presentation is a red macule that expands slowly to form an annular lesion with a bright red outer border and central clearing. Central erythema, induration, necrosis, vesicular changes, or many red rings within an outer ring are also possible.
 - Most pts do not remember the preceding tick bite.

- *Stage 2 (disseminated infection)*: Given that some pts do not notice EM, many pts present within days or weeks after infection with secondary annular skin lesions, nonspecific systemic signs and symptoms, neurologic deficits, or cardiac manifestations due to hematogenous spread.
 - Nonspecific signs and symptoms include severe headache, mild neck stiffness, fever, chills, migratory musculoskeletal pain, arthralgias, malaise, and fatigue. These manifestations subside within a few weeks, even in untreated pts.
 - Neurologic deficits occur in ~15% of pts and may include meningitis; encephalitis; cranial neuritis, including bilateral facial palsy; motor or sensory radiculoneuropathy; mononeuritis multiplex; ataxia; or myelitis. Lymphocytic pleocytosis (~100 cells/ μL) is found in CSF, often along with elevated protein levels and normal or slightly low glucose concentrations.
 - Cardiac involvement occurs in ~8% of pts. Atrioventricular (AV) block of fluctuating degree is most common, but acute myopericarditis is possible. Cardiac involvement usually lasts for only a few weeks but may recur in untreated pts.
- *Stage 3 (persistent infection)*: Of untreated pts in the United States, ~60% develop frank arthritis, usually consisting of intermittent attacks of oligoarticular arthritis in large joints (especially the knees) that last for weeks or months.
 - Joint-fluid cell counts range from 500 to 110,000/ μL (average, 25,000/ μL); the majority of the cells are neutrophils.
 - Arthritis can persist despite eradication of spirochetes, potentially due to infection-induced autoimmunity or retained spirochetal antigens.
 - Chronic neurologic involvement (e.g., subtle encephalopathy affecting memory, mood, or sleep; peripheral neuropathy) is less common. In Europe, severe encephalomyelitis is seen with *B. garinii* infection.
 - Acrodermatitis chronica atrophicans, a late skin manifestation, is seen in Europe and Asia and is associated with *B. afzelii* infection.
- *Post-Lyme syndrome*: For months or years afterward, ~10% of pts have subjective pain, neurocognitive manifestations, or fatigue symptoms—a syndrome indistinguishable from chronic fatigue syndrome and fibromyalgia. There is no evidence that these symptoms are caused by active infection.

■ DIAGNOSIS

Serologic evidence combined with a compatible clinical picture is the usual basis for diagnosis.

- Only 20–30% of pts have positive serologic results in acute-phase samples, whereas 70–80% have positive results in convalescent-phase samples obtained 2–4 weeks later. Of note, serologic tests do not discriminate between active and past disease as both IgM and IgG may persist for years after treatment.
 - Serologic analysis consisting of a two-step approach (ELISA screening with western blot confirmation for cases with positive or equivocal results) is recommended only for pts with at least an intermediate pretest likelihood of having Lyme disease.
 - IgM and IgG testing should be done in the first 2 months of illness, after which IgG testing alone is adequate.
 - CDC-adopted criteria dictate that the IgM western blot must show at least 2 of 3 defined bands and that the IgG western blot must show at least 5 of 10 defined bands to be considered positive.
- PCR is most useful for joint fluid, is less sensitive for CSF, and has little or no utility for plasma or urine.
- Although culture of the organism is possible, it is reserved primarily for research settings.

TREATMENT**Lyme Borreliosis**

- Doxycycline (100 mg bid) is the agent of choice for men and nonpregnant women with localized or disseminated infection and is also effective against anaplasmosis (Chap. 99).
 - Amoxicillin (500 mg tid), cefuroxime (500 mg bid), erythromycin (250 mg qid), and newer macrolides—preferred in that order—are alternative agents.
 - Except in cases of severe neurologic disease and third-degree AV block, the drug can usually be taken by mouth.
 - A 14-day course of treatment for localized infection or a 21-day course for disseminated infection is generally sufficient.
 - Approximately 15% of pts experience a Jarisch-Herxheimer-like reaction during the first 24 h of treatment.
 - For pts with severe objective neurologic abnormalities, IV treatment with ceftriaxone for 14–28 days should be given. Cefotaxime or penicillin is an alternative.
 - Pts with high-degree AV block (PR interval, >0.3 s) should receive IV treatment for at least part of the course; cardiac monitoring is recommended.
 - Pts with Lyme arthritis should be treated with 30 days of oral doxycycline or amoxicillin.
 - For pts who do not respond to oral agents, re-treatment with IV ceftriaxone for 28 days is appropriate.
 - If joint inflammation persists for months after both oral and IV antibiotics, anti-inflammatory agents, disease-modifying anti-rheumatic drugs, or synovectomy may be successful.
 - For pts diagnosed with chronic Lyme disease, no data demonstrate that additional antibiotic therapy is helpful.

PROPHYLAXIS

The risk of infection with *B. burgdorferi* after a recognized tick bite is so low that antibiotic prophylaxis is not routinely indicated. However, if an attached, engorged *I. scapularis* nymph is found or if follow-up will be difficult, a single 200-mg dose of doxycycline, given within 72 h of the tick bite, effectively prevents the disease.

PROGNOSIS

Early treatment results in an excellent prognosis. Most pts recover with minimal or no residual deficits.

ENDEMIC TREPONEMATOSES**MICROBIOLOGY AND EPIDEMIOLOGY**

The endemic treponematoses—yaws (*Treponema pallidum* subspecies *pertenue*), endemic syphilis (*T. pallidum* subspecies *endemicum*), and pinta (*T. carateum*)—are nonvenereal chronic diseases acquired during childhood and caused by organisms closely related to the agent of syphilis, *T. pallidum* subspecies *pallidum*.

- Disease is transmitted by direct contact.
- The most recent World Health Organization (WHO) estimate (1995) suggested that there are 460,000 new cases per year and a prevalence of 2.5 million infected persons.

- Disease is limited to people in rural areas of developing nations and recent émigrés from these regions.

■ CLINICAL MANIFESTATIONS

The major clinical distinctions made between venereal syphilis and the nonvenereal treponematoses are the apparent lack of congenital transmission and of CNS involvement in the nonvenereal infections. However, these distinctions may not be entirely accurate.

- *Yaws* is characterized by the development of one or more primary lesions (“mother yaw”) followed by multiple disseminated skin lesions.
 - At 3–4 weeks after acquisition of the organism, the pt develops a papule that ultimately enlarges to become ulcerated, is associated with regional lymphadenopathy, and heals spontaneously within 6 months.
 - A large proportion of ulcerative lesions in yaws-endemic regions contain *Haemophilus ducreyi*, either as the sole etiologic agent or in combination with *T. pallidum* subspecies *pertenue*.
 - Late gummatous lesions of the skin and long bones affect 10% of untreated persons and are similar to the destructive lesions of leprosy and leishmaniasis.
- *Endemic syphilis* is initially localized to mucocutaneous and mucosal surfaces. Pts develop an intraoral papule, which is followed by mucous patches on the oral mucosa and mucocutaneous lesions resembling the condylomata lata of secondary syphilis. Destructive gummas, osteitis, and gangosa (destruction of the nose, maxilla, palate, and pharynx) are more common in endemic syphilis than in yaws.
- *Pinta* is the most benign of the treponemal infections in that it does not cause destructive lesions or involve tissues other than the skin. The disease has three stages that are characterized by marked changes in skin color.

■ DIAGNOSIS

The diagnosis is based on clinical presentation, dark-field microscopy of scrapings from lesions, and serologic testing (as for venereal syphilis).

TREATMENT

Endemic Treponematoses

WHO-recommended treatment for pts and their contacts includes a single dose of azithromycin (30 mg/kg; maximum, 2 g) or benzathine penicillin (1.2 million units for adults, 600,000 units for children <10 years of age). Doxycycline and tetracycline are probably effective alternatives.

LEPTOSPIROSIS

■ MICROBIOLOGY AND EPIDEMIOLOGY

Leptospire are spirochetal organisms that cause an important zoonosis with a broad spectrum of clinical manifestations.

- Rodents, particularly rats, are the most important reservoir, but leptospirosis affects almost all mammalian species. Transmission can occur during contact with urine, blood, or tissue from infected animals or, more commonly, during exposure to contaminated environments (e.g., during recreational water activities).

- Globally, there are ~1 million severe cases each year, with a mean case–fatality rate of ~10%.

■ CLINICAL MANIFESTATIONS

After an average incubation period of 1–2 weeks, infection by *Leptospira* results in a subclinical infection, an undifferentiated febrile illness, or Weil's disease (the most severe form).

- Leptospirosis is a biphasic illness. The initial *leptospiremic* phase lasts 3–10 days and is characterized by fever; organisms can be cultured from blood during this phase. After another 3–10 days (the *immune* phase), symptoms resolve, and leptospire can be cultured from urine.
 - Nonspecific physical findings may include conjunctival suffusion, nonexudative pharyngeal injection, muscle tenderness, lymphadenopathy, crackles on lung auscultation, jaundice, hepatosplenomegaly, and a transient rash.
- Severe leptospirosis, often referred to as *Weil's syndrome*, encompasses the triad of hemorrhage, jaundice, and acute renal injury. Up to 50% of pts die of septic shock with multiorgan failure and/or severe bleeding in the lungs, GI and urogenital tracts, and skin. Altered mental status may reflect leptospiral meningitis.

■ DIAGNOSIS

An appropriate exposure history combined with any of the protean manifestations of leptospirosis suggests the clinical diagnosis and guides confirmatory testing.

- Definitive diagnosis rests on demonstration of the organism by culture isolation (which takes weeks or months), on a positive PCR result, or on seroconversion or a ≥ 4 -fold rise in antibody titer.
 - Leptospire can be cultured from blood and CSF during the first 7–10 days of illness.
 - Urine cultures are positive in the second week of illness.

TREATMENT

Leptospirosis

- Prompt initiation of antibiotics probably shortens the course of severe leptospirosis and prevents the progression of mild disease.
- For mild disease, oral treatment with doxycycline, azithromycin, ampicillin, or amoxicillin is recommended. In regions where rickettsial diseases are endemic, doxycycline or azithromycin is the drug of choice.
- For severe disease, parenteral treatment with penicillin, ceftriaxone, cefotaxime, or doxycycline should be given. From a pragmatic viewpoint, severe leptospiral disease frequently requires empirical initiation of broad-spectrum parenteral therapy before the diagnosis is confirmed.

RELAPSING FEVER

■ MICROBIOLOGY

Borrelia recurrentis causes louse-borne relapsing fever (LBRF) and is transmitted from person to person by the body louse. Spirochetes are introduced not from the bite itself but from rubbing of the insect's feces into the bite site in response to irritation. Tick-borne relapsing fever (TBRF), a zoonosis usually transmitted

via the bite of various *Ornithodoros* ticks, is caused by multiple *Borrelia* species. *B. miyamotoi* can cause relapsing fever but is transmitted to humans from other mammals by hard ticks (e.g., *Ixodes scapularis*) that also transmit *B. burgdorferi* and other tick-borne illnesses.

■ EPIDEMIOLOGY

LBRF transmission is currently limited to Ethiopia and adjacent countries, with epidemics occurring during famine, natural disaster, and war. TBRF occurs worldwide, with Africa most affected. In North America, most cases of TBRF are due to *B. hermsii* and *B. turicatae* and occur in the western United States and Canada.

■ CLINICAL MANIFESTATIONS

- Both TBRF and LBRF present with a sudden onset of discrete febrile periods separated by afebrile periods of a few days.
 - In LBRF, the first episode of fever persists for 3–6 days and is followed by a single milder episode.
 - In TBRF, multiple febrile periods last 1–3 days each.
 - In both forms, the duration of an afebrile period ranges from 4 to 14 days.
- In addition to fever, pts commonly develop headaches, myalgias, nausea, abdominal pain (due to hepatosplenomegaly), and arthralgias.
 - Petechiae, ecchymoses, and epistaxis are common in LBRF but not in TBRF.
 - Localizing neurologic findings (e.g., Bell's palsy, deafness, visual impairment) are more common in TBRF.

■ DIAGNOSIS

In pts with a compatible history (i.e., a characteristic fever pattern and exposure to body lice, soft-bodied ticks, or *Ixodes* hard-bodied ticks in at-risk geographic regions 1–2 weeks prior to illness onset), laboratory confirmation is made by the detection or isolation of spirochetes from blood during a febrile episode. Microscopic examination of Wright- or Giemsa-stained thin blood smears usually yields positive results if the concentration of spirochetes is $\geq 10^5$ /mL.

- PCR techniques may reveal spirochetes between febrile episodes.
- Serologic confirmation of infection is limited by false-positive results and poor sensitivity.

TREATMENT

Relapsing Fever

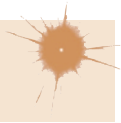
- One dose of doxycycline (200 mg PO), tetracycline (500 mg PO), or penicillin G (400,000–800,000 units IM) is effective for LBRF. A 10-day course of tetracycline (500 mg q6h) or doxycycline (100 mg bid) is preferred for TBRF; erythromycin (500 mg q6h) is an alternative when tetracyclines are contraindicated. The Jarisch-Herxheimer reaction, which has an incidence of ~80% in LBRF and ~50% in TBRF, presents as rigors, fevers, and hypotension within 2–3 h of initiation of antibiotic therapy. Given that some cases are fatal, pts should be monitored for several hours following the first dose of antibiotics.
- Little is known about treatment for *B. miyamotoi* infections, but the guidelines for Lyme disease are probably sufficient.

■ PROGNOSIS

The mortality rates for untreated LBRF and TBRF are 10–70% and 4–10%, respectively. With treatment, the mortality rate is 2–5% for LBRF and <2% for TBRF.

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Rickettsial Diseases

**Microbiology**

Rickettsiae are obligate intracellular gram-negative coccobacilli and short bacilli usually transmitted by tick, mite, flea, or louse vectors. Except in the case of louse-borne typhus, humans are incidental hosts.

Clinical Manifestations

The clinical manifestations of all the acute rickettsial presentations are similar during the first 5 days and consist of nonspecific signs and symptoms: fever, headache, and myalgias with or without nausea, vomiting, and cough. As the course progresses, clinical manifestations—including occurrence of a macular, maculopapular, or vesicular rash; eschar; pneumonitis; and meningoencephalitis—vary from one disease to another. (See [Table 99-1](#) and details below.)

TICK- AND MITE-BORNE SPOTTED FEVERS**■ ROCKY MOUNTAIN SPOTTED FEVER (RMSF)****Epidemiology**

Caused by *R. rickettsii*, RMSF has the highest case–fatality rate of all rickettsial diseases.

- In the United States, the prevalence is highest in the south-central and south-eastern states. Most cases occur between May and September.
- A rare presentation of fulminant RMSF is seen most often in male black pts with G6PD deficiency.
- RMSF is transmitted by different ticks in different geographic areas—e.g., the American dog tick (*Dermacentor variabilis*) transmits RMSF in the eastern two-thirds of the United States and in California, and the Rocky Mountain wood tick (*D. andersoni*) transmits RMSF in the western United States.

Pathogenesis

Rickettsiae are inoculated by the tick after ≥ 6 h of feeding, spread lymphohematogenously, and infect numerous foci of contiguous endothelial cells. Increased vascular permeability, with edema, hypovolemia, and ischemia, causes tissue and organ injury.

Clinical Manifestations

The incubation period is ~ 1 week (range, 2–14 days). After 3 days of nonspecific symptoms, half of pts have a rash characterized by macules appearing on the wrists and ankles and subsequently spreading to the rest of the extremities and the trunk.

- Lesions ultimately become petechial in 41–59% of pts, appearing on or after day 6 of illness in $\sim 74\%$ of all cases that include a rash. The palms and soles become involved after day 5 in 43% of pts but do not become involved at all in 18–64%.
- Pts may develop hypovolemia, prerenal azotemia, hypotension, noncardiogenic pulmonary edema, renal failure, hepatic injury, and cardiac involvement with dysrhythmias. Bleeding is a rare but potentially life-threatening consequence of severe vascular damage.
- CNS involvement—manifesting as encephalitis, focal neurologic deficits, or meningoencephalitis—is an important determinant of outcome. In meningoencephalitis, CSF findings are notable for pleocytosis with a mononuclear-cell or neutrophil predominance, increased protein levels, and normal glucose levels.

TABLE 99-1 Features of Selected Rickettsial Infections

DISEASE	ORGANISM	TRANSMISSION	GEOGRAPHIC RANGE	INCUBATION PERIOD, DAYS	DURATION, DAYS	RASH, %	ESCHAR, %	LYMPHADENOPATHY ^a
Rocky Mountain spotted fever	<i>Rickettsia rickettsii</i>	Tick bite: <i>Dermacentor andersoni</i> , <i>D. variabilis</i>	United States	2–14	10–20	90	<1	+
		<i>Amblyomma cajennense</i> sensu lato, <i>A. aureolatum</i>	Central/South America					
		<i>Rhipicephalus sanguineus</i>	Mexico, Brazil, United States					
Mediterranean spotted fever	<i>R. conorii</i>	Tick bite: <i>R. sanguineus</i> , <i>R. pumilio</i>	Southern Europe, Africa, Middle East, central Asia	5–7	7–14	97	50	+
African tick-bite fever	<i>R. africae</i>	Tick bite: <i>A. hebraeum</i> , <i>A. variegatum</i>	Sub-Saharan Africa, West Indies	4–10	4–19	50	90	+++
Maculatum disease	<i>R. parkeri</i>	Tick bite: <i>A. maculatum</i> , <i>A. triste</i> , <i>A. tigrinum</i>	United States, South America	2–10	6–16	88	94	++
Pacific Coast tick fever	<i>Rickettsia</i> 364D	Tick bite: <i>D. occidentalis</i>	United States	3–9	5–14	14	100	+++
Rickettsialpox	<i>R. akari</i>	Mite bite: <i>Liponyssoides sanguineus</i>	United States, Ukraine, Turkey, Mexico, Croatia	10–17	3–11	100	90	+++
Tick-borne lymphadenopathy	<i>R. slovaca</i>	Tick bite: <i>D. marginatus</i> , <i>D. reticularis</i>	Europe	7–9	17–180	5	100	++++

Flea-borne spotted fever	<i>R. felis</i>	Flea (mechanism undetermined): <i>Ctenocephalides felis</i>	Worldwide	8–16	8–16	80	15	—
Epidemic typhus	<i>R. prowazekii</i>	Louse feces: <i>Pediculus humanus corporis</i> , fleas and lice of flying squirrels, or recrudescence	Worldwide	7–14	10–18	80	None	—
Murine typhus	<i>R. typhi</i>	Flea feces: <i>Xenopsylla cheopis</i> , <i>C. felis</i> , others	Worldwide	8–16	9–18	80	None	—
Human monocytotropic ehrlichiosis	<i>Ehrlichia chaffeensis</i>	Tick bite: <i>A. americanum</i> , <i>D. variabilis</i>	United States	1–21	3–21	26	None	++
Ewingii ehrlichiosis	<i>E. ewingii</i>	Tick bite: <i>A. americanum</i>	United States	1–21	4–21	0	None	
Unnamed ehrlichiosis	<i>E. muris eauclairensis</i>	Tick bite: <i>Ixodes scapularis</i>	United States	Unknown	3–14	12	None	
Human granulocytotropic anaplasmosis	<i>Anaplasma phagocytophilum</i>	Tick bite: <i>I. scapularis</i> , <i>I. ricinus</i> , <i>I. pacificus</i> , <i>I. persulcatus</i>	United States, Europe, Asia	4–8	3–14	Rare	None	—
Unnamed disease	<i>A. capra</i>	<i>I. persulcatus</i>	Northeastern China	Unknown	11–21	17	9	+
Neoehrlichiosis	“ <i>Candidatus Neoehrlichia mikurensis</i> ”	Tick bite: <i>I. ricinus</i> , <i>I. persulcatus</i> , <i>Haemaphysalis concinna</i>	Europe, China	≥8	11–75	10	None	

(Continued)

TABLE 99-1 Features of Selected Rickettsial Infections (Continued)

DISEASE	ORGANISM	TRANSMISSION	GEOGRAPHIC RANGE	INCUBATION PERIOD, DAYS	DURATION, DAYS	RASH, %	ESCHAR, %	LYMPHADENOPATHY ^a
Scrub typhus	<i>Orientia tsutsugamushi</i>	Mite bite: <i>Leptotrombidium deliense</i> , others	Asia, Australia, Pacific and Indian Ocean islands	9–18	6–21	50	35	+++
Q fever	<i>Coxiella burnetii</i>	Inhalation of aerosols of infected parturition material (goats, sheep, cattle, cats, others), ingestion of infected milk or milk products	Worldwide except New Zealand, Antarctica	3–30	5–57	<1	None	—

^a+++++, severe; +++, marked; ++, moderate; +, present in a small proportion of cases; —, not a noted feature.

- Laboratory findings may include increased plasma levels of acute-phase reactants such as C-reactive protein, hypoalbuminemia, hyponatremia, and elevated levels of creatine kinase.

Prognosis

Without treatment, the pt usually dies in 8–15 days; fulminant RMSF can result in death within 5 days. The mortality rate is 3–5% despite the availability of effective antibiotics, mostly because of delayed diagnosis. Survivors of RMSF usually return to their previous state of health.

Diagnosis

Within the first 3 days, diagnosis is difficult, since only 3% of pts have the classic triad of fever, rash, and known history of tick exposure. When the rash appears, RMSF should be considered.

- Immunohistologic examination of a cutaneous biopsy sample from a rash lesion is the only useful diagnostic test during acute illness, with a sensitivity of 70% and a specificity of 100%.
- Serology, most commonly the indirect immunofluorescence assay, is usually positive 7–10 days after disease onset, and a diagnostic titer of $\geq 1:64$ is usually documented.

TREATMENT

Rocky Mountain Spotted Fever

- Doxycycline (100 mg bid PO or IV) is the agent of choice for both children and adults but not for pregnant women and pts allergic to this drug, who should receive chloramphenicol.
- Treatment is given until the pt is afebrile and has been improving (usually 3–5 days after defervescence).

■ OTHER TICK-BORNE SPOTTED FEVERS

- *R. conorii* causes disease in southern Europe, Africa, and Asia. The name for *R. conorii* infection varies by region (e.g., Mediterranean spotted fever, Kenya tick typhus).
 - Disease is characterized by high fever, rash, and—in most locales—an inoculation eschar (*tâche noire*) at the site of the tick bite that appears before the onset of fever.
 - A severe form of disease with a mortality rate of ~50% occurs in pts with diabetes, alcoholism, or heart failure.
- *R. africae* causes African tick-bite fever, which occurs in sub-Saharan Africa and the Caribbean and is a mild illness consisting of headache, fever, eschar, and regional lymphadenopathy.
- Tick-borne spotted fever is diagnosed on the basis of clinical and epidemiologic findings; the diagnosis is confirmed by serology or detection of rickettsiae.

TREATMENT

Other Tick-Borne Spotted Fevers

Doxycycline (100 mg PO bid for 1–5 days) or chloramphenicol (500 mg qid PO for 7–10 days) is effective for treatment. Pregnant pts may be treated with josamycin (3 g/d PO for 5 days).

■ RICKETTSIALPOX

Epidemiology

Rickettsialpox is caused by *R. akari* and is maintained by mice and their mites. Recognized principally in New York City, rickettsialpox has been reported in other urban and rural locations in the United States as well as in Ukraine, Croatia, Mexico, and Turkey.

Clinical Manifestations

A papule forms at the site of the mite bite and develops a central vesicle that becomes a painless black-crust eschar surrounded by an erythematous halo. Lymph nodes draining the region of the eschar enlarge.

- After an incubation period of 10–17 days, malaise, chills, fever, headache, and myalgia mark disease onset.
- A macular rash appears on day 2–6 of illness and evolves sequentially into papules, vesicles, and crusts that heal without scarring.
- If untreated, fever lasts 6–10 days.

TREATMENT

Rickettsialpox

Doxycycline is the drug of choice for treatment.

FLEA- AND LOUSE-BORNE TYPHUS GROUP RICKETTSIOSES

■ ENDEMIC MURINE TYPHUS (FLEA-BORNE)

Etiology and Epidemiology

Caused by *R. typhi*, endemic murine typhus has a rat reservoir and is transmitted by fleas.

- Humans become infected when *Rickettsia*-laden flea feces are scratched into pruritic bite lesions; less often, the flea bite itself transmits the organisms or aerosolized rickettsiae from flea feces are inhaled.
- In the United States, endemic typhus occurs mainly in southern Texas and southern California; globally, it occurs in warm (often coastal) areas throughout the tropics and subtropics.
- Flea bites often are not recalled by pts, but exposure to animals such as cats, opossums, raccoons, skunks, and rats is reported by ~40%.
- Risk factors for severe disease include older age, underlying disease, and treatment with a sulfonamide drug.

Clinical Manifestations

Prodromal symptoms 1–3 days before the abrupt onset of chills and fever include headache, myalgia, arthralgia, nausea, and malaise; nausea and vomiting are nearly universal early in illness.

- Rash is apparent at presentation (usually ~4 days after symptom onset) in 13% of pts; 2 days later, half of the remaining pts develop a maculopapular rash that involves the trunk more than the extremities, is seldom petechial, and rarely involves the face, palms, or soles.
- Pulmonary disease is common, causing a hacking, nonproductive cough in 35% of pts. Almost one-fourth of pts who undergo CXR have pulmonary densities due to interstitial pneumonia, pulmonary edema, and pleural effusions.

- Laboratory abnormalities include anemia, leukopenia early in the course, leukocytosis late in the course, thrombocytopenia, hyponatremia, hypoalbuminemia, mildly increased hepatic aminotransferase levels, and prerenal azotemia.
- Complications may include respiratory failure, hematemesis, cerebral hemorrhage, and hemolysis.
- The duration of untreated disease averages 12 days (range, 9–18 days).

Diagnosis

The diagnosis can be based on culture, PCR, serologic studies of acute- and convalescent-phase sera, or immunohistology, but most pts are treated empirically.

TREATMENT

Endemic Murine Typhus (Flea-Borne)

Doxycycline (100 mg PO bid for 7–15 days) is effective. Ciprofloxacin provides an alternative if doxycycline is contraindicated.

■ EPIDEMIC TYPHUS (LOUSE-BORNE)

Etiology and Epidemiology

Epidemic typhus is caused by *R. prowazekii* and is transmitted by the human body louse. Eastern flying squirrels and their lice and fleas maintain *R. prowazekii* in a zoonotic cycle.

- The louse lives in clothing under poor hygienic conditions, particularly in colder climates and classically at times of war or natural disaster.
- Lice feed on pts with epidemic typhus and then defecate the organism on their subsequent host during their next meal. The pt autoinoculates the organism while scratching.
- *Brill-Zinsser disease* is a recrudescence form of epidemic typhus whose occurrence years after acute illness suggests that *R. prowazekii* remains dormant in the host, with reactivation when immunity wanes.

Clinical Manifestations

Epidemic typhus presents abruptly with the onset of high fevers, prostration, severe headache, cough, and severe myalgias. Photophobia with conjunctival injection and eye pain is also common.

- A rash appears on the upper trunk around the fifth day of illness and spreads to involve all body-surface areas except the face, palms, and soles.
- Confusion and coma, skin necrosis, and gangrene of the digits are noted in severe cases.
- Untreated, the disease is fatal in 7–40% of cases. Pts develop renal failure, multiorgan involvement, and prominent neurologic manifestations.

Diagnosis

Epidemic typhus is sometimes misdiagnosed as typhoid fever. The diagnosis can be based on serology, immunohistochemistry, or detection of the organism in a louse found on a pt.

TREATMENT

Epidemic Typhus (Louse-Borne)

Doxycycline (100 mg bid) is given until 3–5 days after the pt has defervesced, although a one-time dose of 200 mg has sometimes proved effective under epidemic conditions.

■ SCRUB TYPHUS

- *Orientia tsutsugamushi*, the agent of scrub typhus, is transmitted by larval mites or chiggers in environments with heavy scrub vegetation.
- Disease occurs during the wet season. It is endemic in eastern and southern Asia, northern Australia, and the Pacific islands.
- The classic case description includes signs rarely seen in indigenous pts: an eschar at the site of chigger feeding, regional lymphadenopathy, and maculopapular rash. Westerners commonly do not present with all three findings. Severe cases include encephalitis and interstitial pneumonia.
- Scrub typhus can be diagnosed by serologic assays (indirect immunofluorescence, indirect immunoperoxidase, and enzyme immunoassays); PCR analysis of eschars and blood is also effective.

TREATMENT**Scrub Typhus**

A 7- to 15-day course of doxycycline (100 mg bid) or chloramphenicol (500 mg qid) or a 3-day course of azithromycin (500 mg qd) is effective.

EHRlichIOSES AND ANAPLASMOSIS

Four distinct *Ehrlichia* species, two *Anaplasma* species, and one *Neoehrlichia* species—all obligately intracellular organisms—are transmitted by ticks to humans and cause infections that can be severe and prevalent.

■ HUMAN MONOCYTOTROPIC EHRlichIOSIS (HME)**Etiology and Epidemiology**

HME is caused by *Ehrlichia chaffeensis* and, in the United States, generally occurs in southeastern, south-central, and mid-Atlantic states from May to July. The incidence can be as high as 414 cases per 100,000 population.

- *E. chaffeensis* is transmitted by the Lone Star tick (*Amblyomma americanum*), and white-tailed deer are the major reservoir.
- The median age of pts is 52 years; 60% of pts are male.
- *E. ewingii* and *E. muris cauclairensis* cause an illness similar to, but less severe than, that due to *E. chaffeensis*.

Clinical Manifestations

Clinical findings are nonspecific and include fever (97%), headache (70%), myalgia (68%), and malaise (77%). Nausea, vomiting, diarrhea, cough, rash, and confusion may be noted.

- The median incubation period is 8 days.
- Disease can be severe: up to 77% of pts are hospitalized and 2% die. Complications include renal failure, a DIC-like syndrome, pneumonia, a septic shock-like syndrome, adult respiratory distress syndrome, cardiac failure, hepatitis, meningoencephalitis, and hemorrhage.
- Leukopenia (66%), thrombocytopenia (86%), and elevated serum aminotransferase levels (89%) are common.

Diagnosis

Because HME can be fatal, empirical antibiotic therapy based on clinical diagnosis is required. PCR testing before initiation of antibiotic therapy or retrospective serodiagnosis to detect increased antibody titers can be performed. Morulae are seen in <10% of peripheral-blood smears.

TREATMENT**Human Monocytotropic Ehrlichiosis**

Doxycycline (100 mg PO/IV bid) or tetracycline (250–500 mg PO q6h) is effective and should be continued for 3–5 days after defervescence.

■ HUMAN GRANULOCYTOTROPIC ANAPLASMOSIS (HGA)**Etiology and Epidemiology**

HGA is caused by *Anaplasma phagocytophilum* and, in the United States, occurs mainly in northeastern and upper midwestern states.

- The geographic distribution is similar to that of Lyme disease and *Babesia microti* infection, given the shared *Ixodes scapularis* tick vector.
- HGA incidence peaks in May through July, but the disease can occur year-round.
- The epidemiology of HGA is similar to that of HME, with males (59%) and older persons (median age, 51 years) more often affected.

Clinical Manifestations

Given high seroprevalence rates in endemic areas, it appears that most people develop subclinical infections.

- After an incubation period of 4–8 days, pts develop fever (75–100%), myalgia (75%), headache (83%), and malaise (97%).
- Severe complications—renal failure, respiratory distress, a toxic shock–like syndrome, pneumonia, and a DIC- or sepsis-like syndrome—occur most often in elderly pts.
- On laboratory examination, pts are found to have leukopenia (60%), thrombocytopenia (79%), and elevated serum aminotransferase levels (91%).

Diagnosis

HGA should be considered in pts with influenza-like illness during May through December and in pts with atypical severe presentations of Lyme disease.

- Peripheral-blood films may reveal morulae in neutrophils in 20–75% of infections.
- PCR testing before antibiotic therapy or retrospective serologic testing demonstrating a ≥ 4 -fold rise in antibody titer can confirm the diagnosis.

TREATMENT**Human Granulocytotropic Anaplasmosis**

Doxycycline (100 mg PO bid) is effective, and most pts defervesce within 24–48 h. Pregnant women and children <8 years old may be treated with rifampin.

Prevention

HME and HGA are prevented by avoidance of ticks in endemic areas, use of protective clothing and tick repellents, careful tick searches after exposures, and prompt removal of attached ticks.

Q FEVER**Microbiology**

Coxiella burnetii—the etiologic agent of Q fever—is a small, pleomorphic coccobacillus that has a gram-negative cell wall and is located intracellularly.

Epidemiology and Pathogenesis

A worldwide disease, Q fever is a zoonosis. Cattle, sheep, and goats are responsible for most cases of human infection; many other animals can serve as vectors of transmission or as reservoirs of disease.

- *C. burnetii* localizes to the uterus and mammary glands of infected female mammals. It is reactivated in pregnancy and is found at high concentrations in the placenta. At parturition, the organism is dispersed as an aerosol, and infection usually follows inhalation.
- Abattoir workers, veterinarians, farmers, and other persons who have contact with infected animals, particularly with newborn animals or infected products of conception, are at risk.
- In the United States, there are 28–54 cases per year; in Australia, there are 30 cases per 1 million population per year.

Clinical Manifestations

The specific presentation of acute Q fever differs geographically (e.g., pneumonia in Nova Scotia and granulomatous hepatitis in Marseille), potentially reflecting differences in routes of infection or infecting strains; chronic Q fever almost always implies endocarditis.

- *Acute Q fever*: After an incubation period of 3–30 days, pts may present with flulike syndromes, prolonged fever, pneumonia, hepatitis, pericarditis, myocarditis, meningoencephalitis, and infection during pregnancy.
 - Signs and symptoms are often nonspecific (e.g., fever, fatigue, headache, chills, sweats, nausea, vomiting, diarrhea, cough, and occasionally rash).
 - Multiple rounded opacities on CXR in pts in endemic areas are highly suggestive of Q fever pneumonia.
 - The WBC count is usually normal, but thrombocytopenia occurs. During recovery, reactive thrombocytosis can develop.
 - Prolonged fatigue, along with a constellation of nonspecific symptoms (e.g., headaches, myalgias, arthralgias), can follow Q fever (post-Q fever fatigue syndrome).
- *Chronic Q fever*: Pts with *C. burnetii* endocarditis typically have prior valvular heart disease, immunosuppression, or chronic renal failure.
 - Fever is absent or low grade; pts may be ill for >1 year before diagnosis.
 - Valvular vegetations are seen in 21–50% of cases with transthoracic echocardiography but in only 12% with transthoracic echocardiography. The vegetations differ from those in bacterial endocarditis of other etiologies and manifest as endothelium-covered nodules on the valve.
 - The disease should be suspected in all pts with culture-negative endocarditis.
 - Although *C. burnetii* can be isolated by a shell-vial technique, most laboratories are not permitted to attempt isolation because of the organism's highly contagious nature. PCR testing of tissue or biopsy specimens can be used, but serology is the most common diagnostic tool; indirect immunofluorescence is the method of choice.

TREATMENT

Q Fever

- Acute Q fever is treated with doxycycline (100 mg bid for 14 days).
 - Quinolones are also efficacious.
 - If Q fever is diagnosed during pregnancy, trimethoprim-sulfamethoxazole should be administered up to term along with folic acid supplementation (particularly in the first trimester).

- The currently recommended treatment for chronic Q fever is doxycycline (100 mg bid) and hydroxychloroquine (200 mg tid; plasma concentrations maintained at 0.8–1.2 $\mu\text{g}/\text{mL}$) for 18 months.
 - Hydroxychloroquine renders doxycycline bactericidal against *C. burnetii*.
 - The MIC of doxycycline for the pt's isolate should be determined and serum levels monitored, with a goal of a serum level to doxycycline MIC ratio of ≥ 1 .
 - Pts should be advised about photosensitivity and retinal toxicity risks with treatment.
 - Pts who cannot receive doxycycline–hydroxychloroquine should be treated with at least two agents active against *C. burnetii*. The combination of rifampin (300 mg once daily) plus doxycycline (100 mg bid) or ciprofloxacin (750 mg bid) has been used with success.
 - There is no consensus about the duration of this alternative regimen, but it is reasonable to discontinue it when levels of IgG antibody to phase I antigen have decreased by fourfold at 1 year, IgM antibody to phase II antigen has disappeared, and the pt is clinically stable.

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Mycoplasma pneumoniae,
Legionella Species, and
Chlamydia pneumoniae

Mycoplasma pneumoniae, *Legionella* species, and *Chlamydia pneumoniae* are often grouped together as the most important causes of “atypical” community-acquired pneumonia. (For a discussion of urogenital mycoplasmas, see [Chap. 86](#).)

MYCOPLASMA PNEUMONIAE

With a size of only 150–350 nm, mycoplasmas are the smallest free-living organisms. Genome sequence data from many different *Mycoplasma* species have helped define the minimal set of genes necessary for cellular life. Lacking a cell wall and bounded only by a plasma membrane, mycoplasmas colonize mucosal surfaces of the respiratory and urogenital tracts.

■ EPIDEMIOLOGY

M. pneumoniae occurs worldwide with no seasonal pattern. Infection causes upper respiratory tract disease ~20 times more frequently than pneumonia.

- Infection is acquired by inhalation of aerosols, with an incubation period of 2–4 weeks.
- *M. pneumoniae* accounts for ~23% of cases of community-acquired pneumonia in adults.

■ CLINICAL MANIFESTATIONS

The clinical presentation does not help distinguish *M. pneumoniae* pneumonia from pneumonia of any other bacterial etiology.

- Acute *M. pneumoniae* infection manifests as a nonspecific upper-respiratory syndrome with pharyngitis, tracheobronchitis, and/or wheezing.

- Pneumonia develops in 3–13% of infected pts. The most common presenting symptom is a nonproductive cough. Headache, malaise, chills, and fever are common.
- On physical examination, ~80% of pts have wheezes or rales.
- Symptoms usually resolve in 2–3 weeks, and appropriate antimicrobial therapy significantly shortens the duration of clinical illness.
- Infection uncommonly results in critical illness and rarely causes death.
- Extrapulmonary manifestations of *M. pneumoniae* infection are relatively uncommon but include skin eruptions (e.g., erythema multiforme major, rashes), neurologic manifestations (e.g., encephalitis, Guillain-Barré syndrome, acute demyelinating encephalomyelitis), septic arthritis (particularly in pts with hypogammaglobulinemia), and hematologic manifestations (e.g., hemolytic anemia, coagulopathies).

■ DIAGNOSIS

Clinical findings, nonmicrobiologic laboratory tests, and CXR are not useful in distinguishing *M. pneumoniae* pneumonia from pneumonia of other etiologies.

- Acute *M. pneumoniae* infection can be diagnosed by PCR analysis of respiratory tract secretions, which is 65–90% sensitive and 90–100% specific.
- *M. pneumoniae* culture (which requires special medium) is not recommended for routine diagnosis because its sensitivity is ≤60% and growth of the organism can take weeks.
- Serologic testing for IgM and IgG antibodies to *M. pneumoniae* requires acute- and convalescent-phase samples and is therefore less useful for diagnosis of active infections. Moreover, IgM antibodies to *M. pneumoniae* can persist for up to 1 year after acute infection.
- Measurement of cold agglutinin titers is no longer recommended for the diagnosis of *M. pneumoniae* infection because the findings are nonspecific.

TREATMENT

M. pneumoniae Infections

- Antibiotic options include macrolides (azithromycin, 500 mg PO for 1 day followed by 250 mg for 4 days), tetracyclines (doxycycline, 100 mg PO bid for 10–14 days), and respiratory fluoroquinolones (levofloxacin, 500–750 mg PO qd for 10–14 days).
- Ciprofloxacin and ofloxacin are *not* recommended because of their high MICs against *M. pneumoniae*.

LEGIONELLA SPECIES

■ MICROBIOLOGY

Legionellaceae are intracellular aerobic gram-negative bacilli that grow on buffered charcoal yeast extract (BCYE) agar. *L. pneumophila* causes 80–90% of cases of human *Legionella* disease and includes 16 serogroups; serogroups 1, 4, and 6 are most common.

■ EPIDEMIOLOGY

- *Legionella* is found in fresh water and human-constructed water sources. Outbreaks have been traced to drinking water systems and rarely to cooling towers.

- The organisms are transmitted to individuals primarily via aspiration, but can also be transmitted by aerosolization and direct instillation into the lungs during respiratory tract manipulations.
- *Legionella* is an underestimated cause of community-acquired pneumonia, with only ~3% of such cases actually diagnosed. It causes 10–50% of cases of nosocomial pneumonia if the hospital's water system is colonized with the organism.
- Pts who have chronic lung disease, who smoke, and/or who are elderly, immunosuppressed, or recently discharged from the hospital are at particularly high risk for disease.

■ CLINICAL MANIFESTATIONS

Legionellosis manifests as either an acute, febrile, self-limited illness (Pontiac fever) or pneumonia (Legionnaires' disease).

- Pontiac fever is a flulike illness with a 24- to 48-h incubation period. Malaise, fatigue, and myalgias occur in 97% of cases. Fever, chills, and headaches are also very common, but pneumonia does not develop. The disease is self-limited and does not require antimicrobial treatment. Recovery takes place in a few days.
- Legionnaires' disease is more severe than other atypical pneumonias and is more likely to result in ICU admission.
 - After a usual incubation period of 2–10 days, nonspecific symptoms (e.g., fever, malaise, fatigue, headache, anorexia) develop and are followed by a cough that is usually mild and only slightly productive. Chest pain and GI difficulties can be prominent.
 - Radiologic findings are nonspecific, but pleural effusions are present in 28–63% of pts on hospital admission.
 - Legionnaires' disease is not readily distinguishable from pneumonia of other etiologies on the basis of clinical manifestations, but diarrhea, confusion, temperatures $>39^{\circ}\text{C}$ ($>102.2^{\circ}\text{F}$), hyponatremia, increased aminotransferase levels, hematuria, hypophosphatemia, and elevated CPK levels are documented more frequently than in other pneumonias.
 - Extrapulmonary infection results from hematogenous dissemination and most commonly affects the heart (e.g., myocarditis, pericarditis).

■ DIAGNOSIS

The use of *Legionella* testing—especially the *Legionella* urinary antigen test—is recommended for all pts with community-acquired pneumonia.

- Sputum or bronchoscopy specimens can be subjected to direct fluorescent antibody (DFA) staining and culture.
 - DFA testing is rapid and specific but is less sensitive than culture.
 - Cultures on BCYE medium (with antibiotics to suppress competing flora) require 3–5 days to become positive; up to 2 weeks may be needed for non-*pneumophila* species.
- Serologic confirmation requires comparison of acute- and convalescent-phase samples. Detection of the necessary fourfold rise in titers often requires 12 weeks, but a single titer of 1:256 is presumptive evidence for Legionnaires' disease.
- Urinary antigen testing is rapid, inexpensive, easy to perform, reasonably sensitive (70–90%), and highly specific (95–100%). It is useful only for *L. pneumophila* serogroup 1, which causes 80% of disease cases.
 - Urinary antigen is detectable shortly after disease onset and for up to 10 months, even during antibiotic treatment.

TREATMENT*Legionella* Infections

- Newer macrolides (e.g., azithromycin at 500 mg/d IV or PO, with doubling of the first dose considered; or clarithromycin at 500 mg bid IV or PO) or fluoroquinolones (e.g., levofloxacin at 750 mg/d IV or 500 mg/d PO or moxifloxacin at 400 mg/d PO) are most effective.
 - Rifampin (300–600 mg bid) combined with either class of drug is recommended in severe cases.
 - Tetracyclines (doxycycline at 100 mg bid IV or PO) are alternatives.
- Immunocompetent hosts should receive 10–14 days of therapy, but immunocompromised hosts and pts with advanced disease should receive a 3-week course.
 - A 5- to 10-day course of azithromycin is adequate because of this drug's long half-life.
 - A clinical response usually occurs within 3–5 days after the initiation of parenteral therapy, at which point oral therapy can be substituted.

■ PROGNOSIS

Mortality rates approach 80% among immunocompromised pts who do not receive timely therapy. Among immunocompetent hosts, mortality can approach 31% without treatment but ranges from 3% to 11% with appropriate and timely therapy. Fatigue, weakness, and neurologic symptoms can persist for >1 year.

CHLAMYDIA PNEUMONIAE**■ EPIDEMIOLOGY**

C. pneumoniae is a common cause of human respiratory diseases, primarily in young adults.

- Seroprevalence rates of 40–70% demonstrate that *C. pneumoniae* is widespread worldwide. Seropositivity is first detected at school age and then increases by ~10% per decade.
- The role of *C. pneumoniae* in atherosclerotic disease has long been discussed, but large-scale treatment studies have cast doubts on the etiologic role of this organism in this disease.

■ CLINICAL MANIFESTATIONS

The clinical spectrum of *C. pneumoniae* infection includes acute pharyngitis, sinusitis, bronchitis, and pneumonia.

- Pneumonia due to *C. pneumoniae* resembles that due to *M. pneumoniae*. Pts have antecedent upper-respiratory symptoms, fever, nonproductive cough, minimal findings on auscultation, small segmental infiltrates on CXR, and no leukocytosis.
 - Primary infection is more severe than reinfection.
 - Elderly pts can have severe disease.

■ DIAGNOSIS

Serology is the most clinically useful means for diagnosing *C. pneumoniae* infection.

- The diagnosis of acute *C. pneumoniae* infection requires demonstration of a fourfold rise in titer between acute- and convalescent-phase serum samples.
- Culture of the organism is difficult and is not routinely attempted. PCR assays for *C. pneumoniae* are currently available only for research purposes.

TREATMENT***C. pneumoniae* Infections**

- Erythromycin or tetracycline (2 g/d for 10–14 days) is recommended.
- Other macrolides (e.g., azithromycin) or quinolones (e.g., levofloxacin) are alternative agents.

101***Chlamydia trachomatis* and
*Chlamydia psittaci*****■ MICROBIOLOGY**

- Chlamydiae are obligate intracellular bacteria, possess both DNA and RNA (a characteristic that distinguishes them from viruses), and have a cell wall similar to that of gram-negative bacteria.
- These organisms have a complex reproductive cycle and exist in two forms.
 - The *elementary body* (the infective form) is adapted for extracellular survival, while the *reticulate body* is adapted for intracellular survival and multiplication.
 - Within 18–24 h after infection of the cell, reticulate bodies have replicated and begun to condense into elementary bodies that are released to infect other cells or people.
- Three chlamydial species infect humans: *Chlamydia trachomatis*, *C. psittaci*, and *C. pneumoniae*.
 - CF tests and enzyme immunoassays that detect lipopolysaccharide identify chlamydiae only to the genus level.
 - The microimmunofluorescence (MIF) test can differentiate among the three species.
 - For a discussion of *C. pneumoniae*, see [Chap. 100](#).

C. TRACHOMATIS INFECTIONS**■ GENITAL INFECTIONS, INCLUDING
LYMPHOGRANULOMA VENEREUM**

See [Chap. 86](#).

■ TRACHOMA AND ADULT INCLUSION CONJUNCTIVITIS (AIC)**Etiology**

- Trachoma is a chronic conjunctivitis caused by *C. trachomatis* serovars A, B, Ba, and C. Transmission occurs through contact with ocular discharge from infected pts, which is sometimes transferred by flies.
- AIC is an acute eye infection occurring in adults exposed to infected genital secretions and in their newborns. This infection is caused by sexually transmitted *C. trachomatis* strains, usually serovars D–K.

Epidemiology

Trachoma is a leading cause of preventable infectious blindness, with ~6 million pts having been affected. In the hyperendemic regions of northern and sub-Saharan Africa, the Middle East, and parts of Asia, the prevalence of trachoma is ~100% by the third year of life. Reinfection and persistent infection are common.

Clinical Manifestations

Both trachoma and AIC present clinically as conjunctivitis characterized by small lymphoid follicles in the conjunctiva; trachoma usually starts insidiously before 2 years of age.

- With progression of trachoma, there is inflammatory leukocytic infiltration and superficial vascularization (pannus formation) of the cornea.
 - Scarring eventually distorts the eyelids, turning lashes inward and abrading the eyeball (trichiasis and entropion).
 - The corneal epithelium eventually ulcerates, with subsequent scarring and blindness.
 - Destruction of goblet cells, lacrimal ducts, and glands causes dry-eye syndrome (xerosis), with resultant corneal opacity and secondary bacterial corneal ulcers.
- AIC is an acute unilateral follicular conjunctivitis with preauricular lymphadenopathy and presents similarly to acute conjunctivitis due to adenovirus or HSV.
 - Corneal inflammation is evidenced by discrete opacities, punctate epithelial erosions, and superficial corneal vascularization.
 - Left untreated, the disease may persist for 6 weeks to 2 years.

Diagnosis

Clinical diagnosis of trachoma is based on the presence of two of the following signs: lymphoid follicles on the upper tarsal conjunctiva, typical conjunctival scarring, vascular pannus, or limbal follicles.

- Intracytoplasmic chlamydial inclusions are found in 10–60% of Giemsa-stained conjunctival smears from children with severe inflammation.
- Chlamydial nucleic acid amplification tests are more sensitive in detecting infection.

TREATMENT

Trachoma/AIC

- AIC responds to azithromycin (a single 1-g oral dose) or doxycycline (100 mg PO bid for 7 days). Treatment of sexual partners is needed to prevent ocular reinfection and chlamydial genital disease.

C. PSITTACI INFECTIONS

Etiology and Epidemiology

Most avian species can harbor *C. psittaci*, but psittacine birds (e.g., parrots, parakeets) are most often infected. Human infections are uncommon and occur only as a zoonosis.

- Exposure is greatest in poultry workers and in owners of pet birds.
- Present in nasal secretions, excreta, tissues, and feathers of infected birds, *C. psittaci* is transmitted to humans by direct contact with infected birds or by inhalation of aerosols. Transmission from person to person has never been documented.
- As a result of quarantine of imported birds and improved veterinary-hygienic measures, outbreaks and sporadic cases of psittacosis are now rare, with fewer than 50 confirmed cases reported in the United States each year.

Clinical Manifestations

Psittacosis in humans can range in severity from asymptomatic or mild infections to acute primary atypical pneumonia (which can be fatal in 10% of untreated cases) to severe chronic pneumonia.

- After an incubation period of >5–19 days, pts present with fever, chills, muscular aches and pains, severe headaches, hepatomegaly and/or splenomegaly, and GI symptoms.
- Cardiac complications may include endocarditis and myocarditis.

Diagnosis

This diagnosis is confirmed by serologic studies.

- The gold standard is the MIF test.
- Any antibody titer >1:16 or a fourfold rise between paired acute- and convalescent-phase serum samples, in combination with a clinically compatible syndrome, can be used to diagnose psittacosis.

TREATMENT

C. psittaci Infections

- Tetracycline (250 mg PO qid for 3 weeks) is the antibiotic of choice.
- Erythromycin (500 mg PO qid) is an alternative agent.

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Infections with Herpes Simplex Virus, Varicella-Zoster Virus, Cytomegalovirus, Epstein-Barr Virus, and Human Herpesvirus Types 6, 7, and 8



HERPES SIMPLEX VIRUSES

■ MICROBIOLOGY AND PATHOGENESIS

The herpes simplex viruses HSV-1 and HSV-2 are linear, double-stranded DNA viruses that share ~50% sequence homology. Exposure to HSV at mucosal surfaces or abraded skin sites permits viral entry and replication in cells of the epidermis and dermis prior to infection of neuronal cells and development of a latent infection in ganglia.

- Reactivation occurs when normal viral gene expression resumes, with reappearance of the virus on mucosal surfaces.
- Both antibody-mediated and cell-mediated immunity (including type-specific immunity) are clinically important.

■ EPIDEMIOLOGY

HSV-1 is acquired more frequently and at an earlier age than HSV-2. More than 90% of adults have antibodies to HSV-1 by the fifth decade of life. Antibodies

to HSV-2 usually are not detected until adolescence and correlate with sexual activity. The seroprevalence of HSV-2 is higher in the developing than in the developed world; up to 60% of pregnant women in sub-Saharan Africa are seropositive.

- HSV is transmitted by contact with active lesions or with virus shed from mucocutaneous surfaces by asymptomatic persons.
- HSV reactivation is very common: HSV DNA can be detected on 20–30% of days by PCR, with most genital reactivation episodes lasting <6 h.
- The large reservoir of unidentified carriers and the frequent asymptomatic reactivation of HSV-2 have fostered the continued spread of HSV throughout the world.
- HSV-2 infection is associated with a two- to fourfold increase in HIV-1 acquisition; in fact, 33–50% of HIV-1 infections may be attributable to HSV-2 in men who have sex with men and in populations of sub-Saharan Africa.

■ CLINICAL MANIFESTATIONS

Both viral subtypes can cause indistinguishable genital and oral–facial infections. Overall, genital HSV-2 is twice as likely to reactivate as genital HSV-1, and HSV-2 infection recurs 8–10 times more often. In contrast, oral–labial HSV-1 infection recurs more frequently than oral–labial HSV-2 infection. The incubation period for primary infection with either virus is 1–26 days (median, 6–8 days).

Oral–Facial Infections

Primary HSV-1 infection results in gingivostomatitis, pharyngitis, and up to 2 weeks of fever, malaise, myalgia, inability to eat, and cervical adenopathy, with lesions on the palate, gingiva, tongue, lip, face, posterior pharynx, and/or tonsillar pillars and occasional exudative pharyngitis.

- Reactivation of HSV from the trigeminal ganglia is associated with asymptomatic viral excretion in the saliva, intraoral mucosal ulcerations, or ulcers on the vermilion border of the lip or external facial skin.
 - Approximately 50–70% of pts undergoing trigeminal nerve-root decompression and 10–15% of pts undergoing dental extraction develop oral–labial herpes a median of 3 days after the procedure.
 - Reactivation of HSV-1 or VZV in the mandibular portion of the facial nerve causes flaccid paralysis (Bell’s palsy).
- Immunosuppressed pts can have a severe infection that extends into the mucosa and skin, causing friability, necrosis, bleeding, pain, and inability to eat or drink.
- Pts with atopic dermatitis may also develop severe oral–facial HSV infection (*eczema herpeticum*), with extensive skin lesions and occasional visceral dissemination.
- HSV infection is the precipitating event in ~75% of cases of *erythema multiforme*.

Genital Infections (See Chap. 86)

First-episode primary genital herpes is characterized by fever, headache, malaise, and myalgias. Pain, itching, dysuria, vaginal and urethral discharge, and tender inguinal lymphadenopathy are the predominant local symptoms.

- Pts with prior HSV-1 infection have milder cases.
- Reactivation infections are often subclinical or can cause genital lesions or urethritis with dysuria.
- Even without a history of rectal intercourse, perianal lesions can occur as a result of latency established in the sacral dermatome from prior genital tract infection.

Whitlow

In HSV infection of the finger, pts experience an abrupt onset of edema, erythema, pain, and vesicular or pustular lesions of the fingertips that are often confused with the lesions of pyogenic bacterial infection. Fever, lymphadenitis, and epitrochlear and axillary lymphadenopathy are common.

Herpes Gladiatorum

HSV infection caused by trauma to the skin during wrestling can occur anywhere on the body but commonly affects the thorax, ears, face, and hands.

Eye Infections

HSV is the most frequent cause of corneal blindness in the United States.

- HSV keratitis presents as acute onset of pain, blurred vision, chemosis, conjunctivitis, and dendritic corneal lesions. Topical glucocorticoids may exacerbate disease. Recurrences are common.
- Other manifestations include chorioretinitis and acute necrotizing retinitis.

Central and Peripheral Nervous System Infections

In the United States, HSV causes 10–20% of all cases of sporadic viral encephalitis, and 95% of these cases are due to HSV-1 (either primary or reactivated infection). The estimated annual incidence is 2.3 cases per 1 million persons.

- Pts present with an acute onset of fever and focal neurologic symptoms and signs, especially in the temporal lobe. In severe cases, RBCs can be found in the CSF as a result of hemorrhagic necrosis.
- Given the potential severity of infection, antiviral treatment should be started empirically until the diagnosis is confirmed or an alternative diagnosis is made.
- HSV meningitis, which is usually seen in association with primary genital HSV infection, is an acute self-limited disease manifested by headache, fever, and mild photophobia and lasting 2–7 days.
 - Of cases of aseptic meningitis, 3–15% are due to HSV.
 - HSV is the most common cause of recurrent lymphocytic meningitis (Mollaret's meningitis).
- Autonomic dysfunction caused by either HSV or VZV most commonly affects the sacral region, resulting in numbness, tingling of the buttocks or perineal areas, urinary retention, constipation, and impotence.
 - Symptoms take days or weeks to resolve.
 - In rare instances, transverse myelitis or Guillain-Barré syndrome follows HSV infection.

Visceral Infections

HSV infection of visceral organs usually results from viremia; multiple-organ involvement is common, but occasionally only the esophagus, lung, or liver is affected.

- In HSV esophagitis, pts present with odynophagia, dysphagia, substernal pain, weight loss, and multiple oval ulcerations on an erythematous base. Detection of HSV is necessary to distinguish this entity from esophagitis of other etiologies (e.g., *Candida* esophagitis).
- HSV pneumonitis is rare except among severely immunocompromised pts and results in focal necrotizing pneumonitis with a mortality rate of >80%.
- Hepatic HSV infection occurs primarily in immunocompromised pts and is associated with fever, abrupt elevations of bilirubin and serum aminotransferase levels, and leukopenia (<4000 WBCs/ μ L).

Neonatal Infections

The frequency of visceral and/or CNS infection is highest among HSV-infected infants <6 weeks of age; the mortality rate without therapy is 65%.

- Infection is usually acquired perinatally from contact with infected genital secretions during delivery.
- Approximately 50–70% of cases are due to HSV-2. The risk is elevated 10-fold for infants born to a mother who has recently acquired HSV.

■ DIAGNOSIS

PCR is the recommended test for diagnosing HSV. Microscopic evaluation, viral culture (if antiviral sensitivity testing is needed), and serology are also clinically useful for diagnosing HSV infection, but these tests have lower sensitivities.

- Regardless of the detection method, the sensitivity is greater for vesicular rather than ulcerative mucosal lesions, in primary rather than recurrent disease, and in immunocompromised rather than immunocompetent pts.
- A Tzanck smear (Giemsa-stained scrapings from the base of lesions) to detect giant cells or intranuclear inclusions characteristic of both HSV and VZV infections has a low level of sensitivity; its use requires clinicians skilled in this technique.
- Serologic tests can be used to demonstrate prior exposure to HSV; no reliable IgM detection method for defining acute HSV infection is available.

TREATMENT

Infections with Herpes Simplex Viruses

- **Table 102-1** details antiviral chemotherapy for HSV infection.
 - All antiviral agents licensed for use against HSV inhibit the viral DNA polymerase.
 - Acyclovir can crystallize in the renal parenchyma, causing transient renal insufficiency; this drug should be given over the course of 1 h to a well-hydrated pt.
 - Acyclovir-resistant strains of HSV are rare but have been identified, primarily in immunocompromised pts. In general, these isolates are also resistant to valacyclovir and famciclovir, which have similar mechanisms of action.
 - Antiviral drugs neither eradicate latent infection nor affect recurrence after treatment is discontinued.

■ PREVENTION

The use of barrier forms of contraception, especially condoms, decreases the likelihood of HSV transmission, particularly during asymptomatic viral excretion. Chronic daily therapy with valacyclovir can also be partially effective in reducing acquisition of HSV-2, particularly by susceptible women.

VARICELLA-ZOSTER VIRUS

■ MICROBIOLOGY AND PATHOGENESIS

VZV—a double-stranded DNA virus in the family Herpesviridae—has a pathogenic cycle similar to that of HSV. Primary infection is transmitted by the respiratory route. The virus replicates and causes viremia, which is reflected by the

TABLE 102-1 Antiviral Chemotherapy for Herpes Simplex Virus (HSV) Infection**I. Mucocutaneous HSV infections****A. Infections in immunosuppressed pts**

1. *Acute symptomatic first or recurrent episodes:* IV acyclovir (5 mg/kg q8h) or oral acyclovir (400 mg qid), famciclovir (500 mg bid or tid), or valacyclovir (500 mg bid) is effective. Treatment duration may vary from 7 to 14 days. IV therapy may be given for 2–7 days until clinical improvement and followed by oral therapy.
2. *Suppression of reactivation disease (genital or oral-labial):* IV acyclovir (5 mg/kg q8h) or oral valacyclovir (500 mg bid) or acyclovir (400–800 mg 3–5 times per day) prevents recurrences during the 30-day period immediately after transplantation. Longer-term HSV suppression is often used for persons with continued immunosuppression. In bone marrow and renal transplant recipients, oral valacyclovir (2 g/d) is also effective in reducing cytomegalovirus infection. Oral valacyclovir at a dose of 4 g/d has been associated with thrombotic thrombocytopenic purpura after extended use in HIV-positive persons. In HIV-infected persons, oral acyclovir (400–800 mg bid), valacyclovir (500 mg bid), or famciclovir (500 mg bid) is effective in reducing clinical and subclinical reactivations of HSV-1 and HSV-2.

B. Infections in immunocompetent pts**1. Genital herpes**

- a. *First episodes:* Oral acyclovir (200 mg 5 times per day or 400 mg tid), valacyclovir (1 g bid), or famciclovir (250 mg bid) for 7–14 days is effective. IV acyclovir (5 mg/kg q8h for 5 days) is given for severe disease or neurologic complications such as aseptic meningitis.
- b. *Symptomatic recurrent genital herpes:* Short-course (1- to 3-day) regimens are preferred because of low cost, likelihood of adherence, and convenience. Oral acyclovir (800 mg tid for 2 days), valacyclovir (500 mg bid for 3 days), or famciclovir (750 or 1000 mg bid for 1 day, a 1500-mg single dose, or 500 mg stat followed by 250 mg q12h for 2 days) effectively shortens lesion duration. Other options include oral acyclovir (200 mg 5 times per day), valacyclovir (500 mg bid), and famciclovir (125 mg bid for 5 days).
- c. *Suppression of recurrent genital herpes:* Oral acyclovir (400–800 mg bid) or valacyclovir (500 mg daily) is given. Pts with >9 episodes per year should take oral valacyclovir (1 g daily or 500 mg bid) or famciclovir (250 mg bid or 500 mg bid).

2. Oral-labial HSV infections

- a. *First episode:* Oral acyclovir is given (200 mg 5 times per day or 400 mg tid); an oral acyclovir suspension can be used (600 mg/m² qid). Oral famciclovir (250 mg bid) or valacyclovir (1 g bid) has been used clinically. The duration of therapy is 5–10 days.
- b. *Recurrent episodes:* If initiated at the onset of the prodrome, single-dose or 1-day therapy effectively reduces pain and speeds healing. Regimens include oral famciclovir (a 1500-mg single dose or 750 mg bid for 1 day) or valacyclovir (a 2-g single dose or 2 g bid for 1 day). Self-initiated therapy with 6-times-daily topical penciclovir cream effectively speeds healing of oral-labial HSV infection. Topical acyclovir cream has also been shown to speed healing.

(Continued)

TABLE 102-1 Antiviral Chemotherapy for Herpes Simplex Virus (HSV) Infection (Continued)

- c. *Suppression of reactivation of oral-labial HSV:* If started before exposure and continued for the duration of exposure (usually 5–10 days), oral acyclovir (400 mg bid) prevents reactivation of recurrent oral-labial HSV infection associated with severe sun exposure.
3. *Surgical prophylaxis of oral or genital HSV infection:* Several surgical procedures, such as laser skin resurfacing, trigeminal nerve-root decompression, and lumbar disk surgery, have been associated with HSV reactivation. IV acyclovir (3–5 mg/kg q8h) or oral acyclovir (800 mg bid), valacyclovir (500 mg bid), or famciclovir (250 mg bid) effectively reduces reactivation. Therapy should be initiated 48 h before surgery and continued for 3–7 days.
4. *Herpetic whitlow:* Oral acyclovir (200 mg) is given 5 times daily (alternative: 400 mg tid) for 7–10 days.
5. *HSV proctitis:* Oral acyclovir (400 mg 5 times per day) is useful in shortening the course of infection. In immunosuppressed pts or in pts with severe infection, IV acyclovir (5 mg/kg q8h) may be useful.
6. *Herpetic eye infections:* In acute keratitis, topical trifluorothymidine, vidarabine, idoxuridine, acyclovir, penciclovir, and interferon are all beneficial. Debridement may be required. Topical steroids may worsen disease.

II. Central nervous system HSV infections

- A. *HSV encephalitis:* IV acyclovir (10 mg/kg q8h; 30 mg/kg per day) is given for 10 days or until HSV DNA is no longer detected in cerebrospinal fluid.
- B. *HSV aseptic meningitis:* No studies of systemic antiviral chemotherapy exist. If therapy is to be given, IV acyclovir (15–30 mg/kg per day) should be used.
- C. *Autonomic radiculopathy:* No studies are available. Most authorities recommend a trial of IV acyclovir.

III. Neonatal HSV infections: IV acyclovir (60 mg/kg per day, divided into 3 doses) is given. The recommended duration of IV treatment is 21 days. Monitoring for relapse should be undertaken. Continued suppression with oral acyclovir suspension should be given for 3–4 months.

IV. Visceral HSV infections

- A. *HSV esophagitis:* IV acyclovir (15 mg/kg per day) is given. In some pts with milder forms of immunosuppression, oral therapy with valacyclovir or famciclovir is effective.
- B. *HSV pneumonitis:* No controlled studies exist. IV acyclovir (15 mg/kg per day) should be considered.

V. Disseminated HSV infections: No controlled studies exist. IV acyclovir (5 mg/kg q8h) should be tried. Adjustments for renal insufficiency may be needed. No definite evidence indicates that therapy will decrease the risk of death.

VI. Erythema multiforme associated with HSV: Anecdotal observations suggest that oral acyclovir (400 mg bid or tid) or valacyclovir (500 mg bid) will suppress erythema multiforme.

(Continued)

TABLE 102-1 Antiviral Chemotherapy for Herpes Simplex Virus (HSV) Infection (Continued)

- VII. Infections due to acyclovir-resistant HSV:** IV foscarnet (40 mg/kg IV q8h) should be given until lesions heal. The optimal duration of therapy and the usefulness of its continuation to suppress lesions are unclear. Some pts may benefit from cutaneous application of trifluorothymidine or 1% cidofovir gel, both of which must be compounded at a pharmacy. These preparations should be applied once daily for 5–7 days. Topical imiquimod can be considered. The helicase primase inhibitor pritelivir is being studied for treatment of acyclovir-resistant HSV infection. IV cidofovir (5 mg/kg weekly) may be considered.
- VIII. Acyclovir and pregnancy:** No adverse effects to the fetus or newborn have been attributable to acyclovir. Acyclovir can be used in all stages of pregnancy and among women who are breastfeeding (the drug can be found in breast milk). Suppressing acyclovir treatment in late pregnancy reduces the frequency of cesarean delivery among women with recurrent genital herpes. Such treatment may not protect against transmission to neonates.

diffuse and scattered skin lesions in varicella; it then establishes latency in the dorsal root ganglia and can reactivate through unknown mechanisms at a later time.

■ EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

VZV causes two distinct entities: primary infection (varicella or chickenpox) and reactivation infection (herpes zoster or shingles). Humans are the only known reservoir for VZV.

Chickenpox

Pts present with fever, malaise, and rash characterized by maculopapules, vesicles, and scabs in various stages of evolution. The skin lesions are small, with an erythematous base of 5–10 mm, and appear in successive crops over 2–4 days. Severity varies from person to person, but older pts tend to have more severe disease.

- In immunocompetent hosts, the disease is benign and lasts 3–5 days. In contrast, immunocompromised pts have numerous slower-healing lesions (often with a hemorrhagic base) and are more likely to develop visceral complications that, if not treated, are fatal in 15% of cases.
- The incubation period ranges from 10 to 21 days but is usually 14–17 days. Pts are infectious for 48 h before onset of rash and remain infectious until all vesicles have crusted.
- The virus is highly contagious, with an attack rate of 90% among susceptible persons. Historically, children 5–9 years old accounted for half of all cases; vaccination has dramatically changed the epidemiology of infection and has caused a significant decrease in the annualized incidence of chickenpox.
- Complications of varicella include bacterial superinfection of the skin, CNS involvement, pneumonia, myocarditis, and hepatic involvement.
 - Bacterial superinfection is usually caused by *Streptococcus pyogenes* or *Staphylococcus aureus*.
 - CNS involvement, usually manifesting as acute cerebellar ataxia and meningeal irritation ~21 days after the onset of rash, runs a benign course. Aseptic meningitis, encephalitis, transverse myelitis, Guillain-Barré syndrome, or Reye's syndrome (which mandates the avoidance of aspirin administration to children) can occur. There is no specific therapy other than supportive care.

- VZV pneumonia is the most serious complication and develops more frequently among adults (occurring in up to 20% of cases) than among children. The onset comes 3–5 days into illness, with tachypnea, cough, dyspnea, fever, cyanosis, pleuritic chest pain, and hemoptysis. CXR shows nodular infiltrates and interstitial pneumonitis. Resolution of pneumonitis parallels improvement of the skin rash.

Herpes Zoster (Shingles)

Herpes zoster represents a reactivation of VZV from dorsal root ganglia and usually manifests as a unilateral vesicular eruption within a dermatome, often associated with severe pain.

- Dermatomal pain may precede lesions by 48–72 h, and dermatomes T3 to L3 are most frequently involved.
- The usual duration of disease is 7–10 days, but it may take as long as 2–4 weeks for the skin to return to normal.
- With ≥ 1.2 million cases each year in the United States, the incidence is highest among pts ≥ 50 years of age.
- Pts with herpes zoster can transmit infection to seronegative individuals, with consequent chickenpox.
- Complications include zoster ophthalmicus (which can lead to blindness), Ramsay Hunt syndrome (characterized by pain and vesicles in the external auditory canal, loss of taste in the anterior two-thirds of the tongue, and ipsilateral facial palsy), and postherpetic neuralgia (pain persisting for months after resolution of cutaneous disease).
- Immunocompromised pts—particularly those with Hodgkin’s disease and non-Hodgkin’s lymphoma—are at greatest risk for severe zoster and progressive disease. Cutaneous dissemination occurs in 40% of these pts and increases the risk for other complications (pneumonitis, meningoencephalitis, hepatitis).

■ DIAGNOSIS

Definitive diagnosis requires isolation of VZV in culture, detection of VZV by molecular means (PCR, immunofluorescent staining of cells from the lesion base), or serology (seroconversion or a ≥ 4 -fold rise in antibody titer between convalescent- and acute-phase serum specimens).

TREATMENT

Varicella-Zoster Virus Infections

- *Chickenpox*: Antiviral therapy can be helpful if started within 24 h of symptom onset.
 - For children < 12 years of age, acyclovir (20 mg/kg PO q6h) is recommended.
 - For adolescents and adults, acyclovir (800 mg PO five times daily), valacyclovir (1 g PO tid), or famciclovir (250 mg PO tid) for 5–7 days is recommended.
 - Good hygiene, meticulous skin care, and antipruritic drugs are important to relieve symptoms and prevent bacterial superinfection of skin lesions.
- *Zoster*: Lesions heal more quickly with antiviral treatment.
 - Famciclovir (500 mg PO tid for 7 days) or valacyclovir (1 g PO tid for 5–7 days) is preferred over acyclovir (800 mg PO five times daily for 7–10 days), given superior pharmacokinetics and pharmacodynamics.

- *VZV infection in severely immunocompromised pts*: Severely immunocompromised pts should receive parenteral acyclovir, at least at the outset (10 mg/kg IV q8h for 7 days), for chickenpox and herpes zoster to reduce the risk of visceral complications, although this regimen does not speed the healing or relieve the pain of skin lesions.
 - Low-risk immunocompromised pts can be treated with oral valacyclovir or famciclovir.
 - If feasible, immunosuppression should be decreased during concomitant acyclovir administration.
 - *Zoster ophthalmicus*: Antiviral treatment, analgesics for severe pain, and immediate consultation with an ophthalmologist are required.
 - *Postherpetic neuralgia*: Gabapentin, pregabalin, amitriptyline, lidocaine patches, and fluphenazine may relieve pain and can be given along with routine analgesic agents. Prednisone (given along with antiviral therapy at 60 mg/d for the first week of zoster and then at a dose tapered by 50% weekly over the next 2 weeks) can accelerate quality-of-life improvements, including a return to usual activity; prednisone treatment is indicated only for healthy elderly persons with moderate or severe pain at presentation.
-

■ PREVENTION

Three methods are used for the prevention of VZV infections.

- *Active immunization*: For all children and seronegative adults, two doses of a live attenuated varicella vaccine are recommended. Irrespective of serologic status, pts >50 years old should receive a vaccine with 18 times the viral content of varicella vaccine; zoster vaccine reduces the incidence of zoster and postherpetic neuralgia.
- *Passive immunization*: Varicella-zoster immune globulin (VZIG) can be given to VZV-susceptible hosts within 96 h (ideally 72 h) of a significant exposure if the risk of complications from varicella is high (e.g., immunocompromised pts, susceptible pregnant women, premature infants, neonates whose mothers had chickenpox onset within 5 days before or 2 days after delivery).
- *Antiviral treatment*: Seven days after intense exposure, antiviral prophylaxis can be given to high-risk pts who are ineligible for vaccine or for whom the 96-h window after direct contact has passed. This intervention may lessen illness severity.

CYTOMEGALOVIRUS

■ MICROBIOLOGY

CMV is a herpesvirus, has double-stranded DNA, and renders infected cells 2–4 times the size of surrounding cells. These cytomegalic cells contain an eccentrically placed intranuclear inclusion surrounded by a clear halo, with an “owl’s-eye” appearance.

■ EPIDEMIOLOGY

CMV disease is found worldwide. In many regions, nearly all adults are seropositive, as are ~50% of adults in the United States and Canada. Perinatal and early childhood infections are common; ~1% of U.S. newborns are infected.

- The virus can be spread in breast milk, saliva, feces, and urine.
- Transmission requires repeated or prolonged contact as opposed to casual contact. Sexual transmission is common among adolescents and adults, and CMV has been identified in semen and cervical secretions.

- Latent CMV infection persists throughout life unless reactivation is triggered by depressed cell-mediated immunity (e.g., in transplant recipients or HIV-infected pts).

■ PATHOGENESIS

Primary CMV infection is associated with a vigorous T-lymphocyte response; activated CD8+ T cells predominate among atypical lymphocytes.

- Latent infection occurs in multiple cell types and various organs. Chronic antigen stimulation in the presence of immunosuppression (e.g., in the transplantation setting) and certain immunosuppressive agents (e.g., antithymocyte globulin) promote CMV reactivation.
- CMV disease increases the risk of infection with opportunistic pathogens by depressing T-lymphocyte responsiveness.

■ CLINICAL MANIFESTATIONS

The most common presentation is CMV mononucleosis in immunocompetent pts, but disease can be more severe in immunocompromised pts (including newborns).

Congenital CMV Infection

Of infants born to mothers with primary CMV infections during pregnancy, 5–20% will develop clinical manifestations, with a mortality rate of ~5%.

- Petechiae, hepatosplenomegaly, and jaundice are present in 60–80% of cases; microcephaly with or without cerebral calcifications, intrauterine growth retardation, prematurity, and chorioretinitis are less common.
- Laboratory findings include elevated values in LFTs, thrombocytopenia, conjugated hyperbilirubinemia, hemolysis, and increased CSF protein levels.
- Infants with severe disease have ongoing intellectual and/or hearing difficulties.
- Of asymptotically infected infants, 5–25% develop significant psychomotor, hearing, ocular, or dental abnormalities over the next several years.

Perinatal CMV Infection

Perinatal infection with CMV is acquired by breast-feeding or contact with infected maternal secretions (e.g., in the birth canal). Although most pts are asymptomatic, disease similar to—but less severe than—congenital CMV disease can occur.

CMV Mononucleosis

Signs and symptoms last 2–6 weeks and include high fevers, profound fatigue and malaise, myalgias, headache, and splenomegaly. In contrast to EBV infection, exudative pharyngitis and cervical lymphadenopathy are rare in CMV infection.

- Laboratory findings include relative lymphocytosis with >10% atypical lymphocytes, transaminitis, and immunologic abnormalities (e.g., the presence of cryoglobulins, rheumatoid factor, or cold agglutinins).
- The incubation period ranges from 20 to 60 days.
- Recovery is generally complete, but postviral asthenia can persist for months.

CMV Infection in Immunocompromised Pts

CMV is the most common viral pathogen complicating organ transplantation, with the greatest risk of infection 1–4 months after transplantation. HIV-infected pts with CD4+ T cell counts of <50–100/ μ L also are at risk for severe CMV disease.

- Primary CMV infection (including reinfection with a new, donor-derived strain) is more likely than reactivation to cause severe disease with high viral loads.
 - Reactivation infection is common but less important clinically.
 - The transplanted organ is at particular risk; e.g., CMV pneumonitis tends to follow lung transplantation.
 - The risk of severe disease is reduced by antiviral prophylaxis or preemptive therapy.
- Pts present initially with prolonged fever, malaise, anorexia, fatigue, night sweats, and arthralgias or myalgias but can ultimately have multiorgan involvement.
 - Respiratory involvement is evidenced by tachypnea, hypoxia, unproductive cough, and chest radiographs demonstrating bilateral interstitial or reticulonodular infiltrates.
 - GI involvement often includes hepatitis and ulcer formation. Colitis is the most common manifestation in organ transplant recipients.
 - CMV encephalitis, particularly in HIV-infected pts, can occur as either progressive dementia or ventriculoencephalitis characterized by cranial nerve deficits, disorientation, and lethargy.
 - CMV retinitis is an important cause of blindness in pts with advanced AIDS.

■ DIAGNOSIS

Diagnosis requires isolation of CMV or detection of its antigens or DNA in appropriate clinical specimens in conjunction with a compatible clinical syndrome. Immunofluorescence assays for CMV antigens (pp65), PCR, viral culture, and serology are all useful means of detection.

TREATMENT

Cytomegalovirus Infections

- When possible, seronegative donors should be used for seronegative transplant recipients.
- Ganciclovir (5 mg/kg IV bid for 14–21 days followed by 5 mg/kg IV qd) or valganciclovir (the oral prodrug of ganciclovir; 900 mg PO bid for 14–21 days followed by 900 mg PO qd) produces response rates of 70–90% among HIV-infected pts with CMV retinitis or colitis.
 - In severe infections, ganciclovir is often combined with CMV immune globulin.
 - Neutropenia is an adverse reaction to ganciclovir treatment that may require administration of colony-stimulating factors.
 - Prophylactic or suppressive treatment can be given to high-risk transplant recipients (those who are seropositive before transplantation or culture positive without symptoms afterward).
 - Resistance to ganciclovir is common among pts treated for >3 months and is usually related to mutations in the CMV *UL97* gene.
 - For CMV retinitis, some clinicians prefer intravitreal injections of ganciclovir or foscarnet plus oral valganciclovir or intravenous ganciclovir, although no clinical trials have compared these approaches.
- Foscarnet (180 mg/kg qd divided into 2 or 3 doses for 2 weeks, followed by 90–120 mg/kg IV qd) inhibits CMV DNA polymerase and is active against most ganciclovir-resistant CMV isolates. The primary adverse events include electrolyte disturbances and renal dysfunction.

- Cidofovir (5 mg/kg IV per week for 2 weeks followed by 3–5 mg/kg IV every 2 weeks) is a nucleotide analogue that is also effective against ganciclovir-resistant CMV; however, it can cause severe nephrotoxicity by proximal tubular cell injury. The use of saline hydration and probenecid reduces this adverse effect.
- CMV immune or hyperimmune globulin may reduce the risk of CMV disease in seronegative renal transplant recipients and prevent congenital CMV infection in infants born to women with primary CMV infection during pregnancy.

EPSTEIN-BARR VIRUS

■ EPIDEMIOLOGY

EBV is a DNA virus in the family Herpesviridae that infects >90% of persons by adulthood.

- Infectious mononucleosis (IM) is a disease of young adults and is more common in areas with higher standards of hygiene; infection occurs at a younger age in areas with deficient standards of hygiene.
- EBV is spread by contact with oral secretions (e.g., by transfer of saliva during kissing) and is shed in oropharyngeal secretions by >90% of asymptomatic seropositive individuals.

■ PATHOGENESIS

EBV infects the epithelium of the oropharynx and salivary glands as well as B cells in tonsillar crypts prior to a period of viremia.

- B cells undergo polyclonal activation, and memory B cells form the reservoir for EBV. Reactive T cells proliferate, with up to 40% of CD8+ T cells directed against EBV antigens during acute infection.
- Cellular immunity is more important than humoral immunity in controlling infection. If T cell immunity is compromised, EBV-infected B cells may proliferate—a step toward neoplastic transformation.

■ CLINICAL MANIFESTATIONS

The nature of EBV disease depends on the pt's age and immune status: young children typically develop asymptomatic infections or mild pharyngitis, adolescents and adults develop an IM syndrome, and immunocompromised pts can develop lymphoproliferative disease.

- In IM, a prodrome of fatigue, malaise, and myalgia may last for 1–2 weeks before the onset of fever, exudative pharyngitis, and lymphadenopathy with tender, symmetric, and movable nodes; splenomegaly is more prominent in the second or third week.
 - The incubation period is ~4–6 weeks.
 - Earlier studies reported that most pts treated with penicillin derivatives develop a macular rash; these rashes do not represent a true penicillin allergy, nor do they occur more frequently in pts exposed to penicillin derivatives rather than other drugs.
 - Illness lasts for 2–4 weeks, but ~10% of pts have fatigue that persists for ≥6 months. EBV is not, however, a cause of chronic fatigue syndrome.
 - Lymphocytosis occurs in the second or third week, with >10% atypical lymphocytes (enlarged cells with abundant cytoplasm and vacuoles); abnormal liver function is common.

- Complications include CNS disease (e.g., meningitis, encephalitis), Coombs-positive autoimmune hemolytic anemia, splenic rupture, and upper airway obstruction due to hypertrophy of lymphoid tissue.
- Lymphoproliferative disease—i.e., infiltration of lymph nodes and multiple organs by proliferating EBV-infected B cells—occurs in pts with deficient cellular immunity (e.g., pts with AIDS, those with severe combined immunodeficiency, and those receiving immunosuppressive medications). Pts develop fever and lymphadenopathy or GI symptoms.
- Oral hairy leukoplakia—raised, white, corrugated, EBV DNA-containing lesions on the tongue—is an early manifestation of infection with HIV in adults.
- EBV-associated malignancies include Burkitt's lymphoma (~90% of cases in Africa and ~15% of cases in the United States), anaplastic nasopharyngeal carcinoma in southern China, gastric cancer (with ~9% of these tumors positive for EBV), Hodgkin's disease (especially the mixed-cellularity type), and CNS lymphoma (especially HIV-related).

■ DIAGNOSIS

Serologic testing is the mainstay of diagnostic assessment. PCR analysis can be useful in monitoring EBV DNA levels in blood from pts with lymphoproliferative disease.

- Heterophile antibodies ([Figure 102-1](#)) form the basis of most rapid testing, which assesses the ability of serum to agglutinate sheep, horse, or cow erythrocytes after adsorption with guinea pig kidney.
 - The antibodies can persist for up to 1 year after infection.
 - The monospot test for heterophile antibodies is somewhat more sensitive than the classic heterophile test; it is ~75% sensitive and ~90% specific in comparison with EBV-specific serologies.
 - Pts <5 years old and elderly pts usually do not develop heterophile antibodies.
- EBV-specific antibody testing can be used in heterophile-negative pts and in pts with atypical disease. Antibodies to viral capsid antigen occur in >90% of cases, with elevated IgM titers present only during the first 2–3 months of disease.
- Antibodies to Epstein-Barr nuclear antigen are not detected until 3–6 weeks after symptom onset and then persist for life.

TREATMENT

Epstein-Barr Virus Infections

- IM is treated with supportive measures, including rest and analgesia.
 - Excessive physical activity should be avoided in the first month of illness to reduce the possibility of splenic rupture, which necessitates splenectomy.
 - Administration of glucocorticoids may be indicated for some complications of IM; e.g., these agents may be given to prevent airway obstruction or to treat autoimmune hemolytic anemia, hemophagocytic lymphohistiocytosis, or severe thrombocytopenia.
 - Antiviral therapy (e.g., with acyclovir) is generally not effective for IM but is effective for oral hairy leukoplakia.
- Treatment of posttransplantation EBV lymphoproliferative syndrome is generally directed toward reduction of immunosuppression, although other treatments—e.g., with interferon α , antibody to CD20 (rituximab), and donor lymphocyte infusions—have been used with varying success.

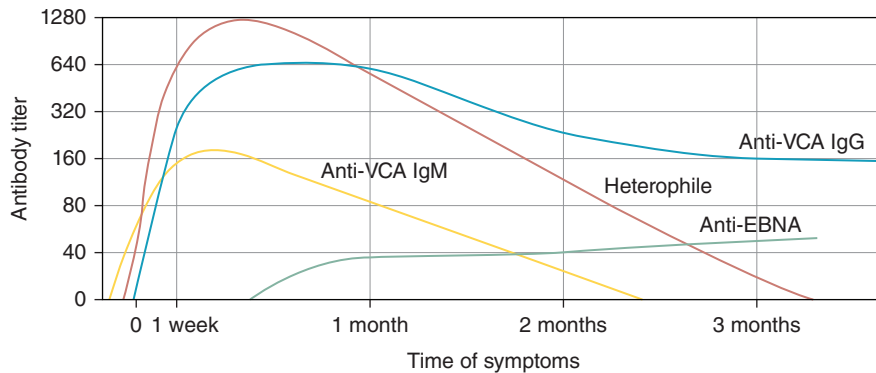


FIGURE 102-1 Pattern of Epstein-Barr virus (EBV) serology during acute infection. EBNA, Epstein-Barr nuclear antigen; VCA, viral capsid antigen. (From Cohen JI: *Epstein-Barr Virus, in Clinical Hematology*. Young NS et al [eds]. Philadelphia, Mosby, 2006.)

HUMAN HERPESVIRUS (HHV) TYPES 6, 7, AND 8

- HHV-6 causes *exanthem subitum* (roseola infantum, a common childhood febrile illness with rash) and 10–20% of febrile seizures without rash in infancy.
 - In older age groups, HHV-6 has been associated with mononucleosis syndromes and—in immunocompromised hosts—with encephalitis, pneumonitis, syncytial giant-cell hepatitis, and disseminated disease.
 - More than 80% of adults are seropositive for HHV-6.
- HHV-7 is frequently acquired during childhood, and infections typically manifest as fever and seizures. The virus is commonly present in saliva.
- HHV-8 infection in healthy children can present as fever and rash; in immunocompromised pts, primary infection may present as fever, splenomegaly, pancytopenia, and rapid-onset Kaposi's sarcoma.
 - HHV-8 is associated with Kaposi's sarcoma, body cavity-based lymphoma in AIDS pts, and multicentric Castleman's disease.
 - Unlike other herpesvirus infections, HHV-8 infection is much more common in some geographic areas (e.g., central and southern Africa) than in others (North America, Asia, northern Europe).
 - The virus appears to be sexually spread and may also be transmitted in saliva, by organ transplantation, and through IV drug use.

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Influenza and Other Viral Respiratory Diseases



INFLUENZA

■ MICROBIOLOGY AND PATHOGENESIS

Influenza A, B, and C viruses are segmented, single-stranded, negative-sense RNA viruses that have on their outer surface prominent spikes formed by two surface glycoproteins, hemagglutinin (H) and neuraminidase (N). Influenza A and B viruses are major human pathogens, but influenza C virus causes only intermittent mild disease.

- Influenza A viruses are subtyped by the H and N antigens.
 - Virus attaches to sialic acid cell receptors via the hemagglutinin. Neuraminidase cleaves the virus from the cell membrane to facilitate its release from the cell.
 - Influenza A viruses undergo antigenic drift (modification of immunogenic epitopes, particularly on the H antigen), which counteracts prevailing immunity, and antigenic shift (reassortment of genes among different isolates), which results in major changes in antigens). The viruses have extensive mammalian and avian reservoirs. These features give influenza A virus the ability to cause a worldwide epidemic (*pandemic*).
- Influenza is transmitted by small- and large-particle droplets. Virus spread is facilitated by the coughing and sneezing that accompany the illness.

■ EPIDEMIOLOGY

Influenza outbreaks occur during cooler months. A typical outbreak begins in early winter and lasts 4–5 weeks in a given community, although its impact on the entire country lasts considerably longer.

- All of the annual influenza A epidemics in the past 50 years have been caused by H1N1 and/or H3N2 strains. H2N2 strains circulated between 1957 and 1968, and H1N1 strains circulated prior to that.

- Potentially pandemic viruses continue to emerge, mostly in Asia, with higher-number hemagglutinins (e.g., H5, H6, H7, H9). It is thought that swine serve as an important intermediary of pandemic strains: these animals can sustain simultaneous infection with swine, human, and avian influenza viruses, which facilitates reassortment of genetic segments of different viruses (enabling antigenic shift).

■ CLINICAL MANIFESTATIONS

Influenza is primarily a sudden-onset respiratory illness causing rhinorrhea, sore throat, conjunctivitis, and cough. Symptoms typically begin within 48–72 h of exposure.

- Physical examination is often notable for nonlocalizing scattered rales, rhonchi, and wheezing. Localized pulmonary findings may suggest relatively complicated pneumonia with a bacterial component.
- Influenza is distinguished from other respiratory illnesses by the greater degree of accompanying fever, fatigue, myalgia, and malaise.
- Systemic symptoms generally resolve within 2–5 days, but respiratory symptoms (e.g., recurrent cough, decreased exercise performance) can persist for ≥ 1 month.
- Complications of influenza (respiratory and extrapulmonary manifestations) are more common among pts < 5 and > 65 years old, pregnant women in the second or third trimester, and pts with chronic disorders (e.g., cardiopulmonary disease, immunosuppression).
 - *Respiratory complications:* Pneumonia (progressive air hunger, localized pulmonary findings on physical or radiographic examination) is the most common complication of influenza. These cases can be due to primary influenza pneumonia and/or secondary bacterial pneumonia.
 - In secondary bacterial pneumonia or mixed viral and bacterial pneumonia, illness may be biphasic, with recrudescence of fever and pulmonary symptoms following recovery from the primary influenza illness.
 - *Extrapulmonary complications:* The most common extrapulmonary manifestation of influenza is myositis (seen more often in influenza B). Other complications include Reye's syndrome, myo/pericarditis, and CNS disease (e.g., encephalitis, transverse myelitis, Guillain-Barré syndrome).
 - Reye's syndrome is a serious complication in children that is associated with influenza B virus (and less commonly with influenza A virus), varicella-zoster virus, and aspirin therapy for the antecedent viral infection.

■ LABORATORY FINDINGS

Reverse-transcription PCR (RT-PCR) of respiratory samples (e.g., throat swabs, nasopharyngeal washes, sputum) is the most sensitive and specific technique for detecting influenza.

- Rapid tests that detect viral antigens yield results quickly and can sometimes distinguish between influenza A and B viruses. These tests are highly specific but exhibit low sensitivity (50–70%).
- Serologic testing requires the availability of acute- and convalescent-phase sera and is useful only retrospectively.

TREATMENT

Influenza

- Neuraminidase inhibitors are used for treatment of influenza A and B viruses. These agents work by limiting the egress of influenza virus from an infected cell.

- If started within 48 h of infection, the neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir) result in the resolution of symptoms 1–2 days sooner than is the case without treatment.
- Neuraminidase inhibitors are recommended for complicated influenza infections in hospitalized pts, even though there is not proof of their efficacy in this setting.
- Oseltamivir and intranasal zanamivir are given twice a day for 5 days.

■ PROPHYLAXIS

Annual vaccination with either an inactivated or a live attenuated vaccine is the main public health measure for prevention of influenza.

- Vaccine strains are generated from influenza A and B viruses that have circulated during the previous influenza season and whose circulation during the upcoming season is predicted.
- For inactivated vaccines, 50–75% protection against influenza is expected if the vaccine virus and the currently circulating viruses are closely related.
- Influenza vaccination is currently recommended for all individuals >6 months of age.
- The efficacy of the live attenuated vaccine has come into question in the last few years.
- The neuraminidase inhibitors can also be used for prophylaxis, either throughout the season or, when a case is recognized in a close contact, in the short term.

OTHER COMMON VIRAL RESPIRATORY INFECTIONS

Viruses are the leading causes of acute lower respiratory tract infection in most populations. Common viral respiratory infections can be categorized by site of anatomic involvement (e.g., alveolar spaces, bronchioles, trachea, conjunctiva, middle-ear spaces), disease syndrome (e.g., rhinitis, pharyngitis, bronchiolitis, pneumonia), or etiologic agent (e.g., respiratory syncytial virus [RSV], human metapneumovirus, parainfluenza virus [PIV], adenovirus). See [Chap. 59](#) for additional details on viral respiratory infections.

■ EPIDEMIOLOGY

- Age is a major determinant of risk for symptomatic disease, with children having more frequent respiratory virus infections than adults.
- Infections with most of the conventional respiratory viruses occur in winter.
- Risk factors for severe disease include underlying lung disease (especially chronic obstructive pulmonary disease), cardiovascular disease, close exposure to infected people, smoking, low socioeconomic status, and male gender.
- Respiratory viruses are generally transmitted by fomites or by large-particle aerosols of respiratory droplets that are spread by coughing or sneezing.
- Culture-based studies have isolated two or more viruses from 5% to 10% of healthy adults with acute respiratory illness.

■ ETIOLOGIC AGENTS

- RSV is a single-stranded, negative-sense, nonsegmented RNA virus and a member of the family Paramyxoviridae. RSV is among the most transmissible of viruses, and infection is ubiquitous, particularly in the first few years of life. Annual epidemics typically occur between October and March in temperate regions. The very young and the elderly are at greatest risk for severe lower

respiratory tract illness and hospitalization. There may be a link between RSV infection in early life and the subsequent development of asthma.

- *Parainfluenza viruses* are a group of four distinct serotypes (designated 1–4) of single-stranded, negative-sense RNA viruses in the family Paramyxoviridae. PIV3 most commonly causes severe disease. Primary infection in children manifests as laryngotracheitis (croup), with subsequent infections limited to the upper respiratory tract.
- *Human metapneumovirus* is also a member of the family Paramyxoviridae and is similar in many respects to RSV, although less virulent. Infections occur first in early childhood, and reinfections are common throughout life. The virus causes both upper and lower respiratory tract disease.
- *Rhinoviruses* are single-stranded, positive-sense RNA viruses in the family Picornaviridae. The more than 100 serotypes of rhinovirus are the most frequent causes of the common cold, causing $\geq 50\%$ of cases. Most infected adults also have radiographic evidence of sinusitis. Rhinovirus may be able to infect the lower respiratory tract as well, although the data are less clear.
- *Adenovirus* is a double-stranded, nonsegmented DNA virus in the family Adenoviridae. Most human respiratory infections are caused by the B and C species and can occur throughout the year. Acute adenovirus infection is frequently associated with pharyngoconjunctival fever. Immunocompromised pts are highly susceptible to severe disease during infection with respiratory adenoviruses.
- Dozens of *coronaviruses* affect animals, and some have the potential to cross over and infect humans. In an outbreak caused by SARS-associated coronavirus (SARS-CoV) that occurred from November 2002 to July 2003, >8000 people were infected and the mortality rate was $\sim 10\%$. Unlike viral pneumonias, SARS lacks upper respiratory symptoms (although cough and dyspnea occur in most pts), and pts present with a nonspecific illness of fever, myalgia, malaise, and chills or rigors. The Middle East respiratory syndrome coronavirus (MERS-CoV) is associated with a 35% mortality rate in humans. This virus is thought to have emerged from bats, and humans are thought to be infected through direct or indirect contact with infected dromedary camels.

■ CLINICAL MANIFESTATIONS

The presentation of a viral respiratory infection depends on the anatomic site affected.

- The common cold is characterized by nasal congestion, sneezing, rhinorrhea, cough, and sore throat.
- Laryngitis is accompanied by hoarseness or dysphonia.
- Acute bronchitis is characterized by a dry or productive cough of <3 weeks' duration; bacteria play a more prominent role in chronic bronchitis.
- Acute pneumonia manifests with fever, cough, sputum production, dyspnea, and chest pain.

■ DIAGNOSIS

The clinical diagnosis of a respiratory syndrome and determination of the anatomic location of infection are based on history, physical examination, and radiography. A specific viral etiology can be determined by specific diagnostic tests. Although virus isolation is the gold standard, the most sensitive tests are RT-PCR assays. Multiplex panels that assay for numerous respiratory viruses and bacterial pathogens are available. However, a positive test for a virus may indicate a recently resolved rather than an acute infection, given that the viral genome can persist in respiratory secretions for weeks.

TREATMENT**Acute Respiratory Virus Infections**

The principal interventions that make a difference in the care of pts with acute respiratory virus infections are supportive and should be implemented meticulously. Antiviral treatment, for which there are limited options, generally is effective only when administered early in the course of illness. Antibiotics do not improve the outcome of uncomplicated respiratory virus infections in otherwise healthy subjects.

- Ribavirin, a nucleoside antimetabolite prodrug, has been used in an aerosol formulation for treatment of children with severe RSV-induced lower respiratory tract infection, but its efficacy is questionable. IV ribavirin has occasionally been used for other viral infections (e.g., due to adenovirus, PIV), but its risk/benefit profile has not been established.
- Cidofovir is a nucleotide analog with activity against a large number of viruses, including adenovirus. IV cidofovir has been effective in the management of severe adenoviral infection in immunocompromised pts but may cause serious nephrotoxicity.

PREVENTION

Given the lack of cross-protection among serotypes for many respiratory viruses, vaccines have been difficult to develop. However, a vaccine against adenovirus serotypes 4 and 7 is used in military recruits, and live attenuated and subunit vaccine candidates against RSV are currently under development. Palivizumab, a humanized mouse monoclonal antibody to the F protein of RSV, is licensed for prevention of RSV hospitalization in high-risk infants; however, it has not been effective for treatment of immunocompetent or immunocompromised RSV-infected pts.

104**Rubeola, Rubella, Mumps, and Parvovirus Infections****MEASLES (RUBEOLA)****DEFINITION AND MICROBIOLOGY**

Measles is a highly contagious disease that is characterized by a prodromal illness of fever, cough, coryza, and conjunctivitis followed by a generalized maculopapular rash. Measles is caused by a nonsegmented, single-strand, negative-sense RNA virus of the genus *Morbillivirus* and the family *Paramyxoviridae*.

EPIDEMIOLOGY

Humans are the only reservoir for measles virus; unvaccinated infants who have lost maternal antibodies account for the bulk of susceptible individuals. However, as measles vaccine coverage increases, the age distribution of the disease shifts upward, with more adolescents and adults affected. The World Health Organization (WHO) Region of the Americas eliminated endemic measles in 2016.

- Routine administration of the measles vaccine has markedly reduced worldwide mortality due to measles; in 2015, there were ~134,200 deaths.

- Pts are contagious for several days before and after the rash appears. The virus is spread primarily via respiratory droplets over short distances. Secondary attack rates among susceptible contacts are >90%.

■ CLINICAL MANIFESTATIONS

Approximately 10 days after infection with measles virus, pts develop fever and malaise, followed by cough, coryza, and conjunctivitis; the characteristic rash occurs 14 days after infection.

- An erythematous, nonpruritic, maculopapular rash begins at the hairline and behind the ears, spreads down the trunk and limbs to include the palms and soles, can become confluent, and begins to fade (in the same order of progression) by day 4.
- Koplik's spots are pathognomonic for measles and consist of bluish-white dots ~1 mm in diameter surrounded by erythema. They appear on the buccal mucosa ~2 days before the rash appears and fade with the onset of rash.
- Pts with impaired cellular immunity may not develop a rash and have a higher case-fatality rate than those with intact immunity.
- Complications include giant-cell pneumonitis, secondary bacterial infection of the respiratory tract (e.g., otitis media, bronchopneumonia), and CNS disorders.
 - Postmeasles encephalitis occurs within 2 weeks of rash onset in ~1 in 1000 cases and is characterized by fever, seizures, and a variety of neurologic abnormalities.
 - Measles inclusion-body encephalitis (MIBE) and subacute sclerosing panencephalitis (SSPE) occur months to years after acute infection and are caused by persistent measles virus infection.
 - MIBE is a fatal complication that primarily affects pts with defects in cellular immunity.
 - SSPE is a progressive disease characterized by seizures and deterioration of cognitive and motor functions, with death occurring 5–15 years after measles virus infection.

■ DIAGNOSIS

The characteristic rash and pathognomonic Koplik's spots permit a clinical diagnosis.

- Serologic testing is the most common method of laboratory diagnosis. Measles-specific IgM is usually detectable within 1–3 days of rash onset.
- Viral culture and reverse-transcription PCR analysis of clinical specimens are used occasionally to detect measles.

TREATMENT

Measles

- Supportive care is the mainstay of treatment, as there is no specific antiviral therapy for measles. Prompt antibiotic therapy for pts with secondary bacterial infections helps reduce morbidity and mortality risks.
- Vitamin A (for children ≥12 months: 200,000 IU/d for 2 days) is recommended by the WHO for all children with measles.

■ PREVENTION

In the United States, children are routinely immunized with two doses of a live attenuated vaccine containing measles, mumps, and rubella (MMR) antigens.

- Vaccine-induced immunity lasts for at least several decades; rates of secondary vaccine failure 10–15 years after immunization are ~5%. In contrast, natural infection leads to lifelong immunity.
- Infants born to women with vaccine-induced measles immunity become susceptible to measles at a younger age than infants born to women with acquired immunity from natural infection.
- Administration of immunoglobulin within 6 days of exposure, which can prevent or modify the disease in immunocompetent persons, is recommended for children <1 year old, immunocompromised pts, and pregnant women. A dose of 0.25 mL/kg is given to healthy pts and a dose of 0.5 mL/kg to immunocompromised hosts, with a maximal dose of 15 mL.

RUBELLA (GERMAN MEASLES)

■ MICROBIOLOGY AND EPIDEMIOLOGY

Rubella is a contagious infectious disease caused by a single-strand, enveloped RNA virus in the family *Togaviridae* and the genus *Rubivirus*.

- In 2015, there were ~22,427 cases of rubella worldwide, although this figure is probably an underestimate because of poor reporting. Since 2004, rubella has not been an endemic disease in the United States.
- Virus is spread via respiratory droplets, and primary implantation and replication occur in the nasopharynx. Placental infection can lead to chronic infection of virtually all fetal organs, which sometimes persists for up to 1 year after birth.

■ CLINICAL MANIFESTATIONS

While acquired rubella infection is generally benign, congenital rubella infection can be more severe.

- *Acquired infection*: With an incubation period of 14 days, acquired rubella is characterized by a generalized maculopapular rash that lasts ≤ 3 days; ~50% of infections are subclinical or without rash.
 - Occipital and/or postauricular lymphadenopathy may occur during the second week after exposure.
 - In older children and adults, the rash may be preceded by a 1- to 5-day prodrome consisting of low-grade fever, malaise, and upper respiratory symptoms.
 - Arthralgias and arthritis are common among adults, particularly women.
- *Congenital infection*: Congenital rubella infection can lead to a number of physical defects, usually involving the eyes (e.g., cataracts), ears (e.g., deafness), and heart (e.g., pulmonary arterial stenosis).
 - Up to 90% of women infected with rubella virus during the first 11 weeks of pregnancy will deliver an infant with congenital rubella.
 - The congenital rubella rate is 20% for maternal infections acquired during the first 20 weeks of pregnancy.

■ DIAGNOSIS

Given the difficulty of diagnosing rubella clinically, serologic testing (for the presence of IgM or a ≥ 4 -fold rise in IgG titer) is generally used for diagnosis.

- If the IgM result is negative for a sample taken within the first 4 days of rash but clinical suspicion remains, testing should be repeated; IgM antibody titers are generally positive for up to 6 weeks.
- Congenital rubella can be diagnosed by detection of IgM antibodies, although titers may be negative during the first month; by isolation of the virus from

throat swabs, urine, or CSF; and/or by an IgG titer that does not decline at the expected rate of a twofold dilution per month.

- In the United States, screening of pregnant women for rubella IgG antibodies is part of routine prenatal care; seronegative women should be vaccinated postpartum. Given the potential for false-positive results, rubella IgM antibody testing is not recommended for pregnant women with no history of illness or contact with a rubella-like illness.

TREATMENT

Rubella

Symptom-based treatment for various manifestations, such as fever and arthralgia, is appropriate. No rubella-specific therapies are available.

■ PREVENTION

As of 2017, 77% of countries holding membership in the WHO had recommended inclusion of a rubella-containing vaccine in the routine childhood vaccination schedule. One dose induces seroconversion in $\geq 95\%$ of persons ≥ 1 year of age and provides long-term (potentially lifelong) immunity.

- Pregnant women should not receive the vaccine, and pregnancy should be avoided for at least 28 days after vaccination.
- Immunoglobulin does not prevent rubella virus infection after exposure and therefore is not recommended as routine postexposure prophylaxis.

MUMPS

■ DEFINITION AND MICROBIOLOGY

Mumps is an acute systemic communicable viral infection whose most distinctive feature is swelling of one or both parotid glands. It is caused by mumps virus, a negative-strand nonsegmented RNA paramyxovirus.

■ EPIDEMIOLOGY

The estimated annual global incidence of mumps is 100–1000 cases per 100,000 population in countries without national mumps vaccination programs. Following the introduction of a two-dose vaccination schedule and passage of school immunization laws in the United States, there were fewer than 400 cases annually until an outbreak in 2006. Since then, the number of cases per year has increased threefold even though vaccine coverage among kindergarteners has remained stable. College students are now most frequently affected, a finding that suggests waning of vaccine immunity.

- The incubation period of mumps is ~19 days, and humans are the only natural hosts.
- Mumps virus is transmitted by respiratory secretions and fomites. Pts are contagious from 1 week before to 1 week after symptom onset and are most contagious 1–2 days before symptom onset.

■ CLINICAL MANIFESTATIONS

Up to half of infections are asymptomatic or lead to nonspecific respiratory symptoms.

- A prodrome involving low-grade fever, malaise, myalgia, headache, and anorexia may precede the development of parotitis and last for 1–7 days.

- Pts with parotitis typically have difficulty eating, swallowing, and/or talking and may have an earache. The parotitis is bilateral in two-thirds of cases, although the two sides may not be involved synchronously.
- Glandular swelling disappears within 1 week.
- Epididymo-orchitis is the second most common manifestation of mumps, developing in 15–30% of cases in postpubertal males.
 - Orchitis, characterized by a painful, tender, and enlarged testis, is bilateral in 10–30% of cases and resolves within 1 week.
 - Oophoritis (manifested by lower abdominal pain and vomiting) occurs in ~5% of women with mumps.
 - Sterility after mumps is rare.
- Symptomatic CNS disease (e.g., aseptic meningitis) occurs in <10% of pts and is usually self-limited.
 - Mumps deafness, which may or may not be related to CNS infection, occurs in 0.001–0.1% of cases.
- Less common manifestations include pancreatitis, myocarditis, thyroiditis, nephritis, and arthritis. Mumps in pregnancy does not appear to lead to premature birth, low birth weight, or fetal malformations.

■ DIAGNOSIS

Laboratory diagnosis is generally based on detection of viral RNA in clinical samples (e.g., buccal or throat swab, CSF, urine, seminal fluid) via reverse-transcription PCR or serology. Serologic assays are of limited utility since IgM may not be detectable <3 days or >6 weeks after symptom onset and IgG titers often exhibit little fluctuation between acute- and convalescent-phase samples.

TREATMENT

Mumps

Mumps is generally a benign, self-resolving illness in which symptom-based and supportive therapies are most helpful.

■ PREVENTION

Current U.S. recommendations are for a two-dose vaccination schedule, with the first dose at ≥ 1 year old and the second dose at least 28 days after the first. Outbreaks, such as those occurring in 2006 in the United States, the United Kingdom, and Canada, demonstrate that vaccine-induced immunity is not lifelong.

PARVOVIRUS INFECTION

■ MICROBIOLOGY

Parvovirus B19 (B19V), a nonenveloped single-stranded DNA virus of the family Parvoviridae, is the only member of this family shown definitively to cause significant human disease.

■ EPIDEMIOLOGY

B19V exclusively infects humans, is endemic worldwide, and is transmitted via the respiratory route. By the age of 15 years, $\geq 50\%$ of children are seropositive. Of elderly pts, $>90\%$ have detectable antibody.

■ PATHOGENESIS

B19V replicates in erythroid progenitors, which are among the few cells that express the B19V receptor, blood group P antigen (globoside). Infection leads to high-titer viremia and arrest of erythropoiesis. When an IgM and IgG antibody response is mounted, normal erythropoiesis resumes.

■ CLINICAL MANIFESTATIONS

Most B19V infections are asymptomatic or are associated with only a mild non-specific illness.

- *Erythema infectiosum (fifth disease)*: The main manifestation of symptomatic B19V disease, erythema infectiosum presents as a low-grade fever ~7–10 days after exposure and a facial “slapped-cheek” rash (more common among children) a few days later. Two or three days after the facial rash develops, a lacy, reticular macular rash may spread to the extremities.
- *Polyarthropathy syndrome*: Arthralgias, typically symmetric and affecting the small joints of the hands and occasionally the ankles, knees, and wrists, occur in ~50% of adults (more commonly women). Most cases resolve in a few weeks, but some persist for months.
- *Transient aplastic crisis (TAC)*: Pts with chronic hemolytic conditions (e.g., hemoglobinopathies, autoimmune hemolytic anemia) can develop aplastic crisis with B19V infection that can be life-threatening. Pts display symptoms associated with severe anemia.
- *Pure red-cell aplasia/chronic anemia*: Immunosuppressed pts can develop persistent anemia with reticulocytopenia, high levels of B19V DNA in serum, and absent or low levels of B19V IgG. B19V occasionally causes a hemophagocytic syndrome.
- *Hydrops fetalis*: B19V infection during pregnancy can lead to hydrops fetalis and/or fetal loss. The risk of transplacental fetal infection is ~30%, and the risk of fetal loss (which occurs predominantly early in the second trimester) is ~9%. The risk of congenital infection is <1%.

■ DIAGNOSIS

Diagnosis in immunocompetent pts generally relies on detection of B19V-specific IgM antibodies, which can be detected coincident with the rash in erythema infectiosum or by day 3 of TAC.

- B19V-specific IgG is detectable by the seventh day of illness and persists for life.
- Detection of B19V DNA via quantitative PCR should be used to diagnose early TAC or chronic anemia. In acute infection, the viremia load can be $>10^{12}$ B19V DNA IU/mL of serum; pts with TAC or chronic anemia generally have $>10^5$ B19V IU/mL.

TREATMENT

Parvovirus Infection

- Treatment of B19V infection is generally supportive as no specific therapy exists. TAC should be treated with transfusions as needed.
- In pts receiving immunosuppressive agents, treatment should be reduced to the extent feasible to allow an immune response. IV immunoglobulin (400 mg/kg daily for 5–10 days) may cure or ameliorate persistent B19V infection in immunosuppressed pts.

105 Enterovirus Infections



■ MICROBIOLOGY

- Enteroviruses are so named because of their ability to multiply in the GI tract, but they do not typically cause gastroenteritis.
- Enteroviruses are members of the family Picornaviridae and encompass >115 human serotypes: 3 serotypes of poliovirus, 21 serotypes of coxsackievirus A, 6 serotypes of coxsackievirus B, 28 serotypes of echovirus, enteroviruses 68–71, and multiple enteroviruses (beginning with enterovirus 73) recently identified by molecular techniques. In the United States, 58% of all enterovirus infections are caused by coxsackieviruses A6, A9, and B4; echoviruses 6, 11, 18, and 30; and human parechovirus 3.

■ PATHOGENESIS

- Studies of poliovirus infection form the basis of our understanding of enteroviral pathogenesis.
- After ingestion, poliovirus infects GI-tract mucosal epithelial cells, spreads to regional lymph nodes, causes viremia, and replicates in the reticuloendothelial system; in some cases, a second round of viremia occurs.
- Virus gains access to the CNS either via the bloodstream or via direct spread from neural pathways.
- Virus is present in blood for 3–5 days. It is shed from the oropharynx for up to 3 weeks and from the GI tract for up to 12 weeks after infection. Hypogammaglobulinemic pts can shed virus for >20 years.
- Infection is controlled by humoral and secretory immunity in the GI tract.

■ EPIDEMIOLOGY

- Enteroviruses cause disease worldwide, especially in areas with crowded conditions and poor hygiene.
- Infants and young children are most often infected and are the most frequent shedders.
- Transmission takes place mainly by the fecal–oral route, but airborne transmission and placental transmission have been described.
- The incubation period ranges from 2 to 14 days but usually is <1 week in duration. Pts are most infectious shortly before and after the onset of symptoms.

■ CLINICAL MANIFESTATIONS

Poliovirus

After an incubation period of 3–6 days, ~5% of pts present with a minor illness (abortive poliomyelitis) that is characterized by fever, malaise, sore throat, myalgias, and headache and that usually resolves within 3 days.

- *Asymptomatic infection*: >90% of all infections
- *Aseptic meningitis (nonparalytic poliomyelitis)*: occurs in ~1% of pts. Examination of CSF reveals normal glucose and protein concentrations and lymphocytic pleocytosis (with PMNs sometimes predominating early).
- *Paralytic disease*: the least common form, presenting ≥1 day after aseptic meningitis as severe back, neck, and muscle pain as well as gradually developing motor weakness
 - The weakness is usually asymmetric and proximal and is most common in the legs. The arms and the abdominal, thoracic, and bulbar muscles are also frequently involved.
 - Paralysis generally occurs only during the febrile phase.

- Physical examination reveals weakness, fasciculations, decreased muscle tone, and reduced or absent reflexes in affected areas; hyperreflexia may precede the loss of reflexes. Bulbar paralysis is associated with dysphagia, difficulty handling secretions, or dysphonia.
- Respiratory insufficiency due to aspiration or neurologic involvement may develop. Severe medullary infection may lead to circulatory collapse.
- Most pts recover some function, but around two-thirds have residual neurologic sequelae.
- *Vaccine-associated poliomyelitis*: The risk of acquiring poliomyelitis after vaccination with the live oral vaccine is estimated to be 1 case per 2.5 million doses and is ~2000 times higher among immunodeficient persons, especially pts with hypo- or agammaglobulinemia.
- *Postpolio syndrome*: new weakness 20–40 years after poliomyelitis. Onset is insidious, progression is slow, and plateau periods can last 1–10 years.

Other Enteroviruses

In the United States, 5–10 million cases of symptomatic enteroviral disease other than poliomyelitis occur each year. More than 50% of nonpoliovirus enterovirus infections are subclinical.

- *Nonspecific febrile illness (summer grippé)*: Pts present with acute-onset fever, malaise, and headache, with occasional upper respiratory symptoms. Disease resolves within a week. Disease frequently occurs during the summer and early fall.
- *Generalized disease of the newborn*: Neonates, typically within the first week of life, present with an illness resembling bacterial sepsis, with fever, irritability, and lethargy.
 - Myocarditis, hypotension, hepatitis, DIC, meningitis, and pneumonia are complications.
 - A history of a recent flu-like illness in the mother should prompt consideration of this disease.
- *Aseptic meningitis and encephalitis*: Enteroviruses cause 90% of cases of aseptic meningitis among children and young adults in which an etiologic agent can be identified; 10–35% of viral encephalitis cases are due to enteroviruses.
 - Pts have an acute onset of fever, chills, headache, photophobia, nausea, and vomiting, with meningismus on examination. Diarrhea, rashes, myalgias, pleurodynia, myocarditis, and herpangina may occur. Encephalitis is much less common and is usually mild, with an excellent prognosis in healthy hosts.
 - CSF examination reveals pleocytosis, with PMNs sometimes predominating early but a shift to lymphocyte predominance within 24 h. Total cell counts usually do not exceed 1000/ μ L. CSF glucose and protein levels are typically normal.
 - Symptoms resolve within 1 week, but CSF abnormalities persist longer.
- *Pleurodynia (Bornholm disease)*: Pts have an acute onset of fever associated with spasms of pleuritic chest pain (more common among adults) or upper abdominal pain (more common among children) that typically last 15–30 min. Fever subsides when pain resolves.
 - Coxsackievirus B is the most common cause.
 - Disease lasts for a few days and can be treated with NSAIDs and heat application to the affected muscles.
- *Myocarditis and pericarditis*: Enteroviruses (e.g., coxsackievirus B) cause up to one-third of cases of acute myocarditis. Pts have upper respiratory symptoms followed by fever, chest pain, dyspnea, arrhythmias, and occasionally heart failure.

- Disease occurs most often in newborns (who are most severely ill), adolescents, and young adults.
- A pericardial friction rub, ST-segment and T-wave abnormalities on electrocardiography, and elevated serum levels of myocardial enzymes can be present.
- Up to 10% of pts develop chronic dilated cardiomyopathy.
- *Exanthems*: Enterovirus infection is the leading cause of exanthems among children in the summer and fall. Echoviruses 9 and 16 are common causes.
- *Hand-foot-and-mouth disease*: generally due to coxsackievirus A16 and enterovirus 71. Pts present with fever, anorexia, and malaise, which are followed by sore throat and vesicles on the buccal mucosa, tongue, and dorsum or palms of the hands and occasionally on the palate, uvula, tonsillar pillars, or feet.
 - The disease is highly infectious, with attack rates of almost 100% among young children. Symptoms resolve within a week.
 - Epidemics of enterovirus 71 infection occurred in Taiwan in 1998 and have occurred annually in China since 2008, with hundreds of thousands of cases and hundreds of deaths each year. These epidemics were associated with CNS disease (e.g., brain-stem encephalitis, seizures), myocarditis, and pulmonary hemorrhage. Deaths occurred primarily among children ≤ 5 years old.
- *Herpangina*: usually caused by coxsackievirus A infection. Pts develop fever, sore throat, odynophagia, and grayish-white papulovesicular lesions on an erythematous base that ulcerate and are concentrated in the posterior portion of the mouth.
 - Lesions can persist for weeks.
 - In contrast to herpes simplex stomatitis, enteroviral herpangina is not associated with gingivitis.
- *Acute hemorrhagic conjunctivitis*: associated with enterovirus 70 and coxsackievirus A24. Pts experience an acute onset of severe eye pain, blurred vision, photophobia, and watery eye discharge; edema, chemosis, and subconjunctival hemorrhage are evident. Symptoms resolve within 10 days.

■ DIAGNOSIS

- Enterovirus can be isolated from throat or rectal swabs, stool, and/or normally sterile body fluids.
 - Positive results for normally sterile body fluids, such as CSF and serum, reflect disease.
 - In contrast, positive stool and throat cultures may simply reflect colonization.
- In general, serotyping is not clinically useful outside of epidemiologic studies.
- PCR detects all serotypes that infect humans, with high sensitivity (70–100%) and specificity (>80%).
 - PCR of CSF is less likely to be positive if pts present ≥ 3 days after meningitis onset or with enterovirus 71 infection.
 - PCR of serum is also useful in disseminated disease.

TREATMENT

Enterovirus Infections

- Most enteroviral illness resolves spontaneously, but immunoglobulin may be helpful in pts with γ globulin defects and chronic infection.
- Glucocorticoids are contraindicated.

■ PREVENTION AND ERADICATION

- Hand hygiene, use of gowns and gloves, and enteric precautions (for 7 days after disease onset) prevent nosocomial transmission of enteroviruses during epidemics.
- The availability of poliovirus vaccines and the implementation of polio eradication programs have largely eliminated disease due to wild-type poliovirus; in 2016, there were 37 cases of wild-type polio, all of which occurred in Nigeria, Pakistan, and Afghanistan—the only countries where polio remains endemic. Wild-type poliovirus types 2 and 3 are no longer circulating anywhere in the world. Outbreaks and sporadic disease due to vaccine-derived poliovirus occur.
- Both oral poliovirus vaccine (OPV) and inactivated poliovirus vaccine (IPV) induce IgG and IgA antibodies that persist for at least 5 years.
- Most developing countries, particularly those with persistent wild-type poliomyelitis, use OPV because of its lower cost and ease of administration. The suboptimal seroconversion rate among children in low-income countries, even after multiple OPV doses, contributes to difficulties in eradication.
- Most industrialized countries have adopted all-IPV childhood vaccination programs.
 - Unvaccinated adults in the United States do not need routine poliovirus vaccination but should receive three doses of IPV (the second dose 1–2 months after the first and the final dose 6–12 months later) if they are traveling to polio-endemic areas or might be exposed to wild-type poliovirus in their communities or workplaces.
- Adults at increased risk of exposure who have received their primary vaccination series should receive a single dose of IPV.

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**Insect- and Animal-Borne
Viral Infections****RABIES****■ MICROBIOLOGY**

Rabies is a zoonosis generally transmitted to humans by the bite of a rabid animal and caused by rabies virus—a nonsegmented, negative sense, single-strand RNA virus in the family Rhabdoviridae. Each animal reservoir harbors distinct rabies virus variants.

■ EPIDEMIOLOGY

Worldwide, canine rabies causes ~59,000 human deaths each year, most of them affecting rural populations and children in Asia and Africa.

- Endemic canine rabies has been eliminated in the United States and most other resource-rich countries but persists in bats, raccoons, skunks, and foxes. In 2015, there were 5508 confirmed animal cases of rabies in the United States.
- Bats (especially silver-haired and tricolored bats) cause most human cases in North America, although there may be no known history of a bat bite or other bat exposure.

■ PATHOGENESIS

The incubation period can range from a few days to >1 year but is usually 20–90 days. During most of this period, rabies virus is present at or close to the site of the bite.

- The virus binds to postsynaptic nicotinic acetylcholine receptors and spreads centripetally along peripheral nerves toward the CNS at a rate of up to ~250 mm/d. Establishment of CNS infection is followed by centrifugal spread along peripheral nerves to other tissues, including salivary glands—hence the excretion of virus in the saliva of rabid animals.
- The most characteristic pathologic CNS finding is the *Negri body*—an eosinophilic cytoplasmic inclusion that is composed of rabies virus proteins and viral RNA and is found primarily within Purkinje cells of the cerebellum and in pyramidal neurons of the hippocampus.

■ CLINICAL MANIFESTATIONS

Rabies usually presents as atypical encephalitis with preservation of consciousness; the disease may be difficult to recognize after the onset of coma. This disease, which usually leads to death despite aggressive therapy, has three phases.

- *Prodrome*: Pts have fever, headache, malaise, nausea, vomiting, and anxiety or agitation lasting 2–10 days. Paresthesias, pain, or pruritus near the site of exposure (which has usually healed at this point) is found in 50–80% of cases and strongly suggests rabies.
- *Acute neurologic phase*: Pts present with the encephalitic (furious) form of rabies in 80% of cases and with the paralytic form in 20%.
 - *Encephalitic form*: Pts develop signs and symptoms common to other viral encephalitides (e.g., fever, confusion, hallucinations, combativeness, and seizures) that last 2–10 days. Autonomic dysfunction is common and includes hypersalivation, gooseflesh, cardiac arrhythmia, and/or priapism.
 - A distinguishing feature of rabies is prominent early brainstem dysfunction resulting in hydrophobia and aerophobia (involuntary, painful contraction of the diaphragm and the accessory respiratory, laryngeal, and pharyngeal muscles in response to swallowing liquid or exposure to a draft of air).
 - Hypersalivation and pharyngeal dysfunction produce characteristic foaming at the mouth.
 - Death usually occurs within days of brainstem involvement. With aggressive supportive care, late complications include cardiopulmonary failure, disturbances of water balance (syndrome of inappropriate antidiuretic hormone secretion or diabetes insipidus), and GI hemorrhage.
 - *Paralytic form*: For unknown reasons, muscle weakness predominates but cardinal features of rabies encephalitis (hyperexcitability, hydrophobia, aerophobia) are lacking. Muscle weakness usually begins in the bitten extremity and proceeds to quadriparesis.
- *Coma and death*: Even with aggressive supportive measures, recovery is rare. Death usually occurs within 2 weeks.

■ DIAGNOSIS

In North America, the diagnosis is often considered relatively late in the clinical course. Rabies should be considered for pts with acute atypical encephalitis or acute flaccid paralysis (including those in whom Guillain-Barré syndrome is suspected).

- Most routine laboratory tests in rabies are normal or nonspecific; it is important to test for alternative, potentially treatable diagnoses.
- Negative antemortem rabies-specific laboratory tests never exclude a diagnosis of rabies, and tests may need to be repeated after an interval for diagnostic confirmation.

- In a previously unimmunized pt, serum neutralizing antibodies to rabies virus are diagnostic, but these antibodies may not be present until late in the disease course. The presence of rabies virus–specific neutralizing antibodies in CSF suggests rabies encephalitis, regardless of immunization status.
- Reverse-transcription PCR (RT-PCR) can detect virus in fresh saliva samples, CSF, and skin and brain tissues.
- Direct fluorescent antibody testing is highly sensitive and specific and can be applied to brain tissue or skin biopsy samples from the nape of the neck (where virus is found in cutaneous nerves at the base of hair follicles).

TREATMENT

Rabies

Management is palliative and supportive. There is no established treatment for rabies.

■ PREVENTION

Rabies is almost uniformly fatal but is nearly always preventable with appropriate postexposure prophylaxis during the incubation period. Only 15 pts have survived infection with rabies virus, and only one of these pts had not received rabies vaccine before disease onset.

- An algorithm for rabies postexposure prophylaxis is depicted in [Fig. 106-1](#).
 - Local wound care (e.g., thorough washing, debridement of devitalized tissue) can greatly reduce the risk of rabies.
 - Inactivated rabies vaccine should be given as soon as possible (1 mL IM in the deltoid region), with doses repeated on days 3, 7, and 14 for previously unvaccinated pts; previously vaccinated pts require booster doses only on days 0 and 3.
 - All previously unvaccinated pts should receive human rabies immune globulin (RIG, 20 IU/kg; 40 IU/kg for equine RIG) no later than 7 days after the first vaccine dose. The entire dose should be infiltrated at the site of the bite; if not anatomically feasible, the residual RIG should be given IM at a distant site.
- Preexposure prophylaxis is occasionally given to persons at high risk (including certain travelers to rabies-endemic areas). The primary vaccine schedule consists of doses on days 0, 7, and 21 or 28.

INFECTIONS CAUSED BY ARTHROPOD- AND RODENT-BORNE VIRUSES

■ MICROBIOLOGY AND PATHOGENESIS

Most zoonotic viruses only incidentally infect and produce disease in humans; only a few agents are regularly spread among humans by arthropods.

- The major families of arthropod- and rodent-borne viruses include the Arenaviridae, Bunyaviridae, Flaviviridae, Hantaviridae, Nairoviridae, Orthomyxoviridae, Peribunyaviridae, Phenuiviridae, Reoviridae, Rhabdoviridae, and Togaviridae—all RNA viruses.
- Arthropod-borne viruses infect the vector after a blood meal from a viremic vertebrate (usually nonhuman); after spreading throughout the vector and ultimately reaching the salivary glands, the viruses can be transmitted to another vertebrate during a blood meal.

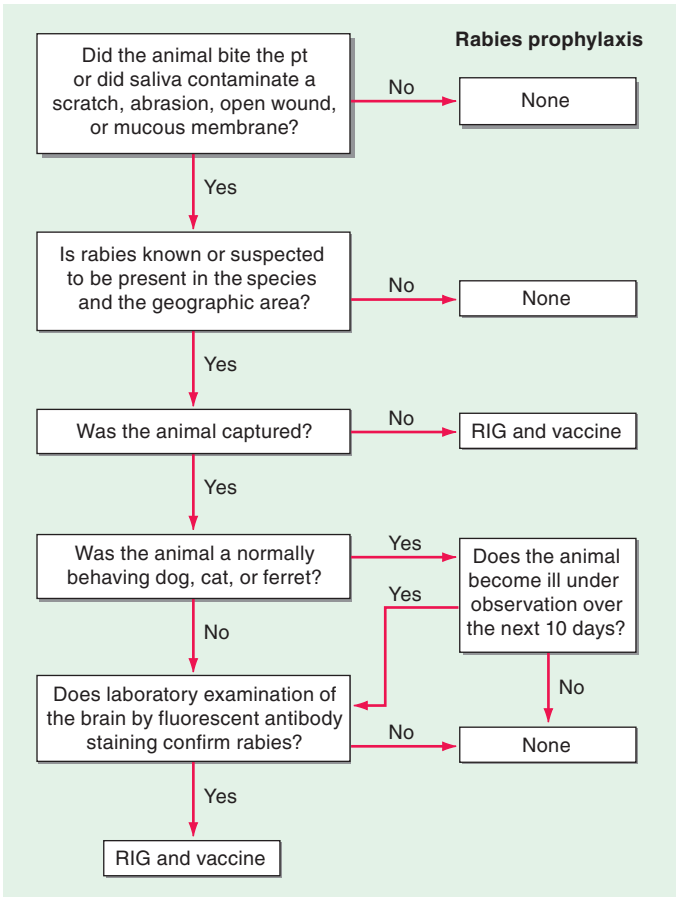


FIGURE 106-1 Algorithm for rabies postexposure prophylaxis. RIG, rabies immune globulin. (From L Corey, in *Harrison's Principles of Internal Medicine*, 15th ed. E Braunwald et al [eds]: New York, McGraw-Hill, 2001; adapted with permission.)

- Humans become infected with rodent-borne viruses by inhalation of aerosols containing the viruses and through close contact with chronically infected rodents and their excreta.

■ CLINICAL MANIFESTATIONS

Infection is usually subclinical. When disease does occur, it generally does so in one of five occasionally overlapping clinical syndromes: fever and myalgia, encephalitis, arthritis and rash, pulmonary disease, or viral hemorrhagic fever (VHF).

Fever and Myalgia

This is the most common syndrome associated with zoonotic viruses. Typically, pts have an acute onset of fever, chills, severe myalgia, malaise, and headache; true arthritis is not found. Complete recovery after 2–5 days of illness is usual. Important examples include the following.

- *Lymphocytic choriomeningitis (LCM)*: This infection is transmitted from chronically infected mice and pet hamsters via aerosols of excreta and secretions. About one-fourth of infected pts have a 3- to 6-day febrile phase, a brief remission, and then recurrent fever, severe headache, nausea, vomiting, and meningeal signs lasting ~1 week.
 - Other manifestations include transient alopecia, arthritis, pharyngitis, cough, maculopapular rash, and orchitis.
 - Pregnant women can have mild infection yet pass on the virus to the fetus, who can develop hydrocephalus, microcephaly, and/or chorioretinitis.
 - The diagnosis should be considered when an adult has aseptic meningitis and any of the following applies: autumn seasonality, a well-marked febrile prodrome, a low CSF glucose level, or CSF mononuclear cell counts >1000/ μ L.
 - LCM viremia is most likely in the initial febrile phase of illness. LCM can also be diagnosed by IgM-capture ELISA of serum or CSF or by RT-PCR of CSF.
- *Dengue*: With ~390 million cases annually, dengue is probably the most important arthropod-borne viral disease worldwide. The four serotypes of dengue virus are all transmitted by the mosquito *Aedes aegypti*, which is also a vector for yellow fever. After an incubation period of 4–7 days, pts experience the sudden onset of fever, frontal headache, retroorbital pain, back pain, severe myalgia (*break-bone fever*), adenopathy, palatal vesicles, and scleral injection.
 - The illness usually lasts 1 week, and a maculopapular rash often appears near the time of defervescence (usually on day 3–5).
 - A second infection with a different dengue serotype can lead to severe dengue (previously called *dengue hemorrhagic fever*; see “Hemorrhagic Fever,” next).
 - The diagnosis is made by IgM ELISA or paired serologic tests during recovery or by antigen-detection ELISA or RT-PCR during the acute phase. Virus is easily isolated from blood during the acute phase by inoculation of mosquitoes or mosquito cell culture. Leukopenia, thrombocytopenia, and increased serum aminotransferase levels may be documented.
- *Zika virus disease*: Zika virus was originally discovered in Uganda in 1947, with only 14 cases identified prior to 2007. Since then, there have been several outbreaks throughout Southeast Asia and the South Pacific as well as a larger worldwide epidemic that started in Brazil in 2015. Human infections are typically asymptomatic or benign and self-resolving, with characteristic low-grade fever, headache, malaise, nonpurulent conjunctivitis, myalgia, and arthralgia. In the most recent outbreak, Zika virus infection has been associated with congenital infections (resulting in microcephaly and neurologic birth defects) and Guillain-Barré syndrome. Although most human infections are transmitted by infected female mosquitoes, transmission also occurs perinatally or via sexual intercourse, breastfeeding, or transfusion of blood products.

Encephalitis

Depending on the causative virus, the ratio of clinical to subclinical disease, the mortality rate, and residua vary widely. The pt usually presents with a prodrome of nonspecific signs and symptoms (e.g., fever, abdominal pain, sore throat, respiratory signs) that is followed quickly by headache, meningeal signs, photophobia, and vomiting; involvement of deeper structures leads to lethargy, cognitive deficits, focal neurologic signs, and coma. Acute encephalitis usually lasts from a few days to 2–3 weeks, and recovery may be slow and incomplete. Treatable causes of encephalitis (e.g., HSV) should be ruled out promptly. Some important examples of arboviral encephalitides follow.

- *Japanese encephalitis*: This infection is present throughout Asia and the western Pacific islands. A Parkinsonian presentation and seizures are typical in severe

cases. An effective vaccine (ideally given on days 0 and 28, with the second dose administered ≥ 1 week prior to travel) is available and is indicated for summer travelers to rural Asia, where the risk can be as high as 1 case per 5000 travelers per week.

- *West Nile encephalitis*: Present throughout the Western Hemisphere and now the leading cause of arboviral encephalitis in the United States, West Nile virus is a common cause of febrile disease without CNS infection, but it occasionally causes aseptic meningitis or encephalitis. Encephalitis, serious sequelae, and death are more common among elderly pts, diabetic and hypertensive pts, and pts with previous CNS disease. Unusual clinical features include chorioretinitis, flaccid paralysis, and initial presentation with focal neurologic deficits.
- *Eastern equine encephalitis (EEE)*: EEE occurs primarily within endemic swampy foci along the eastern coast of the United States during the summer and early fall. EEE is one of the most severe arboviral diseases and is characterized by rapid onset, rapid progression, high mortality risk (50–75%), and frequent residua. PMN-predominant pleocytosis of the CSF within the first 1–3 days of disease is an indication of severity.

Arthritis and Rash

Alphaviruses are common causes of arthritis accompanied by a febrile illness and maculopapular rash, usually during the summer in temperate climates. Examples include the following.

- *Sindbis virus*: Found in northern Europe and southern Africa, this virus, which has an incubation period of < 1 week, causes a maculopapular rash that often vesiculates on the trunk and extremities. The arthritis of this condition is multiarticular, migratory, and incapacitating, with resolution of the acute phase in a few days; joint pain may persist for months or years.
- *Chikungunya virus*: Found primarily in Africa, Asia, and the Caribbean, this virus has an incubation period of 2–10 days and results in the abrupt onset of fever, severe arthralgias, migratory polyarthritis mainly affecting small joints, and a rash that begins coincident with defervescence at day 2–3 of illness.
- *Barmah Forest and Ross River viruses*: As causes of epidemic polyarthritis in Australia and the eastern Pacific Islands, these viruses produce a rash and disabling symmetrical joint pain, typically in the absence of other prominent constitutional symptoms, after an incubation period of 7–9 days. Because of joint pain, only ~50% and 90% of pts can resume normal activities at 4 weeks and 3 months, respectively. However, 55–75% of infected pts are asymptomatic.

Pulmonary Disease

After a prodrome (e.g., fever, malaise, myalgias, GI disturbances) of ~3–4 days, pts with hantavirus (cardio)pulmonary syndrome [H(C)PS] enter a cardiopulmonary phase marked by tachycardia, tachypnea, and mild hypotension. Over the next few hours, the illness may rapidly progress to severe hypoxemia and respiratory failure; the mortality rate is ~30–40% with good management. Pts surviving the first 2 days of hospitalization usually recover with no residua.

- The disease is linked to rodent exposure. Sin Nombre virus infects the deer mouse and is the most important virus causing H(C)PS in the United States.
- Thrombocytopenia (an important early clue), hemoconcentration, proteinuria, and hypoalbuminemia are typical.
- IgM testing of acute-phase serum may give positive results, even during the prodromal stage, and can confirm the diagnosis. RT-PCR of blood clots or tissue usually gives a positive result in the first 7–9 days of illness.
- Treatment is nonspecific and requires intensive respiratory management and other supportive measures.

Viral Hemorrhagic Fever

The VHF syndrome is a constellation of findings based on vascular instability and decreased vascular integrity. All VHF syndromes begin with the abrupt onset of fever and myalgia and can progress to severe prostration, headache, dizziness, photophobia, abdominal and/or chest pain, anorexia, and GI disturbances. On initial physical examination, there is conjunctival suffusion, muscular or abdominal tenderness to palpation, hypotension, petechiae, and periorbital edema. Laboratory examination usually reveals elevated serum aminotransferase levels, proteinuria, and hemoconcentration. Shock, multifocal bleeding, and CNS involvement (encephalopathy, coma, convulsions) are poor prognostic signs. Early recognition is important; appropriate supportive measures and, in some cases, virus-specific therapy can be instituted.

- *Lassa fever*: Endemic and epidemic in West Africa, Lassa fever has a more gradual onset than other VHF syndromes. Bleeding is evident in 15–30% of cases. A maculopapular rash is often noted in light-skinned pts with Lassa fever.
 - Pregnant women have higher mortality rates, and the fetal death rate is ~90%.
 - Pts with high-level viremia or a serum aspartate aminotransferase level of >150 IU/mL are at an elevated risk of death. The administration of ribavirin (32 mg/kg IV \times 1 dose, followed by 16 mg/kg q6h for 4 days and then 8 mg/kg q8h for 6 days), which appears to reduce this risk, should be considered.
- *Junin/Argentinian and Machupo/Bolivian HF syndromes*: These syndromes resemble Lassa fever; however, thrombocytopenia, bleeding, and CNS dysfunction (e.g., confusion, cerebellar signs) are common.
 - Passive antibody treatment for Junin/Argentinian HF is effective, and an effective vaccine exists.
 - Ribavirin at the doses recommended for Lassa fever is likely to be effective in all South American VHF syndromes.
- *Rift Valley fever*: Although Rift Valley fever virus typically causes fever and myalgia, VHF can occur with prominent liver involvement, renal failure, and probably DIC.
 - Retinal vasculitis can occur in ~10% of otherwise mild infections, and pts' vision can be permanently impaired.
 - There is no proven therapy for Rift Valley fever. A live attenuated vaccine is in trials.
- *HF with renal syndrome (HFRS)*: This entity is most often caused in Europe by Puumala virus, in the Balkans by Dobrava-Belgrade virus, and in eastern Asia by Hantaan virus.
 - Severe cases of HFRS evolve in identifiable stages: the *febrile* stage with myalgia, lasting 3 or 4 days; the *hypotensive* stage, often associated with shock and lasting from a few hours to 48 h; the *oliguric* stage with renal failure, lasting 3–10 days; and the *polyuric* stage with diuresis and hyposthenuria.
 - Infections with Puumala virus result in a much-attenuated picture but the same general presentation.
 - IgM-capture ELISA is positive within 2 days of admission and confirms the diagnosis.
 - The mainstay of therapy is expectant management of shock and renal failure. Ribavirin may reduce rates of mortality and morbidity in severe cases if treatment is begun within the first 4 days of illness.
- *Yellow fever*: A former cause of major epidemics, yellow fever causes a typical VHF syndrome with prominent hepatic necrosis, most commonly in urban South America and Africa. Pts are viremic for 3–4 days and can have jaundice,

hemorrhage, black vomit, anuria, and terminal delirium. Vaccination of visitors to endemic areas and control of the mosquito vector *A. aegypti* prevent disease.

- **Severe dengue:** Previous infection with a heterologous dengue virus serotype may elicit nonprotective antibodies and exacerbate disease if pts are reinfectd. In mild cases, lethargy, thrombocytopenia, and hemoconcentration occur 2–5 days after typical dengue fever, usually at the time of defervescence. In severe cases, frank shock occurs, with cyanosis, hepatomegaly, ascites and pleural effusions, and GI bleeding. The period of shock lasts 1–2 days.
 - The risk decreases considerably after age 12. Severe dengue is more common among females than among males, among whites than among blacks, and among well-nourished than among malnourished persons; it is also more common if dengue virus 1—as opposed to dengue virus 4—precedes infection with dengue virus 2.
 - With good care, the overall mortality rate is as low as 1%. Control of *A. aegypti*, the mosquito vector, is the key to control of the disease.

EBOLA AND MARBURG VIRUS INFECTIONS

■ MICROBIOLOGY

The family Filoviridae contains two genera, *Marburgvirus* and *Ebolavirus*, that consist of negative-sense, single-strand RNA viruses capable of infecting humans. *Ebolavirus* has five species named for their original sites of recognition, and *Marburgvirus* has two species.

- Both Marburg virus and Ebola virus are biosafety level 4 pathogens because of high mortality rates (except for Reston virus, an Ebola virus, which is non-pathogenic for humans) and aerosol infectivity.

■ EPIDEMIOLOGY

- Filoviruses pathogenic for humans are exclusively endemic to Equatorial Africa.
- As of October 2017, there had been 31,602 human filovirus infections and 13,350 deaths (mortality rate, 41.7%), the overwhelming majority of which occurred during an outbreak in 2014–2015.
- Since the discovery of filoviruses in 1967, there have been ~50 natural host-to-human spillover events. Bats are thought to be the reservoir for Marburg and Ebola viruses.
- Human-to-human transmission occurs through direct contact or exposure to infected bodily fluids and tissues; there is no evidence of such transmission by aerosol or respiratory droplets.

■ PATHOGENESIS

The pathogenic hallmarks of filovirus infection include pronounced suppression of the immune system, severe disturbance of the clotting system, and impairment of vascular integrity. Although petechiae, ecchymoses, and other hemorrhagic signs are detected in internal organs, mucous membranes, and skin, actual severe blood loss is a rare event.

■ CLINICAL MANIFESTATIONS

After a 3- to 25-day incubation period, pts develop a biphasic syndrome with a 1- to 2-day relative remission separating the two phases.

- The first phase lasts 5–7 days and is characterized by an abrupt onset of fever, chills, severe headache, cough, myalgia, pharyngitis, and arthralgia and the development of a maculopapular rash.

- The second phase involves the GI tract (e.g., abdominal pain, vomiting, diarrhea), respiratory tract (e.g., chest pain, cough), vascular system (e.g., postural hypotension, edema), CNS (e.g., confusion, headache, coma), and hemorrhagic manifestations.
- Early leukopenia followed by leukocytosis with a left shift, thrombocytopenia, elevated levels of liver enzymes, and prolonged coagulation is common.
- Pts typically die 4–14 days after infection. Survivors may have prolonged and incapacitating sequelae (e.g., arthralgia, asthenia, iridocyclitis, hearing loss, psychosis, transverse myelitis).
- Filoviruses can persist in the liver, eyes, or testicles of survivors for months after convalescence and can be reactivated (causing recurrent disease) or transmitted sexually.

■ DIAGNOSIS

High concentrations of virus in blood can be documented by antigen-capture ELISA, virus isolation, or RT-PCR. Other diagnoses that must be excluded (as they closely mimic infection with Ebola or Marburg virus) include other VHFs (particularly yellow fever), falciparum malaria, typhoid fever, and gram-negative septicemia.

TREATMENT

Ebola and Marburg Virus Infections

- Any treatment must be administered under increased safety precautions by experienced specialists using appropriate personal protective equipment (e.g., gowns, gloves, shoe covers, face shields) to prevent further transmission.
- Treatment of filovirus infections is entirely supportive as no efficacious virus-specific therapy is available.
- Several experimental therapies, including a monoclonal antibody cocktail (ZMapp) and vaccines, are currently being evaluated and have demonstrated some promise in small-scale studies.

107 HIV Infection and AIDS



■ DEFINITION

AIDS was originally defined empirically by the Centers for Disease Control and Prevention (CDC) as “the presence of a reliably diagnosed disease that is at least moderately indicative of an underlying defect in cell-mediated immunity in the absence of any known cause for such a defect.” Following the recognition of the causative virus, HIV, and the development of sensitive and specific tests for HIV infection, the definition of AIDS has undergone substantial revision. The current surveillance definition categorizes HIV-infected persons on the basis of clinical conditions associated with HIV infection and CD4+ T lymphocyte counts (Tables 197-1, and 197-2, pp. 1394, in HPIM-20). From a practical standpoint, the clinician should view HIV disease as a spectrum of disorders ranging from primary infection, with or without the acute HIV syndrome, to the asymptomatic infected state, to advanced disease characterized by opportunistic infections and neoplasms.

■ ETIOLOGY AND TRANSMISSION

AIDS is caused by infection with the human retroviruses HIV-1 or 2. HIV-1 is the most common cause worldwide. These viruses are passed through sexual contact; through transfusion of contaminated blood or blood products; through sharing of contaminated needles and syringes among injection drug users (IDUs); intrapartum or perinatally from mother to infant; or via breast milk. There is a definite, though small, occupational risk of infection for health care workers and laboratory personnel who work with HIV-infected specimens, usually through injury from contaminated sharp instruments. The risk of transmission of HIV from an infected health care worker to his or her pts through invasive procedures is extremely low.

■ EPIDEMIOLOGY

As of November 1, 2017, an estimated 1.8 million people have been infected with HIV and 1.1 million people are currently living with HIV in the United States; approximately 13% of these individuals are unaware that they are infected. Approximately 693,000 people with an AIDS diagnosis have died. However, the death rate from AIDS has decreased substantially over the past two decades, primarily due to the increased use of effective antiretroviral drugs. An estimated 40,000 individuals are newly infected each year in the United States; this figure has remained stable for at least 15 years. Among adults and adolescents newly diagnosed with HIV infection in 2017, ~80% were men and ~20% were women. Of new HIV/AIDS diagnoses, 68% were due to male-to-male sexual contact, 23% to heterosexual contact, and 6% to IDUs. HIV infection/AIDS is a global pandemic, especially in developing countries. At the end of 2017, the estimated number of cases of HIV infection worldwide was ~36.9 million, more than two-thirds of which were in sub-Saharan Africa; ~47% of cases were in women and 2.6 million were in children. In 2017, there were 1.8 million new HIV infections worldwide and 940,000 deaths.

■ PATHOPHYSIOLOGY AND IMMUNOPATHOGENESIS

The hallmark of HIV disease is a profound immunodeficiency resulting from a progressive quantitative and qualitative deficiency of the subset of T lymphocytes referred to as *helper T cells* that are defined phenotypically by the expression on the cell surface of the CD4 molecule, which serves as the primary cellular receptor for HIV. A co-receptor must be present with CD4 for efficient entry of HIV-1 into target cells. The two major co-receptors for HIV-1 are the chemokine receptors CCR5 and CXCR4. The CD4+ T lymphocyte and less so cells of monocyte lineage are the principal cellular targets of HIV.

Primary Infection

Following initial transmission, the virus infects CD4+ cells, predominantly T lymphocytes, but also monocytes, or bone marrow-derived dendritic cells. Both during this initial stage and later in infection, the lymphoid system is a major site for the establishment and propagation of HIV infection. The gut-associated lymphoid tissue (GALT) plays a role in the establishment of infection and in the early depletion of memory CD4+ T cells.

Essentially all pts undergo a viremic stage during primary infection; in some pts this is associated with the “acute retroviral syndrome,” a mononucleosis-like illness (see below). This phase is important in disseminating virus to lymphoid and other organs throughout the body, and viral replication is ultimately contained only partially by the development of an HIV-specific immune response.

Establishment of Chronic and Persistent Infection

Despite the robust immune response that is mounted following primary infection, the virus is not cleared from the body. Instead, a chronic infection develops that persists for a median time of 10 years before the untreated pt becomes

clinically ill. During this period of clinical latency, the number of CD4+ T cells gradually declines, and few if any clinical signs and symptoms may be evident. However, active viral replication can almost always be detected as plasma viremia and in lymphoid tissue. The level of steady-state viremia (referred to as the *viral set point*) at ~6 months to 1 year post-infection has important prognostic implications for the progression of HIV disease; individuals with a low viral set point at 6 months to 1 year after infection progress to AIDS more slowly than do those whose set point is very high at this time (Fig. 197-22, p. 1410, in HPIM-20).

Advanced HIV Disease

In untreated pts or in pts in whom therapy has not controlled viral replication (see next), after some period of time (often years), CD4+ T cell counts will fall below a critical level (~200/ μ L) and pts become highly susceptible to opportunistic diseases. The presence of a CD4+ T cell count <200/ μ L or an AIDS-defining opportunistic disease establishes a diagnosis of AIDS. Control of plasma viremia by effective antiretroviral therapy, particularly maintaining the plasma viral load consistently at <50 copies of RNA per mL, even in individuals with low CD4+ T cell counts, has dramatically increased survival in these pts, including those whose CD4+ T cell counts may not increase significantly as a result of therapy.

■ IMMUNE ABNORMALITIES IN HIV DISEASE

A broad range of immune abnormalities has been documented in HIV-infected pts, resulting in varying degrees of immunodeficiency. These include both quantitative and qualitative defects in lymphocytes, and qualitative defects in monocyte/macrophage and natural killer (NK) cell function. Autoimmune phenomena also have been observed.

■ IMMUNE RESPONSE TO HIV INFECTION

Both humoral and cellular immune responses to HIV develop soon after primary infection (see summary in Table 197-7 and Fig. 197-27, p. 1422, in HPIM-20). Humoral responses include antibodies with HIV binding and neutralizing activity, as well as antibodies participating in antibody-dependent cellular cytotoxicity (ADCC). Cellular immune responses include the generation of HIV-specific CD4+ and CD8+ T lymphocytes, as well as NK cells and mononuclear cells mediating ADCC. CD8+ T lymphocytes may also suppress HIV replication in a noncytolytic, non-MHC-restricted manner. This effect is mediated by soluble factors such as the CC-chemokines RANTES (CCL5), MIP-1 α (CCL3), and MIP-1 β (CCL4). For the most part, the natural immune response to HIV is not adequate. Broadly reacting neutralizing antibodies against HIV are not easily generated in infected individuals, and eradication of the virus from infected individuals by naturally occurring immune responses has not been reported.

■ DIAGNOSIS OF HIV INFECTION

Laboratory diagnosis of HIV infection depends on the demonstration of anti-HIV antibodies and/or the detection of HIV or one of its components.

The standard screening test for HIV infection is the detection of anti-HIV antibodies using an enzyme immunoassay (EIA). This test is highly sensitive (>99.5%) and is quite specific. Most commercial EIA kits are able to detect antibodies to both HIV-1 and 2 and many also detect the HIV core antigen p24. The Western blot detects antibodies to HIV antigens of specific molecular weights. Antibodies to HIV begin to appear within 2 weeks of infection, and the period of time between initial infection and the development of detectable antibodies is rarely >3 months. Plasma p24 antigen levels rise during the first few weeks following infection, prior to the appearance of anti-HIV antibodies. A guideline for the use of these serologic tests in the diagnosis of HIV infection is depicted in Fig. 107-1.

HIV can be cultured directly from peripheral blood cells, plasma, or tissue, but this is most commonly done in a research setting. HIV genetic material can be

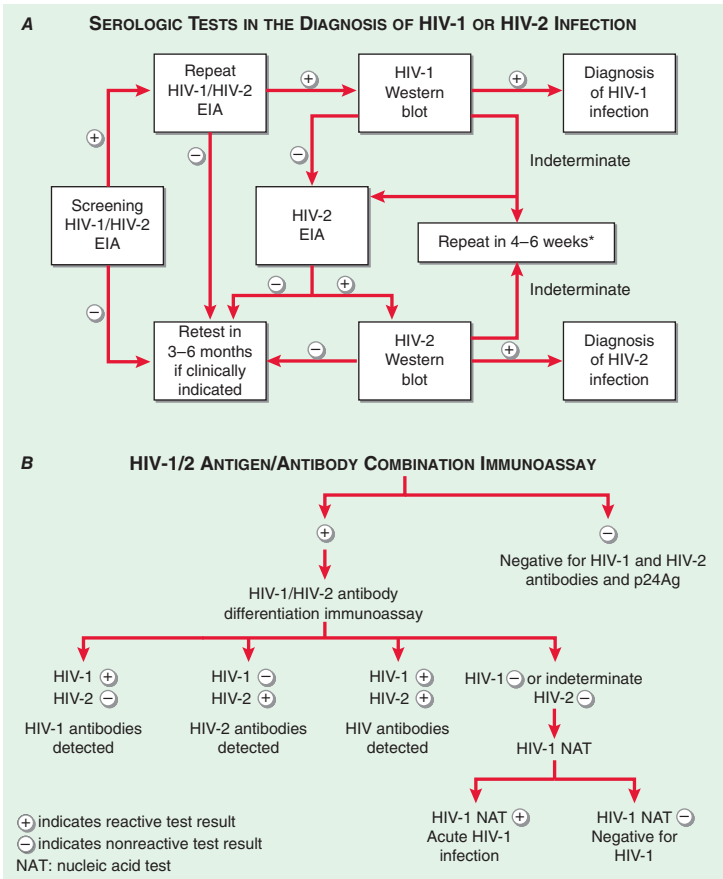


FIGURE 107-1 Serologic tests for the diagnosis of HIV-1 or HIV-2 infection. A. Algorithm including the use of a Western blot. *Stable indeterminate Western blot 4–6 weeks later makes HIV infection unlikely. However, it should be repeated twice at 3-month intervals to rule out HIV infection. Alternatively, one may test for HIV-1 p24 antigen or HIV RNA. EIA, enzyme immunoassay. **B.** CDC algorithm not including the use of a Western blot. (Adapted from CDC Stacks: Quick reference guide—Laboratory testing for the diagnosis of HIV infection: updated recommendations 2014. Available from <https://stacks.cdc.gov/view/cdc/23446>.)

detected using reverse transcriptase PCR (RT-PCR), branched DNA (bDNA), or nucleic acid sequence–based assay (NASBA). These tests are useful in pts with a positive or indeterminate EIA and an indeterminate Western blot. Such tests turn positive early in infection and will usually be positive in pts in whom serologic testing may be unreliable (such as those with hypogammaglobulinemia).

■ LABORATORY MONITORING OF PTS WITH HIV INFECTION

Measurement of the CD4+ T cell count and level of plasma HIV RNA are important components of the routine evaluation and monitoring of HIV-infected individuals. The CD4+ T cell count is a generally accepted indicator of the immunologic

competence of the pt with HIV infection, and there is a close relationship between the CD4+ T cell count and the clinical manifestations of AIDS (Fig. 197-32, p. 1428, in HPIM-20). Pts with CD4+ T cell counts $<200/\mu\text{L}$ are at higher risk of infection with *Pneumocystis jiroveci*. Once the count declines to $<50/\mu\text{L}$, pts are also at higher risk for developing cytomegalovirus (CMV) disease and infection with *Mycobacterium avium intracellulare*. Pts should have their CD4+ T cell count measured at the time of diagnosis and every 3–6 months thereafter. (Measurements may be done more frequently with declining counts.) While the CD4+ T cell count provides information on the current immunologic status, the HIV RNA level predicts what will happen to the CD4+ T cell count in the near future. Measurements of plasma HIV RNA levels should be made at the time of HIV diagnosis and every 3–4 months thereafter in the untreated pt. Measurement of plasma HIV RNA is also useful in making therapeutic decisions about antiretroviral therapy (see next). Following the initiation of therapy or any change in therapy, HIV RNA levels should be monitored approximately every 4 weeks until the effectiveness of the therapeutic regimen is determined, ideally by achieving an undetectable plasma viral load. During therapy, levels of HIV RNA should be monitored every 3–6 months to evaluate the continuing effectiveness of therapy.

The sensitivity of an individual's HIV virus(es) to different antiretroviral agents can be tested by either genotypic or phenotypic assays. In the hands of experts, the use of resistance testing to select a new antiretroviral regimen in pts failing their current regimen leads to a -0.5-log greater decline in viral load compared with the efficacy of regimens selected solely on the basis of drug history. HIV resistance testing may also be of value in selecting an initial treatment regimen in geographic areas with a high prevalence of baseline resistance.

■ CLINICAL MANIFESTATIONS OF HIV INFECTION

A complete discussion is beyond the scope of this short chapter; however, the major clinical features of the various stages of HIV infection are summarized next (see also Chap. 197, HPIM-20).

Acute HIV (Retroviral) Syndrome

Approximately 50–70% of infected individuals experience an acute syndrome following primary infection. The acute syndrome follows infection by 3–6 weeks. It can have multiple clinical features (Table 107-1), lasts 1–2 weeks, and resolves spontaneously as an immune response to HIV develops and the viral load diminishes from its peak levels. Most pts will then enter a phase of clinical latency, although occasionally rapidly progressive immunologic and clinical deterioration occurs.

TABLE 107-1 Clinical Findings in the Acute HIV Syndrome

General	Neurologic
Fever	Meningitis
Pharyngitis	Encephalitis
Lymphadenopathy	Peripheral neuropathy
Headache/retroorbital pain	Myelopathy
Arthralgias/myalgias	Dermatologic
Lethargy/malaise	Erythematous maculopapular rash
Anorexia/weight loss	Mucocutaneous ulceration
Nausea/vomiting/diarrhea	

Source: From Tindall B, Cooper DA: Primary HIV infection: Host responses and intervention strategies. AIDS 5:1, 1991.

Asymptomatic Infection

The length of time between HIV infection and development of disease in untreated individuals varies greatly; however, the median is estimated to be 10 years. HIV disease with active viral replication usually progresses during this asymptomatic period, and, in the absence of combination antiretroviral therapy (cART) CD4+ T cell counts invariably fall. The rate of disease progression is directly correlated with plasma HIV RNA levels. Pts with high levels of HIV RNA progress to symptomatic disease faster than do those with low levels of HIV RNA.

Symptomatic Disease

Symptoms of HIV disease can develop at any time during the course of HIV infection. In general, the spectrum of illness changes as the CD4+ T cell count declines. The more severe and life-threatening complications of HIV infection occur in pts with CD4+ T cell counts <200/ μ L. Overall, the clinical spectrum of HIV disease is constantly changing as individuals live longer and new and better approaches to treatment and prophylaxis of opportunistic infections are developed. In addition, a variety of neurologic, cardiovascular, renal, metabolic, and hepatic problems are increasingly seen associated with HIV infection and may be a direct consequence of HIV infection. The key element to treating symptomatic complications of HIV disease, whether primary or secondary, is achieving good control of HIV replication through the use of cART and instituting primary and secondary prophylaxis as indicated. Major clinical syndromes seen in the symptomatic stage of HIV infection are summarized below.

- *Persistent generalized lymphadenopathy*: Palpable adenopathy at two or more extrainguinal sites that persists for >3 months without explanation other than HIV infection. Many pts will go on to disease progression.
- *Constitutional symptoms*: Fever persisting for >1 month, involuntary weight loss of >10% of baseline, diarrhea for >1 month in absence of explainable cause.
- *Neurologic disease*: Most common is HIV-associated neurocognitive disease (HAND); other neurologic complications include opportunistic infections such as toxoplasmosis and cryptococcal meningitis, primary CNS lymphoma, CNS Kaposi's sarcoma, aseptic meningitis, myelopathy, peripheral neuropathy, and myopathy.
- *Secondary infectious diseases*: Common secondary infectious agents include *P. jiroveci* (pneumonia), CMV (chorioretinitis, colitis, pneumonitis, adrenalitis), *Candida albicans* (oral thrush, esophagitis), *M. avium intracellulare* (localized or disseminated infection), *M. tuberculosis* (pulmonary or disseminated), *Cryptococcus neoformans* (meningitis, disseminated disease), *Toxoplasma gondii* (encephalitis, intracerebral mass lesion), herpes simplex virus (severe mucocutaneous lesions, esophagitis), *Cryptosporidium* spp. or *Isospora belli* (diarrhea), JC virus (progressive multifocal leukoencephalopathy), bacterial pathogens (pneumonia, sinusitis, skin).
- *Secondary neoplasms*: Kaposi's sarcoma (cutaneous and visceral, more fulminant course than in non-HIV-infected pts), lymphoma (primarily B cell, may be CNS or systemic). Kaposi's sarcoma, body cavity lymphomas and multicentric Castleman's disease are associated with HHV-8 infection while the B cell lymphomas are often associated with EBV.
- *Other diseases*: A variety of organ-specific syndromes can be seen in HIV-infected individuals, either as primary manifestations of the HIV infection or as complications of treatment. Diseases commonly associated with aging are also seen with an increased frequency in HIV infection.

TREATMENT**HIV Infection (See also Chap. 197, HPIM-20)**

General principles of pt management include counseling, psychosocial support, and screening for infections and other conditions and require comprehensive knowledge of the disease processes associated with HIV infection.

ANTIRETROVIRAL THERAPY (SEE TABLE 107-2)

The cornerstone of medical management of HIV infection is combination antiretroviral therapy, or cART. Suppression of HIV replication is an important component in prolonging life as well as in improving the quality of life of pts with HIV infection. Data from observational studies and randomized controlled trials have demonstrated that with few exceptions cART should be administered to everyone who is HIV infected and that it is also associated with a profoundly decreased risk of transmitting infection to an uninfected partner. However, several important questions related to the treatment of HIV disease lack definitive answers. Among them are what is the best initial cART regimen, when should a given regimen be changed, and which drugs in a regimen should be changed when a change is made. Currently available treatment guidelines facilitate these choices (see below). The drugs that are currently licensed for the treatment of HIV infection are listed in Table 107-2. These drugs fall into four main categories: those that inhibit the viral reverse transcriptase enzyme, those that inhibit the viral protease enzyme, those that inhibit viral entry, and those that inhibit the viral integrase enzyme. In addition, more than a dozen combination drugs that combine two or more agents have been licensed (Table 107-2A). There are numerous drug–drug interactions that must be taken into consideration when using antiretroviral medications.

Nucleoside/Nucleotide Analogues

These agents act by causing premature DNA-chain termination during the reverse transcription of viral RNA to proviral DNA and should be used in combination with other antiretroviral agents. The most common usage is together with another nucleoside/nucleotide analogue and a nonnucleoside reverse transcriptase inhibitor or a protease inhibitor (see below).

Nonnucleoside Reverse Transcriptase Inhibitors

These agents interfere with the function of HIV-1 reverse transcriptase by binding to regions outside the active site and causing conformational changes in the enzyme that render it inactive. Five members of this class, *nevirapine*, *delavirdine*, *efavirenz*, *etravirine*, and *rilpivirine* are currently available for clinical use. These drugs are licensed for use in combination with other antiretrovirals.

Protease Inhibitors

These drugs are potent and selective inhibitors of the HIV-1 protease enzyme and are active in the nanomolar range. As with other classes of antiretroviral drugs, the protease inhibitors should be used only in combination with other antiretroviral drugs.

HIV Entry Inhibitors

These agents act by interfering with the binding of HIV to its receptor or co-receptor or by interfering with the process of fusion. A variety of small molecules that bind to HIV-1 co-receptors are currently in clinical trials. The first drugs in this class to be licensed are the fusion inhibitor *enfuvirtide* and the entry inhibitor *maraviroc*.

TABLE 107-2 Antiretroviral Drugs Most Commonly Used in the Treatment of HIV Infection

DRUG	STATUS	INDICATION	DOSE IN COMBINATION	SUPPORTING DATA	TOXICITY
Nucleoside or nucleotide reverse transcriptase inhibitors					
Zidovudine (AZT, azidothymidine, *Retrovir, 3'azido-3'-deoxythymidine)	Licensed	Treatment of HIV infection in combination with other antiretroviral agents	200 mg q8h or 300 mg bid	19 vs 1 death in original placebo-controlled trial in 281 pts with AIDS or ARC	Anemia, granulocytopenia, myopathy, lactic acidosis, hepatomegaly with steatosis, headache, nausea, nail pigmentation, lipid abnormalities, lipomatrophy, hyperglycemia
		Prevention of maternal-fetal HIV transmission		In pregnant women with CD4+ T cell count $\geq 200/\mu\text{L}$, AZT PO beginning at weeks 14–34 of gestation plus IV drug during labor and delivery plus PO AZT to infant for 6 weeks decreased transmission of HIV by 67.5% (from 25.5% to 8.3%); $n = 363$	
Lamivudine (EpiVir, 2'3'-dideoxy-3'-thiacytidine, 3TC)	Licensed	In combination with other antiretroviral agents for the treatment of HIV infection	150 mg bid 300 mg qd	In combination with AZT superior to AZT alone with respect to changes in CD4+ T cell counts in 495 pts who were zidovudine-naïve and 477 pts who were zidovudine-experienced; overall CD4+ T cell counts for the zidovudine group were at baseline by 24 weeks, while in the group treated with zidovudine plus lamivudine, they were 10–50 cells/ μL above baseline; 54% decrease in progression to AIDS/death compared with AZT alone	Flare of hepatitis in HBV-co-infected pts who discontinue drug

(Continued)

TABLE 107-2 Antiretroviral Drugs Most Commonly Used in the Treatment of HIV Infection (Continued)

DRUG	STATUS	INDICATION	DOSE IN COMBINATION	SUPPORTING DATA	TOXICITY
Emtricitabine (FTC, Emtriva)	Licensed	In combination with other antiretroviral agents for the treatment of HIV infection	200 mg qd	Comparable to lamivudine in combination with stavudine and nevirapine/efavirenz	Hepatotoxicity in HBV-co-infected pts who discontinue drug, skin discoloration
Abacavir (Ziagen)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents	300 mg bid	Abacavir + AZT + 3TC equivalent to indinavir + AZT + 3TC with regard to viral load suppression (~60% in each group with <400 HIV RNA copies/mL plasma) and CD4+ T cell increase (~100/ μ L in each group) at 24 weeks	Hypersensitivity reaction in HLA-B5701+ individuals (can be fatal); fever, rash, nausea, vomiting, malaise or fatigue, and loss of appetite
Tenofovir disoproxil fumarate (Viread)	Licensed	For use in combination with other antiretroviral agents when treatment is indicated	300 mg qd	Reduction of ~0.6 log in HIV-1 RNA levels when added to background regimen in treatment-experienced pts	Renal, osteomalacia, flare of hepatitis in HBV-co-infected pts who discontinue drug
Tenofovir alafenamide (Vemlidy)	Licensed	In combination with emtricitabine and other antiretroviral agents for treatment of HIV-1 infection	25 mg qd	92% of pts treated in combination with emtricitabine, elvitegravir, and cobicistat had HIV-1 RNA levels <50 copies/mL	Nausea, less renal toxicity than tenofovir disoproxil fumarate

Non-nucleoside reverse transcriptase inhibitors					
Nevirapine (Viramune)	Licensed	In combination with other antiretroviral agents for treatment of progressive HIV infection	200 mg/d × 14 days then 200 mg bid or 400 mg extended release qd	Increase in CD4+ T cell count, decrease in HIV RNA when used in combination with nucleosides	Skin rash, hepatotoxicity
Efavirenz (Sustiva)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents	600 mg qhs	Efavirenz + AZT + 3TC comparable to indinavir + AZT + 3TC with regard to viral load suppression (a higher percentage of the efavirenz group achieved viral load <50 copies/mL, but the discontinuation rate in the indinavir group was unexpectedly high, accounting for most treatment “failures”); CD4 cell increase (~140/μL in each group) at 24 weeks	Rash, dysphoria, elevated liver function tests, drowsiness, abnormal dreams, depression, lipid abnormalities, potentially teratogenic
Etravirine (Intelence)	Licensed	In combination with other antiretroviral agents in treatment-experienced pts whose HIV is resistant to nonnucleoside reverse transcriptase inhibitors and other antiretroviral medications	200 mg bid	Higher rates of HIV RNA suppression to <50 copies/mL (56% vs 39%); greater increases in CD4+ T cell count (89 vs 64 cells) compared to placebo when given in combination with an optimized background regimen	Rash, nausea, hypersensitivity reactions

(Continued)

TABLE 107-2 Antiretroviral Drugs Most Commonly Used in the Treatment of HIV Infection (Continued)

DRUG	STATUS	INDICATION	DOSE IN COMBINATION	SUPPORTING DATA	TOXICITY
Rilpivirine (Edurant)	Licensed	In combination with other drugs in previously untreated pts when treatment is indicated	25 mg qd	Noninferior to efavirenz with respect to suppression at week 48 in 1368 treatment-naïve individuals, except in pts with pretherapy HIV RNA levels >100,000 where it was inferior	Nausea, dizziness, somnolence, vertigo, less CNS toxicity, and rash than efavirenz
Protease inhibitors					
Ritonavir (Norvir)	Licensed	In combination with other antiretroviral agents for treatment of HIV infection when treatment is warranted	600 mg bid (also used in lower doses as pharmacokinetic booster)	Reduction in the cumulative incidence of clinical progression or death from 34% to 17% in pts with CD4+ T cell count <100/μL treated for a median of 6 months	Nausea, abdominal pain, hyperglycemia, fat redistribution, lipid abnormalities, may alter levels of many other drugs, paresthesias, hepatitis
Atazanavir (Reyataz)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents	400 mg qd or 300 mg qd + ritonavir 100 mg qd when given with efavirenz	Comparable to efavirenz when given in combination with AZT + 3TC in a study of 810 treatment-naïve pts; comparable to nelfinavir when given in combination with stavudine + 3TC in a study of 467 treatment-naïve pts	Hyperbilirubinemia, PR prolongation, nausea, vomiting, hyperglycemia, fat maldistribution, rash transaminase elevations, renal stones
Darunavir (Prezista)	Licensed	In combination with 100 mg ritonavir for combination therapy in treatment-experienced adults	600 mg + 100 mg ritonavir twice daily with food	At 24 weeks, pts with prior extensive exposure to antiretrovirals treated with a new combination including darunavir showed a -1.89-log change in HIV RNA levels and a 92-cell increase in CD4+ T cells compared with -0.48 log and 17 cells in the control arm	Diarrhea, nausea, headache, skin rash, hepatotoxicity, hyperlipidemia, hyperglycemia

Entry inhibitors					
Enfuvirtide (Fuzeon)	Licensed	In combination with other agents in treatment-experienced pts with evidence of HIV-1 replication despite ongoing anti-retroviral therapy	90 mg SC bid	In treatment of experienced pts, superior to placebo when added to new optimized background (37% vs 16% with <400 HIV RNA copies/mL at 24 weeks; + 71 vs + 35 CD4+ T cells at 24 weeks)	Local injection reactions, hypersensitivity reactions, increased rate of bacterial pneumonia
Maraviroc (Selzentry)	Licensed	In combination with other antiretroviral agents in adults infected with only CCR5-tropic HIV-1	150–600 mg bid depending on concomitant medications (see text)	At 24 weeks, among 635 pts with CCR5-tropic virus and HIV-1 RNA >5000 copies/mL despite at least 6 months of prior therapy with at least 1 agent from 3 of the 4 antiretroviral drug classes, 61% of pts randomized to maraviroc achieved HIV RNA levels <400 copies/mL compared with 28% of pts randomized to placebo	Hepatotoxicity, nasopharyngitis, fever, cough, rash, abdominal pain, dizziness, musculoskeletal symptoms
Ibalizumab (Trogarzo)	Licensed	In combination with other antiretroviral agents in pts with multidrug-resistant HIV-1	Single loading dose of 2000 mg followed by a maintenance dose of 800 mg every 2 weeks	At 25 weeks, 50% of pts with multi-drug resistant HIV-1 with HIV-1 RNA >1000 copies/mL treated with an optimized background of 1 active drug and ibalizumab achieved HIV RNA levels <200 copies/mL	Rash, diarrhea, nausea
Integrase inhibitor					
Raltegravir (Isentress)	Licensed	In combination with other antiretroviral agents	400 mg bid	At 24 weeks, among 436 pts with 3-class drug resistance, 76% of pts randomized to receive raltegravir achieved HIV RNA levels <400 copies/mL compared with 41% of pts randomized to receive placebo	Nausea, headache, diarrhea, CPK elevation, muscle weakness, rhabdomyolysis

(Continued)

TABLE 107-2 Antiretroviral Drugs Most Commonly Used in the Treatment of HIV Infection (Continued)

DRUG	STATUS	INDICATION	DOSE IN COMBINATION	SUPPORTING DATA	TOXICITY
Elvitegravir (Available only in combination with cobicistat, tenofovir, and emtricitabine [Stribild])	Licensed	Fixed-dose combination	1 tablet daily	Noninferior to raltegravir or atazanavir/ritonavir in treatment-experienced pts	Diarrhea, nausea, upper respiratory infections, headache
Dolutegravir (Tivicay)	Licensed	In combination with other antiretroviral agents	50 mg daily for treatment-naïve pts 50 mg twice daily for treatment-experienced pts or those also receiving efavirenz or rifampin	Noninferior to raltegravir, superior to efavirenz or darunavir/ritonavir	Insomnia, headache, hypersensitivity reactions, hepatotoxicity
Bictegravir (Available only in combination with tenofovir alafenamide and emtricitabine [Biktarvy])	Licensed	For treatment of HIV infection in adults	50 mg bictegravir/ 25 mg tenofovir alafenamide/ 200 mg emtricitabine qd	Noninferior to dolutegravir/tenofovir/emtricitabine and noninferior to dolutegravir/abacavir/lamivudine	Nausea, diarrhea, headache

*Initial trade names are provided. Generic forms may be available.

Abbreviations: ARC, AIDS-related complex; NRTIs, nonnucleoside reverse transcriptase inhibitors.

TABLE 107-2A Combination Formulations of Antiretroviral Drugs

NAME	COMBINATION
Atripla ^a	Tenofovir disoproxil fumarate + emtricitabine + efavirenz
Biktarvy ^a	Tenofovir alafenamide + emtricitabine + bicitegravir
Cimduo	Tenofovir disoproxil fumarate + lamivudine
Combivir	Zidovudine + lamivudine
Complera ^a	Tenofovir disoproxil fumarate + emtricitabine + rilpivirine
Descovy	Tenofovir alafenamide + emtricitabine
Dutrebis	Raltegravir + lamivudine
Epzicom	Abacavir + lamivudine
Evotaz	Atazanavir + cobicistat
Genvoya ^a	Tenofovir alafenamide + emtricitabine + elvitegravir + cobicistat
Juluca	Dolutegravir + rilpivirine
Kaletra	Lopinavir + ritonavir
Odefsey ^a	Tenofovir alafenamide + emtricitabine + rilpivirine
Prezcobix	Darunavir + cobicistat
Stribild ^a	Tenofovir disoproxil fumarate + emtricitabine + elvitegravir + cobicistat
Symfi ^a	Tenofovir disoproxil fumarate + lamivudine + efavirenz (600 mg)
Symfi Lo ^a	Tenofovir disoproxil fumarate + lamivudine + efavirenz (400 mg)
Triumeq ^a	Abacavir + lamivudine + dolutegravir
Truvada	Tenofovir disoproxil fumarate + emtricitabine
Trizivir	Zidovudine + lamivudine + abacavir

^aComplete, once-daily, single tablet regimens.

HIV Integrase Inhibitors

These drugs interfere with the integration of proviral DNA into the host cell genome. The first agent in this class, *raltegravir*, was approved in 2007 for use in treatment-experienced pts. Three other integrase inhibitors, *dolutegravir*, *elvitegravir*, and *bicitegravir* are also licensed.

Choice of Antiretroviral Treatment Strategy

The large number of available antiretroviral agents make the subject of antiretroviral therapy one of the more complicated in the management of HIV-infected pts.

The principles of therapy for HIV infection have been articulated by a panel sponsored by the U.S. Department of Health and Human Services (Table 107-3). At present, most guidelines recommend cART for anyone with a diagnosis of HIV infection. In addition, one may wish to administer a 4-week course of therapy to uninfected individuals immediately following a high-risk exposure to HIV (see next).

When the decision to initiate therapy is made, the physician must decide which drugs to use in the initial regimen. The options for initial therapy most commonly in use today are listed in Table 107-4. There are no clear data at present on which to base a distinction between these approaches.

Following the initiation of therapy, one should expect a 1-log (tenfold) reduction in plasma HIV RNA within 1–2 months; eventually a decline in plasma HIV RNA to <50 copies/mL; and a rise in CD4+ T cell count of 100–150/μL during the first year. Failure to achieve and maintain an HIV RNA level <50 copies/mL is an indication to consider a change in therapy. Other reasons for changing therapy are listed in Table 107-5. When changing therapy because of treatment failure, it is important to attempt to provide a regimen with at least two new drugs. In the pt in whom a change is made for reasons of drug toxicity, a simple replacement of one drug is reasonable.

TABLE 107-3 Principles of Therapy of HIV Infection

1. Ongoing HIV replication leads to immune system damage, progression to AIDS, and systemic immune activation.
2. Plasma HIV RNA levels indicate the magnitude of HIV replication and the rate of CD4+ T cell destruction. CD4+ T cell counts indicate the current level of competence of the immune system.
3. Maximal suppression of viral replication is a goal of therapy; the greater the suppression, the less likely the appearance of drug-resistant quasiespecies.
4. The most effective therapeutic strategies involve the simultaneous initiation of combinations of effective anti-HIV drugs with which the pt has not been previously treated and that are not cross-resistant with antiretroviral agents that the pt has already received.
5. The antiretroviral drugs used in combination regimens should be used according to optimum schedules and dosages.
6. The number of available drugs is limited. Any decisions on antiretroviral therapy have a long-term impact on future options for the pt.
7. Women should receive optimal antiretroviral therapy regardless of pregnancy status.
8. The same principles apply to children and adults. The treatment of HIV-infected children involves unique pharmacologic, virologic, and immunologic considerations.
9. Compliance is an important part of ensuring maximal effect from a given regimen. The simpler the regimen, the easier it is for the pt to be compliant.

Source: Modified from *Principles of Therapy of HIV Infection*, USPHS, and the Henry J. Kaiser Family Foundation.

Treatment of Secondary Infections and Neoplasms

Specific for each infection and neoplasm (see [Chap. 197](#), in HPIM-20).

Prophylaxis against Secondary Infections

(See also [Table 197-11](#), pp. 1431-1433, in HPIM-20.)

Primary prophylaxis is clearly indicated for *P. jiroveci* pneumonia (especially when CD4+ T cell counts fall to <200 cells/ μ L), for *M. avium* complex infections in pts with CD4+ T cell counts <50 cells/ μ L, and for *M. tuberculosis* infections in pts with a positive PPD or anergy if at high risk of TB. Vaccination with influenza and pneumococcal polysaccharide vaccines is generally recommended for

TABLE 107-4 Initial Combination Regimens Recommended for Most Treatment-Naïve Pts Regardless of HIV RNA Level or CD4 Count

- Dolutegravir + tenofovir* + emtricitabine**
- Raltegravir + tenofovir* + emtricitabine**
- Bictegravir + tenofovir* + emtricitabine**
- Elvitegravir + cobicistat + tenofovir* + emtricitabine**
- Dolutegravir + abacavir + lamivudine** (only for those HLA-B*5701 negative)

*Tenofovir alafenamide and tenofovir disoproxil fumarate are two forms of tenofovir approved by FDA. Tenofovir alafenamide has fewer bone and renal toxicities while tenofovir disoproxil fumarate is associated with lower lipid levels.

**Lamivudine may substitute for emtricitabine and vice versa.

Source: Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, USPHS.

TABLE 107-5 Indications for Changing Antiretroviral Therapy in Pts with HIV Infection^a

Less than a 1-log drop in plasma HIV RNA by 4 weeks following the initiation of therapy

A reproducible significant increase (defined as threefold or greater) from the nadir of plasma HIV RNA level not attributable to intercurrent infection, vaccination, or test methodology

Persistently declining CD4+ T cell numbers

Clinical deterioration

Side effects

^aGenerally speaking, a change should involve the initiation of at least two drugs felt to be effective in the given pt. The exception to this is when change is being made to manage toxicity, in which case a single substitution is reasonable.

Source: *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*, USPHS.

all pts and may need to be repeated in those with CD4+ T cell counts <200/ μ L when their counts increase to >200/ μ L. Secondary prophylaxis, when available, is indicated for virtually every infection experienced by HIV-infected pts until they have significant immunologic recovery.

■ HIV AND THE HEALTH CARE WORKER

There is a small but definite risk to health care workers of acquiring HIV infection via needle stick exposures, large mucosal surface exposures, or exposure of open wounds to HIV-infected secretions or blood products. The risk of HIV transmission after a skin puncture by an object contaminated with blood from a person with documented HIV infection is ~0.3%, compared with a 20–30% risk for hepatitis B infection from a similar incident. Postexposure prophylaxis may be effective in decreasing the likelihood of acquisition of infection through accidental exposure in the health care setting. In this regard, a U.S. Public Health Service working group has recommended that chemoprophylaxis be given as soon as possible after occupational exposure. While the precise regimen remains a subject of debate, the U.S. Public Health Service guidelines recommend a combination of two nucleoside analogue reverse transcriptase inhibitors plus a third drug given for 4 weeks for high-risk or otherwise complicated exposures. Regardless of which regimen is used, treatment should be initiated as soon as possible after exposure and take into account any available resistance data on the infecting virus.

Prevention of exposure is the best strategy and includes following universal precautions and proper handling of needles and other potentially contaminated objects.

Transmission of TB is another potential risk for all health care workers, including those dealing with HIV-infected pts. All workers should know their PPD status, which should be checked yearly.

■ VACCINES

A clinical trial conducted in Thailand demonstrated moderate (31% effective) protection against acquisition of HIV infection. However, this modest degree of efficacy does not justify deployment of the vaccine; active investigation continues in the pursuit of a safe and effective vaccine against HIV, including focusing on the induction of broadly neutralizing antibodies to HIV.

■ PREVENTION

Education, counseling, and behavior modification along with the consistent and correct use of condoms in risk situations remain the cornerstones of HIV prevention efforts. Avoidance of shared needle use by IDUs is critical. If possible, breast-feeding should be avoided by HIV-positive women, as the virus can be transmitted to infants via this route. In societies where withholding of

breast-feeding is not feasible, treatment of the mother, if possible, greatly decreases the chances of transmission. Recent studies have demonstrated the important role of medically supervised adult male circumcision in the prevention of acquisition of heterosexually transmitted HIV infection in men. In addition, pre-exposure prophylaxis (PrEP) with Truvada, a single pill formulation containing emtricitabine and tenofovir that has been approved for PrEP in men who have sex with men and in heterosexual men and women engaging in risk behaviors, has proven to be an effective means of prevention of HIV acquisition. Finally, treatment of the HIV-infected partner in heterosexual discordant couples has proved highly effective in preventing transmission of HIV to the uninfected partner.

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Pneumocystis Pneumonia, Candidiasis, and Other Fungal Infections



GENERAL CONSIDERATIONS

- *Yeasts* (e.g., *Candida*, *Cryptococcus*) appear microscopically as round, budding forms; *molds* (e.g., *Aspergillus*, *Rhizopus*) appear as filamentous forms called *hyphae*; and *dimorphic fungi* (e.g., *Histoplasma*) are spherical in tissue but appear as molds in the environment.
 - *Endemic fungi* (e.g., *Coccidioides*) are not part of the normal human microbiota and infect hosts preferentially by inhalation.
 - *Opportunistic fungi* (e.g., *Candida* and *Aspergillus*) invade the host from normal sites of colonization (e.g., mucous membranes or the GI tract).
- Definitive diagnosis of any fungal infection requires histopathologic identification of the fungus invading tissue and accompanying evidence of an inflammatory response.
 - Other tests that detect antigens (e.g., for *Histoplasma*, *Cryptococcus*, *Aspergillus*) or antibody (e.g., for *Coccidioides*) have different degrees of specificity and sensitivity.

ANTIFUNGAL AGENTS

■ AMPHOTERICIN B (AmB)

AmB is the broadest-spectrum antifungal agent but has significant toxicities, including nephrotoxicity, fever, chills, and nausea.

- AmB has fungicidal activity and is available only for parenteral administration.
- Lipid formulations lack nephrotoxicity and infusion reactions; whether there is a clinically significant difference in efficacy between the deoxycholate and lipid formulations remains controversial.

■ AZOLES

The azoles' mechanism of action is inhibition of ergosterol synthesis in the fungal cell wall, resulting in fungistatic activity. Azoles cause little or no nephrotoxicity and are available in oral preparations.

- *Fluconazole*: Fluconazole is available in both oral and IV formulations, has a long half-life, and penetrates into most body fluids, including ocular fluids and CSF.
 - Toxicity is minimal but includes (usually reversible) hepatotoxicity and—at high doses—alopecia, muscle weakness, dry mouth, and metallic taste.

- Fluconazole is useful for coccidioidal and cryptococcal meningitis and for candidemia, but it is notably ineffective against aspergillosis or mucormycosis.
- This drug is effective as fungal prophylaxis in bone-marrow and high-risk liver transplant recipients.
- *Voriconazole*: Available in oral and IV formulations, voriconazole is considered the first-line agent against *Aspergillus* and has a broader spectrum than fluconazole against *Candida* species (including *C. glabrata* and *C. krusei*). It is also active against *Scedosporium*, *Fusarium*, and *Coccidioides*.
 - Disadvantages of voriconazole (compared to fluconazole) include multiple drug interactions, hepatotoxicity, skin rashes (including photosensitivity), visual disturbances, and the need to monitor drug levels.
 - As it is metabolized completely by the liver, dose adjustments are required in pts with liver failure. Dose adjustments for renal insufficiency are not required, but—given the presence of cyclodextrin—the parenteral formulation should be avoided in pts with severe renal insufficiency.
- *Itraconazole*: Available in oral and IV formulations, itraconazole is the drug of choice for mild to moderate blastomycosis and histoplasmosis. It is approved by the FDA for use in febrile neutropenic pts, although most centers use other azoles for prophylaxis and treatment in these pts. Disadvantages of itraconazole include its poor penetration into CSF, the use of cyclodextrin in both the oral suspension and the IV preparation, the variable absorption of the drug in capsule form, and the need for monitoring of blood levels in pts taking capsules for disseminated mycoses.
- *Posaconazole*: Approved for prophylaxis of aspergillosis and candidiasis in high-risk immunocompromised pts, posaconazole is also effective against fluconazole-resistant *Candida* isolates and may be useful as salvage therapy for some other fungal infections.
- *Isavuconazole*: Approved for aspergillosis and mucormycosis, although clinical experience is still somewhat limited.

■ ECHINOCANDINS

The echinocandins, including caspofungin, anidulafungin, and micafungin, act by inhibiting the β -1,3-glucan synthase that is necessary for fungal cell wall synthesis. These agents are considered fungicidal for *Candida* and fungistatic for *Aspergillus*.

- Among the safest antifungal agents, echinocandins offer broad-spectrum fungicidal activity against all *Candida* species, and caspofungin has been efficacious as salvage therapy for aspergillosis.
- If anidulafungin or micafungin is used in combination with cyclosporine, no dose adjustment is needed for either drug.

■ FLUCYTOSINE

Flucytosine has excellent CSF penetration, but development of resistance has led to its almost always being used in combination with AmB (e.g., for cryptococcal meningitis). Adverse effects include bone marrow suppression.

■ GRISEOFULVIN AND TERBINAFINE

Griseofulvin is used primarily for ringworm infection. Terbinafine is used for onychomycosis and ringworm and is as effective as itraconazole.

■ TOPICAL AGENTS

Many drug classes are used for topical treatment of common fungal skin infections: azoles (e.g., clotrimazole, miconazole), polyene agents (e.g., nystatin), and other classes (e.g., ciclopirox olamine, terbinafine).

PNEUMOCYSTIS PNEUMONIA (PCP)

Pneumocystis, an opportunistic fungal pulmonary pathogen, is an important cause of pneumonia in immunocompromised hosts.

■ MICROBIOLOGY

- *P. jirovecii* infects humans, whereas *P. carinii*—the original species described—infests rats.
- Developmental stages include the small trophic form, the cyst, and the intermediate precyst stage.

■ EPIDEMIOLOGY

- *Pneumocystis* is found worldwide, and most people are exposed to the organism early in life.
- Infections resulting from environmental sources and person-to-person transmission have been demonstrated; the role of airborne transmission is unclear.
- Defects in cellular and humoral immunity (e.g., due to HIV infection, malignancy, transplantation, immunosuppressive medications) predispose to PCP. The incidence among HIV-infected pts is inversely related to the CD4⁺ T cell count: ≥80% of cases occur at counts of <200 cells/ μ L, and most cases develop at counts of <100/ μ L.

■ PATHOGENESIS

- The organisms are inhaled into the alveolar space, where they proliferate, provoking a mononuclear cell response. Alveoli become filled with and are damaged by proteinaceous material, with consequently increased alveolar-capillary injury and surfactant abnormalities.
- On histology, alveoli are seen to be filled with foamy, vacuolated exudates.

■ CLINICAL MANIFESTATIONS

- Pts develop dyspnea, fever, and nonproductive cough.
 - HIV-infected pts often have an indolent course that presents as mild exercise intolerance or chest tightness without fever or cough. Over days to months, these pts develop the more typical symptoms of PCP.
 - Some pts with HIV infection and most pts with other types of immunosuppression have more acute disease that progresses over a few days to respiratory failure.
- Physical examination findings are nonspecific and invariably include hypoxemia. Pts may initially have a normal chest examination but later, without treatment, develop diffuse rales and signs of consolidation.
- Serum levels of LDH may be elevated because of pulmonary damage, but this finding is neither sensitive nor specific.
- CXR classically reveals bilateral diffuse interstitial infiltrates that are perihilar and symmetrical, although this finding is not specific for PCP. Cysts and pneumothoraces are common CXR findings, especially in HIV-infected pts. Chest CT shows diffuse ground-glass opacities in virtually all pts with PCP, and a normal chest CT essentially rules out the diagnosis.
- Rare cases of disseminated infection have been described, generally involving lymph nodes, spleen, and liver.

■ DIAGNOSIS

- Histopathologic staining makes the definitive diagnosis.
 - Cell-wall stains (e.g., methenamine silver) are used for *Pneumocystis* cysts and Wright-Giemsa stains for the nuclei of all developmental stages.
 - Immunofluorescence with monoclonal antibodies increases diagnostic sensitivity.
- The demonstration of organisms in bronchoalveolar lavage fluid is almost 100% sensitive and specific for PCP in immunocompromised pts.

- While detection of organisms in expectorated sputum or throat swabs has very low sensitivity, detection in an induced sputum sample can be—depending on the experience of the center conducting the test—highly sensitive (up to 90%) and specific.
- DNA amplification by PCR is most sensitive but may not distinguish colonization from infection.

TREATMENT

Pneumocystis Infections

- The regimen of choice is trimethoprim-sulfamethoxazole (TMP-SMX) for 14 days to non-HIV-infected pts with mild disease and for 21 days to all other pts. For doses and adverse effects of TMP-SMX and alternative regimens, see [Table 108-1](#).
- For HIV-infected (and likely all) pts with moderate to severe cases (a room air $P_{aO_2} \leq 70$ mmHg or a $PA_{O_2} - P_{aO_2}$ gradient ≥ 35 mmHg), adjunctive glucocorticoids improve the survival rate.
- For pts with HIV infection who present with PCP before the initiation of antiretroviral therapy (ART), ART should usually be started within the first 2 weeks of therapy for PCP.
- Pts typically do not respond to therapy for 4–8 days. Pts whose condition continues to deteriorate after 3–4 days or has not improved after 7–10 days should be reevaluated for other infectious processes, for failure of initial anti-*Pneumocystis* treatment, and for noninfectious processes (e.g., CHF, pulmonary emboli) that may be causing pulmonary dysfunction.

TABLE 108-1 Treatment of *Pneumocystis*^a

DRUG(S)	DOSE, ROUTE	ADVERSE EFFECTS
First-choice agent		
TMP-SMX	TMP (5 mg/kg) plus SMX (25 mg/kg) q6–8h PO or IV (i.e., 2 double-strength tablets tid or qid)	Fever, rash, cytopenias, hepatitis, hyperkalemia
Alternative agents		
Atovaquone	750 mg bid PO	Rash, fever, hepatitis
Clindamycin	300–450 mg q6h PO or 600 mg q6–8h IV	Hemolysis (G6PD deficiency), methemoglobinemia, neutropenia, rash
plus Primaquine	15–30 mg qd PO	
Pentamidine	3–4 mg/kg qd IV	Hypotension, azotemia, cardiac arrhythmias (torsades des pointes), pancreatitis, dysglycemias, hypocalcemia, neutropenia, hepatitis
Adjunctive agent		
Prednisone or methylprednisolone	40 mg bid \times 5 d, 40 mg qd \times 5 d, 20 mg qd \times 11 d; PO or IV	Peptic ulcer disease, hyperglycemia, mood alteration, hypertension

^aTreatment can be administered for 14 days to non-HIV-infected pts with mild disease and for 21 days to all other pts.

Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; TMP-SMX, trimethoprim-sulfamethoxazole.

■ PROGNOSIS

- Factors that influence mortality risk include advanced age, high degree of immunosuppression, preexisting lung disease, low serum albumin level, need for mechanical ventilation, and development of a pneumothorax.

■ PREVENTION

- The most effective method for preventing PCP is to eliminate the cause of immunosuppression (e.g., withdraw immunosuppressive therapy, treat HIV infection).
- Prophylaxis is indicated for HIV-infected pts with CD4+ T cell counts of <200/ μ L. Guidelines for other compromised hosts are less clear, but prophylaxis should be considered for pts receiving >20 mg of prednisone daily (or its equivalent) for \geq 30 days.
- For prophylactic regimens, see [Table 108-2](#). TMP-SMX is the drug of choice.

CANDIDIASIS**■ MICROBIOLOGY AND EPIDEMIOLOGY**

Candida is a small, thin-walled, ovoid yeast that reproduces by budding and occurs in three forms in tissue: blastospores, pseudohyphae, and hyphae.

- *Candida* is ubiquitous in nature and inhabits the GI tract, the female genital tract, and the skin. Dissemination probably results from fungal entry into the

TABLE 108-2 Prophylaxis of Pneumocystosis

DRUG(S)	DOSE, ROUTE	COMMENTS
First-choice agent		
TMP-SMX	1 tablet (double- or single-strength) qd PO	Incidence of hypersensitivity is high. Rechallenge for non-life-threatening hypersensitivity; consider dose-escalation protocol.
Alternative agents		
Dapsone	50 mg bid or 100 mg qd PO	Hemolysis is associated with G6PD deficiency.
Dapsone <i>plus</i> Pyrimethamine	50 mg qd PO 50 mg weekly PO	Leucovorin ameliorates cytopenias due to pyrimethamine.
Leucovorin	25 mg weekly PO	
Dapsone <i>plus</i> Pyrimethamine <i>plus</i> Leucovorin	200 mg weekly PO 75 mg weekly PO 25 mg weekly PO	Leucovorin ameliorates cytopenias due to pyrimethamine.
Pentamidine	300 mg monthly via Respigard II nebulizer	Aerosol may cause bronchospasm. Pentamidine is probably less effective than TMP-SMX or dapsone regimens.
Atovaquone	1500 mg qd PO	Requires fatty meal for optimal absorption

Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; TMP-SMX, trimethoprim-sulfamethoxazole.

bloodstream from mucosal surfaces after the organisms have multiplied to large numbers as a result of bacterial suppression by antibacterial drugs.

- *C. albicans* is common, but non-*albicans* species (e.g., *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*) now cause ~50% of all cases of candidemia and disseminated candidiasis.
 - *Candida* spp. represent the fourth most common blood-culture isolate from hospitalized pts in the United States.
 - Pts with a compromised immune system, pts with indwelling catheters, pts with severe burns, and neonates of low birth weight are at risk for hematogenous dissemination.

■ CLINICAL MANIFESTATIONS

The severity of candidal infections ranges from mild to life-threatening, with deep organ infections being at the more severe end of the spectrum.

- *Mucocutaneous candidiasis*
 - Thrush is characterized by white, adherent, painless, discrete or confluent patches in the mouth, on the tongue, or in the esophagus.
 - Vulvovaginal candidiasis presents as pruritus, pain, and a vaginal discharge that may contain whitish “curds.”
 - Other cutaneous infections include paronychia, balanitis, and intertrigo (erythematous irritation with pustules in skin folds).
 - Chronic mucocutaneous candidiasis is a heterogeneous infection of hair, nails, skin, and mucous membranes that persists despite therapy and is associated with a dysfunctional immune system.
- *Deeply invasive candidiasis*: These infections are most commonly due to hematogenous seeding of organs during candidemia, but they can also be due to contiguous spread of organisms after disruption of normal anatomic barriers (e.g., kidney infection associated with an indwelling urinary catheter).
 - Nearly any organ can be infected, but the brain, chorioretina, heart, and kidneys are most commonly involved. Except in neutropenic pts, the liver and spleen are less often infected.
 - Skin involvement manifests as macronodular lesions.
 - Chorioretinal or skin involvement predicts a high probability of abscess formation in deep organs from generalized hematogenous seeding.

■ DIAGNOSIS

The most challenging aspect of diagnosis is determining which pts have hematogenously disseminated disease; recovery of *Candida* from sputum, urine, or peritoneal catheters may reflect colonization rather than deep infection.

- The diagnosis of *Candida* infection is established by visualization of pseudohyphae or hyphae in the presence of inflammation in appropriate clinical samples.
- The β -glucan test has a negative predictive value of ~90% and can help exclude disseminated disease.

TREATMENT

Candidiasis

- *Mucocutaneous candidiasis*: Azoles are preferred; nystatin is an alternative.
 - Topical applications are appropriate when possible.
 - Oral therapy can be used for vulvovaginal infections (fluconazole, 150 mg PO as a single dose) and esophageal infections (fluconazole, 100–200 mg/d; or itraconazole, 200 mg/d).

- *Candidemia and suspected disseminated candidiasis*: All pts with candidemia should be treated with a systemic antifungal agent for at least 2 weeks after the last positive blood culture.
 - Lipid formulations of AmB, echinocandins, and fluconazole or voriconazole are all effective; no agent within a given class is clearly superior to the others.
 - The choice of antifungal drug depends on local epidemiology and susceptibility profiles.
 - Neutropenic or hemodynamically unstable pts should be treated with broader-spectrum agents (e.g., AmB, echinocandins) until the pathogen is specifically identified and a clinical response assessed.
 - An echinocandin is often started empirically, pending speciation and sensitivity information, with subsequent adjustment of therapy as needed.
 - When possible, foreign materials (e.g., catheters) should be removed or replaced.
 - All pts with candidemia should undergo an ophthalmologic examination because of high rates of *Candida* endophthalmitis, which may require partial vitrectomy.
 - *Candida* endocarditis should be treated with valve removal and long-term antifungal administration (see [Chap. 83](#)).
 - *Candida* meningitis is often treated with a polyene plus flucytosine (25 mg/kg qid).
 - Successful treatment of *Candida*-infected prosthetic material (e.g., an artificial joint) nearly always requires removal of the infected material followed by long-term antifungal therapy.
-

■ PREVENTION

Allogeneic stem cell and high-risk liver transplant recipients typically receive prophylaxis with fluconazole (400 mg/d). Some centers also use antifungal prophylaxis for neutropenic pts.

ASPERGILLOSIS

■ MICROBIOLOGY AND EPIDEMIOLOGY

Aspergillus, a mold with septate hyphae branching at 45° angles, has vast numbers of conidia (spores). It has a worldwide distribution and typically grows in decomposing plant materials and in bedding. *A. fumigatus* is responsible for most cases of invasive aspergillosis, almost all cases of chronic aspergillosis, and most allergic syndromes.

- Inhalation is common; only intense exposures cause disease in healthy, immunocompetent individuals.
- The primary risk factors for invasive aspergillosis are profound neutropenia, glucocorticoid use, therapy with immune modulators (e.g., TNF- α inhibitors, ibrutinib), severe liver disease, influenza infection, and extracorporeal membrane oxygenation therapy.
- Pts with chronic pulmonary aspergillosis have a wide spectrum of underlying pulmonary diseases (e.g., tuberculosis, sarcoidosis).

■ CLINICAL MANIFESTATIONS

More than 80% of invasive disease cases involve the lungs; in pts who are significantly immunocompromised, virtually any organ can be affected.

- *Invasive pulmonary aspergillosis*: Pts can be asymptomatic or can present with fever, cough, chest discomfort, hemoptysis, and shortness of breath.
 - Acute and subacute forms have courses of ≤ 1 month and 1–3 months, respectively.
 - Early diagnosis requires a high index of suspicion, screening for circulating antigen (in leukemia), and urgent CT of the chest.
- *Invasive sinusitis*: Pts have fever, nasal or facial discomfort, and nasal discharge. The sinuses are involved in 5–10% of cases of invasive aspergillosis; sinus involvement is especially likely in leukemic pts and hematopoietic stem cell transplant recipients.
- *Bronchitis*: Pts present with recurrent chest infections that only partially improve with antibiotics, significant dyspnea, and cough productive of thick sputum plugs. Pts typically have bronchiectasis or cystic fibrosis but are not significantly immunocompromised.
- *Disseminated aspergillosis*: *Aspergillus* disseminates from lung to brain, skin, thyroid, bone, and other organs, after which pts develop skin lesions and deteriorate clinically over 1–3 days, with fever and signs of mild sepsis. Blood cultures are usually negative.
 - *Cerebral aspergillosis*: Single or multiple lesions, hemorrhagic infarction, and cerebral abscess are common. The presentation can be acute or subacute, with mood changes, focal signs, seizures, and a decline in mental status. MRI is the most useful investigation.
 - *Cutaneous aspergillosis*: Dissemination of *Aspergillus* occasionally results in cutaneous features, usually an erythematous or purplish nontender area that develops into a necrotic eschar.
- *Chronic pulmonary aspergillosis*: Pts develop one or more cavities that expand over months or years, with pulmonary symptoms (including hemoptysis), fatigue, and weight loss. Pericavitary infiltrates and multiple cavities are typical, and *Aspergillus* nodules may be present. Without treatment, pulmonary fibrosis can develop.
 - *Aspergillomas* (fungal balls) are a late manifestation of chronic pulmonary aspergillosis. Pt presentations range from no symptoms to significant complications (e.g., hemoptysis). Roughly 10% of fungal balls resolve spontaneously.
- *Chronic sinusitis*: Pts develop one of three presentations: a fungal ball in the maxillary sinus; chronic invasive sinusitis that is slowly destructive; or chronic granulomatous sinusitis, which is most common in the Middle East and India and is often caused by *A. flavus*.
- *Allergic bronchopulmonary aspergillosis (ABPA)*: A hypersensitivity reaction leads to bronchial plugging, coughing fits, and dyspnea, primarily affecting asthmatics and pts with cystic fibrosis. Total IgE levels are usually >1000 IU/mL.

■ DIAGNOSIS

Culture, molecular testing, antigen detection, and histopathology usually confirm the diagnosis; ~40% of cases of invasive aspergillosis are diagnosed only at autopsy.

- Culture may be falsely positive (e.g., in pts with airway colonization) or falsely negative; only 10–30% of pts with invasive *Aspergillus* have a positive culture at any time.
- Galactomannan antigen testing of serum from high-risk pts is best done prospectively, as positive results precede clinical disease; false-positive results can occur (in association, for example, with certain β -lactam/ β -lactamase inhibitor antibiotic combinations).

- A *halo sign* on high-resolution thoracic CT scan (a localized ground-glass appearance representing hemorrhagic infarction surrounding a nodule) suggests the diagnosis.

TREATMENT

Aspergillosis

- See [Table 108-3](#) for recommended treatments and doses. The duration of treatment for pts with invasive aspergillosis varies from ~3 months to years, depending on the host and the response.
- Surgical treatment is important for some forms of aspergillosis (e.g., maxillary sinus fungal ball; single aspergilloma; invasive disease of bone, heart valve, brain, or sinuses).

OUTCOME

- Invasive aspergillosis is curable if immune reconstitution occurs, whereas allergic and chronic forms are not. The overall mortality rate is 30–70% with treatment, but the disease is uniformly fatal without therapy.

CRYPTOCOCCOSIS

MICROBIOLOGY AND EPIDEMIOLOGY

Cryptococcus is a yeast-like fungus. *C. neoformans* and *C. gattii* are pathogenic for humans and can cause cryptococcosis; most clinical laboratories do not routinely distinguish between these species.

- Worldwide, there are ~1 million cases of cryptococcosis, with >600,000 deaths annually. Most cases are in pts with AIDS.
- Cryptococcosis due to *C. neoformans* is rare in the absence of impaired immunity; in contrast, *C. gattii*-related disease often occurs in immunocompetent pts.
- *C. neoformans* is found in soil contaminated with pigeon droppings, whereas *C. gattii* is associated with eucalyptus trees. Most cases are acquired via inhalation, which results in pulmonary infection.

CLINICAL MANIFESTATIONS

The clinical manifestations of cryptococcosis reflect the site of fungal infection, usually involving the CNS and/or the lungs.

- CNS involvement most commonly presents as chronic meningoencephalitis, with headache, fever, lethargy, sensory and memory deficits, cranial nerve paresis, visual deficits, and meningismus (absent in some cases) lasting for weeks.
- Pulmonary cryptococcosis is generally asymptomatic but can present as cough, increased sputum production, and chest pain. *Cryptococcomas* are granulomatous pulmonary masses associated with *C. gattii* infections.
- Skin lesions are common in pts with disseminated cryptococcosis and can be highly variable, including papules, plaques, purpura, vesicles, tumor-like lesions, and rashes.

DIAGNOSIS

Diagnosis requires the demonstration of *C. neoformans* in normally sterile tissue (e.g., positive cultures of CSF or blood).

TABLE 108-3 Treatment of Aspergillosis^a

INDICATION	PRIMARY TREATMENT	PRECAUTIONS	SECONDARY TREATMENT	COMMENTS
Invasive disease ^b	Voriconazole, isavuconazole	Drug interactions (especially with rifampin and carbamazepine) ^c	AmB, caspofungin, posaconazole, micafungin	As primary therapy, voriconazole and isavuconazole have a 20% higher response rate than AmB. Therapeutic drug monitoring is recommended for voriconazole.
Prophylaxis	Posaconazole tablet, itraconazole solution	Diarrhea and vomiting with itraconazole, vincristine interaction	Micafungin, aerosolized AmB	Some centers monitor plasma levels of itraconazole and posaconazole.
Single aspergilloma	Surgery	Multicavity disease: poor outcome of surgery, medical therapy preferable	Itraconazole, voriconazole, intracavity AmB	Single large cavities with an aspergilloma are best resected.
Chronic pulmonary disease ^b	Itraconazole, voriconazole	Poor absorption of itraconazole capsules with proton pump inhibitors or H ₂ blockers	Posaconazole, IV AmB, IV micafungin	Resistance may emerge during treatment, especially if plasma drug levels are subtherapeutic.
ABPA/SAFS ("fungal asthma")	Itraconazole	Some glucocorticoid interactions, including with inhaled formulations	Voriconazole, posaconazole	Long-term therapy is helpful in most cases. No evidence indicates whether therapy modifies progression to bronchiectasis/fibrosis.

^aFor information on duration of therapy, see text.

^bAn infectious disease consultation is appropriate for these pts.

^cOnline drug-interaction resource: www.aspergillus.org.uk/content/antifungal-drug-interactions.

Note: After loading doses, the oral dose is usually 200 mg bid for voriconazole and itraconazole, 300 mg qd for posaconazole tablets, and 200 mg qd for isavuconazole. The IV dose of voriconazole for adults is 6 mg/kg twice at 12-h intervals (loading doses) followed by 4 mg/kg q12h; a larger dose is required for children and teenagers; a lower dose may be safer for persons >70 years of age. Plasma monitoring is helpful in optimizing the dosage. The IV dose of isavuconazole is 200 mg tid for 2 days (loading dose) followed by 200 mg qd. Caspofungin is given as a single loading dose of 70 mg and then at 50 mg/d; some authorities use 70 mg/d for pts weighing >80 kg, and lower doses are required with hepatic dysfunction. Micafungin is given as 50 mg/d for prophylaxis and as at least 150 mg/d for treatment; this drug has not yet been approved by the U.S. Food and Drug Administration (FDA) for this indication. AmB deoxycholate is given at a daily dose of 1 mg/kg if tolerated. Several strategies are available for minimizing renal dysfunction. Lipid-associated AmB is given at 3 mg/kg (AmBisome) or 5 mg/kg (Abelcet). Different regimens are available for aerosolized AmB, but none is FDA approved. Other considerations that may alter dose selection or route include age; concomitant medications; renal, hepatic, or intestinal dysfunction; and drug tolerability.

Abbreviations: AmB, amphotericin B; ABPA, allergic bronchopulmonary aspergillosis; SAFS, severe asthma with fungal sensitization.

- India ink smear of CSF is a useful rapid diagnostic technique but may yield negative results in pts with a low fungal burden.
- Cryptococcal antigen testing of CSF and/or serum provides strong presumptive evidence for cryptococcosis; such testing often yields negative results in pulmonary cryptococcosis and is of limited utility in monitoring response to therapy.

TREATMENT

Cryptococcosis

- Immunocompetent pts
 - Pulmonary cryptococcosis is treated with fluconazole (200–400 mg/d) for 3–6 months.
 - Severe extrapulmonary cryptococcosis may initially require AmB (0.5–1.0 mg/kg daily for 4–6 weeks).
 - CNS disease is treated with an induction phase of AmB (0.5–1.0 mg/kg qd) followed by prolonged consolidation therapy with fluconazole (400 mg/d).
 - Meningoencephalitis is treated with AmB (0.5–1.0 mg/kg) plus flucytosine (100 mg/kg) daily for 6–10 weeks or with the same drugs at the same dosages for 2 weeks followed by fluconazole (400 mg/d) for ≥ 10 weeks.
- Immunosuppressed pts are treated with the same initial regimens except that maintenance therapy with fluconazole is given for a prolonged period (sometimes throughout life) to prevent relapse.
 - HIV-infected pts with CNS involvement are typically treated with AmB (0.7–1.0 mg/kg daily) plus flucytosine (100 mg/kg qd) for at least 2 weeks followed by fluconazole (400 mg/d) for 10 weeks and then by lifelong maintenance therapy with fluconazole (200 mg/d).
 - An alternative regimen involves fluconazole (400–800 mg/d) plus flucytosine (100 mg/kg qd) for 6–10 weeks followed by fluconazole (200 mg/d) as maintenance therapy.
- Newer triazoles (e.g., voriconazole, posaconazole) appear effective, but clinical experience is still limited.

MUCORMYCOSIS

■ MICROBIOLOGY AND EPIDEMIOLOGY

Mucormycosis is caused by fungi of the order Mucorales, most commonly *Rhizopus oryzae* and *R. delemar*; despite the name of the disease, *Mucor* species are only rarely the cause.

- Mucorales have characteristic wide (≥ 6 - to 30- μm), thick-walled, ribbon-like, aseptate hyphal elements that branch at right angles.
- These ubiquitous environmental fungi primarily affect pts with diabetes, solid organ or hematopoietic stem cell transplants, prolonged neutropenia, malignancy, and deferoxamine treatment for iron overload syndromes.

■ CLINICAL MANIFESTATIONS

Mucormycosis is highly invasive and relentlessly progressive, with a mortality rate of $>40\%$. The disease is usually categorized by the anatomic site involved.

- *Rhino-orbital-cerebral mucormycosis*: In this, the most common form of the disease, pts initially have nonspecific symptoms that include eye or facial pain

and facial numbness followed by the onset of conjunctival suffusion, blurry vision, and soft tissue swelling.

- If untreated, the infection can spread from the ethmoid sinus to the orbit (affecting extraocular muscle function and being associated with proptosis and chemosis) and then to the brain (frontal lobe or cavernous sinus).
- The visual appearance of infected tissue may progress from normal to erythematous to violaceous to a black necrotic eschar.
- *Pulmonary mucormycosis*: In this second most common manifestation, pts typically present with fever, dyspnea, cough, and chest pain. Angioinvasion results in necrosis, cavitation, and/or hemoptysis. Differentiation from aspergillosis is critical as treatment regimens differ; the presence of ≥ 10 pulmonary nodules, pleural effusion, or concomitant sinusitis makes mucormycosis more likely.
- *Cutaneous mucormycosis*: Caused by external implantation or hematogenous dissemination, necrotizing fasciitis due to mucormycosis has a mortality rate of $\sim 80\%$.
- *Gastrointestinal mucormycosis*: Classically a disease of premature infants, GI mucormycosis is increasing in incidence among immunocompromised adults. Adult pts present with GI bleeding and fungating masses in the stomach, with possible progression to visceral perforation.
- *Hematogenously disseminated mucormycosis*: Infection can disseminate from any primary site of infection to any organ (most commonly the brain), and widely disseminated disease has a mortality rate of $>90\%$.

■ DIAGNOSIS

Although definitive diagnosis requires a positive culture from a sterile site, a positive culture from a nonsterile site (e.g., sputum or bronchoalveolar lavage [BAL] fluid) or the detection of Mucorales on the surface of histopathology samples from a pt with a consistent clinical history should prompt treatment pending confirmation of the diagnosis.

- The fact that only $\sim 50\%$ of pts have positive cultures is due, in part, to the organisms' being killed by the tissue homogenization required for preparation of culture.
- The laboratory should be notified that mucormycosis is being considered so that tissue sections instead of tissue homogenates can be cultured.

TREATMENT

Mucormycosis

- The successful treatment of mucormycosis requires three steps: (1) early initiation of therapy; (2) rapid reversal of underlying predisposing risk factors, if possible; and (3) surgical debridement, when possible.
- AmB (AmB deoxycholate, 1–1.5 mg/kg qd; or liposomal AmB, 5–10 mg/kg qd) is preferred.
 - Some experts prefer combinations of echinocandins and liposomal AmB, given improved survival rates in animal studies.
 - Although posaconazole and isavuconazole have in vitro activity against Mucorales, few clinical data support their use.
 - Initial clinical trials suggest that liposomal AmB combined with deferasirox (an iron chelator that is fungicidal for clinical isolates of Mucorales; 20 mg/kg PO qd for 2–4 weeks) results in improved survival rates.

- Treatment should be continued until (1) resolution of clinical signs and symptoms of infection and (2) resolution of underlying immunosuppression.

HISTOPLASMOSIS

■ MICROBIOLOGY AND EPIDEMIOLOGY

Histoplasma capsulatum, a dimorphic fungus, causes histoplasmosis.

- Mycelia are infectious and have microconidial and macroconidial forms. Microconidia are inhaled, reach the alveoli, and are transformed into yeasts with occasional narrow budding. A granulomatous reaction results; in pts with impaired cellular immunity, infection may disseminate.
- Histoplasmosis is the most prevalent endemic mycosis in North America and is also found in Central and South America, Africa, and Asia. In the United States, histoplasmosis is endemic in the Ohio and Mississippi river valleys.
- The fungus is found in soil, particularly that enriched by droppings of birds and bats.

■ CLINICAL MANIFESTATIONS

Depending on the intensity of exposure, the immune status of the exposed individual, and the underlying lung architecture of the host, disease can range from asymptomatic to life-threatening.

- Immunocompetent pts usually have asymptomatic or mild and self-limited disease.
 - Approximately 1–4 weeks after exposure, some pts develop a flu-like illness with fever, chills, sweats, headache, myalgia, anorexia, cough, dyspnea, and chest pain; 5–10% of pts with acute histoplasmosis develop arthralgia or arthritis, often associated with erythema nodosum.
 - Hilar or mediastinal lymphadenopathy may occur and can cause vascular or tracheoesophageal compression.
- Immunocompromised pts, who are more likely to develop progressive disseminated histoplasmosis (PDH), account for ~70% of cases.
 - The clinical spectrum ranges from a rapidly fatal course with diffuse interstitial or reticulonodular lung infiltrates, shock, and multiorgan failure to a subacute course with focal organ involvement, hepatosplenomegaly, thrombocytopenia, fever, and weight loss.
 - Meningitis, oral mucosal ulcerations, GI ulcerations, and adrenal insufficiency can occur.
- Chronic cavitary histoplasmosis most often affects smokers with structural lung disease (e.g., emphysema) and presents as productive cough, dyspnea, low-grade fever, night sweats, and weight loss.

■ DIAGNOSIS

Fungal culture remains the gold standard (Table 108-4), but cultures are often negative in less severe cases and may take up to 1 month to become positive.

- In PDH, the culture yield is highest for BAL fluid, bone marrow aspirate, and blood; cultures of sputum or bronchial washings are usually positive in chronic pulmonary histoplasmosis.
- Fungal stains of cytopathology or biopsy materials may be helpful in diagnosing PDH.
- *Histoplasma* antigen assay of body fluids (e.g., blood, urine, CSF, BAL fluid) is useful in diagnosing PDH or acute disease and in monitoring the response to treatment.
- Serology can be helpful in diagnosis but requires ≥ 1 month for antibody production.

TABLE 108-4 Recommendations for the Diagnosis and Treatment of Histoplasmosis

TYPE OF HISTOPLASMOSIS	DIAGNOSTIC TESTS	TREATMENT RECOMMENDATIONS	COMMENTS
Acute pulmonary, moderate to severe illness with diffuse infiltrates and/or hypoxemia	<i>Histoplasma</i> antigen (BAL fluid, serum, urine) Cytopathology on and fungal culture of BAL fluid	Lipid AmB (3–5 mg/kg per day) ± glucocorticoids for 1–2 weeks; then itraconazole (200 mg bid) for 12 weeks. Monitor renal and hepatic function.	Pts with mild cases usually recover without therapy, but itraconazole should be considered if the pt's condition has not improved after 1 month.
Chronic/cavitary pulmonary	<i>Histoplasma</i> serology (immunodiffusion and complement fixation) Fungal culture of sputum or BAL fluid	Itraconazole (200 mg qd or bid) for at least 12 months. Monitor hepatic function.	Continue treatment until radiographic findings show no further improvement. Monitor for relapse after treatment is stopped.
Progressive disseminated	<i>Histoplasma</i> antigen (serum, urine) Fungal culture of blood or bone marrow aspirate Cytopathology on biopsy of affected organ	Lipid AmB (3–5 mg/kg per day) for 1–2 weeks; then itraconazole (200 mg bid) for at least 12 months. Monitor renal and hepatic function.	Liposomal AmB is preferred, but the AmB lipid complex may be used because of cost. Chronic maintenance therapy may be necessary if the degree of immunosuppression cannot be reduced.
Central nervous system	<i>Histoplasma</i> antigen and serology of CSF Fungal culture of CSF	Liposomal AmB (5 mg/kg per day) for 4–6 weeks; then itraconazole (200 mg bid or tid) for at least 12 months. Monitor renal and hepatic function.	A longer course of lipid AmB is recommended because of the high risk of relapse. Itraconazole should be continued until CSF or CT abnormalities clear.

Abbreviations: AmB, amphotericin B; BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid.

TREATMENT**Histoplasmosis**

- See Table 108-4 for treatment recommendations.
- Fibrosing mediastinitis, which represents a chronic fibrotic reaction to past mediastinal histoplasmosis rather than an active infection, does not respond to antifungal therapy.

COCCIDIOIDOMYCOSIS**■ MICROBIOLOGY AND EPIDEMIOLOGY**

Coccidioidomycosis is caused by the two species of the dimorphic soil-dwelling fungus *Coccidioides*: *C. immitis* and *C. posadasii*. These organisms exist as branching, filamentous molds.

- Coccidioidomycosis is confined to the Western Hemisphere between the latitudes of 40°N and 40°S. The disease is highly endemic in California, Arizona, and other areas of the southwestern United States, with ~43 cases per 100,000 residents in 2011; northern Mexico and localized regions in Central and South America also account for cases of infection.
- Direct exposure to soil harboring *Coccidioides* increases risk, but infection, which results from inhalation of airborne arthroconidia, can occur without overt soil exposure and may be related to other climatic factors (e.g., periods of dryness after rainy seasons).

■ CLINICAL MANIFESTATIONS

Approximately 60% of infected pts are asymptomatic; the remaining 40% have primarily pulmonary disease characterized by fever, cough, and pleuritic chest pain.

- Primary pulmonary infection is sometimes associated with erythema nodosum, erythema multiforme, arthralgias, and arthritis.
 - A history of night sweats, profound fatigue, eosinophilia, and hilar or mediastinal lymphadenopathy suggests the disease.
 - Pneumonic complications include pulmonary nodules (resembling pulmonary malignancies) and pulmonary cavities (a thin-walled lesion in a bronchus that is associated with cough, hemoptysis, and pleuritic chest pain).
- Disseminated infection affects <1% of infected pts, most commonly pts with depressed cellular immunity and pregnant women.
 - Common sites for dissemination include bone, skin, joint, soft tissue, and meninges.
 - Pts with meningitis present with persistent headache, lethargy, confusion, mild to moderate nuchal rigidity, and CSF with lymphocytic pleocytosis and profound hypoglycorrhachia. The mortality rate is ~100% without treatment.

■ DIAGNOSIS

Clinical findings that suggest coccidioidomycosis include eosinophilia, hilar or mediastinal adenopathy on radiographic imaging, marked fatigue, and failure to improve with antibiotic therapy. Serology and culture are the primary means of diagnosis. The laboratory should be alerted about the possible diagnosis to avoid exposure.

- Tube-precipitin (TP) and complement-fixation (CF) assays, immunodiffusion, and an enzyme immunoassay (EIA) are available to detect IgM and IgG antibodies.

- TP antibody does not gauge disease progression and is not found in CSF.
- Rising CF titers in serum are associated with clinical progression, and CF antibody in CSF indicates meningitis.
- EIA frequently yields false-positive results.
- Examination of sputum or other respiratory fluids after Papanicolaou, Gomori methenamine silver, or calcofluor white staining reveals spherules in many pts with pulmonary disease.

TREATMENT

Coccidioidomycosis

- The vast majority of pts with coccidioidomycosis do not require treatment. Exceptions include the following:
 - Pts with focal primary pneumonia *and* underlying cellular immunodeficiency or prolonged symptoms (i.e., symptoms persisting for ≥ 2 months, night sweats occurring for >3 weeks, weight loss of $>10\%$, a serum CF antibody titer of $>1:16$, and extensive pulmonary involvement apparent on CXR) should be treated with fluconazole (≥ 400 mg/d) or itraconazole (400–600 mg/d).
 - Pts with diffuse pulmonary disease are often treated initially with AmB (deoxycholate, 0.7–1 mg/kg IV qd; liposomal, 3–5 mg/kg IV qd), with a switch to prolonged therapy with an oral triazole once clinical improvement occurs.
 - Pts with chronic pulmonary disease or disseminated infection are treated with a triazole for ≥ 1 year. Relapse occurs in 15–30% of individuals once therapy is discontinued.
 - Pts with meningitis require lifelong triazole therapy; fluconazole is the drug of choice. If triazole therapy fails, intrathecal or intraventricular AmB may be used. Relapse occurs in 80% of pts when therapy is stopped.
 - Surgical extirpation of pulmonary cavities >4 cm in diameter should be considered.

BLASTOMYCOSIS

■ MICROBIOLOGY AND EPIDEMIOLOGY

Blastomyces dermatitidis is a dimorphic fungus that is found in the southeastern and south-central states bordering the Mississippi and Ohio river basins, in areas of the United States and Canada bordering the Great Lakes and the St. Lawrence River, and sporadically in Africa, the Middle East, and India. Infection is caused by inhalation of *Blastomyces* from moist soil rich in organic debris.

■ CLINICAL MANIFESTATIONS

Acute pulmonary infection can present as abrupt-onset fever, chills, pleuritic chest pain, myalgias, and arthralgias. However, most pts with pulmonary blastomycosis have chronic indolent pneumonia with fever, weight loss, productive cough, and hemoptysis. Skin disease is common and can present as verrucous (more common) or ulcerative lesions. Blastomycosis can include osteomyelitis in one-fourth of infections and CNS disease in $\sim 40\%$ of pts with AIDS.

■ DIAGNOSIS

Smears of clinical samples or cultures of sputum, bronchial washings, pus, or tissue are required for diagnosis. Antigen detection in urine and serum may help diagnose infection and monitor pts during therapy.

TREATMENT**Blastomycosis**

- Every pt should be treated because of the high risk of dissemination.
 - For immunocompetent pts with nonsevere disease that does not involve the CNS, itraconazole (200–400 mg/d for 6–12 months) is recommended.
 - Immunocompetent pts with severe disease or CNS manifestations should be treated initially with AmB (deoxycholate, 0.7–1 mg/kg IV qd; liposomal, 3–5 mg/kg IV qd); once their clinical condition improves, therapy can be switched to itraconazole (or, for those with CNS disease, fluconazole, 800 mg/d).
 - Immunocompromised pts with any form of infection should be treated initially with AmB, with a switch to a triazole, as above, once clinical improvement has occurred.

MALASSEZIA INFECTION

Malassezia species are components of the normal skin flora and can cause tinea (pityriasis) versicolor, round scaly patches of hypo- or hyperpigmented skin on the neck, chest, or upper arms. *M. furfur* causes catheter-related fungemia in premature neonates receiving IV lipids by central venous catheter. Topical creams and lotions for 2 weeks are effective in treating superficial *Malassezia* infections; fungemia caused by *Malassezia* species is treated with AmB or fluconazole, prompt removal of the catheter, and discontinuation of the lipid infusion.

SPOROTRICHOSIS**■ MICROBIOLOGY AND EPIDEMIOLOGY**

Sporothrix schenckii is a dimorphic fungus found worldwide in soil, on plants, and on animals. Infection, which results from inoculation of the organism into the skin, is most common among people who participate in landscaping, gardening, or tree farming.

■ CLINICAL MANIFESTATIONS

Lymphocutaneous sporotrichosis involves secondary lesions (papules that are not very painful and often ulcerate) developing along lymphatic channels proximally from the initial site of inoculation. Other presentations include a fixed lesion (verrucous or ulcerative) at the initial site of inoculation without lymphatic spread, osteoarticular disease (chronic synovitis or septic arthritis in alcoholics), pulmonary disease (most common among pts with chronic obstructive pulmonary disease), and disseminated disease (numerous skin lesions with occasional spread to visceral organs in immunocompromised pts).

■ DIAGNOSIS

Culture of material from a skin lesion or histopathologic examination of a skin biopsy sample can confirm the diagnosis.

TREATMENT**Sporotrichosis**

- Cutaneous and lymphocutaneous sporotrichosis is treated with itraconazole (200 mg/d) until 2–4 weeks after lesions resolve, usually for a total of 3–6 months.

- For extracutaneous disease, itraconazole (200 mg bid for ≥ 12 months) can be given, but initial therapy with liposomal AmB (3–5 mg/kg qd) is more effective for life-threatening pulmonary disease or disseminated infection.

PARACOCCIDIOIDOMYCOSIS

Paracoccidioidomycosis (South American blastomycosis) is caused by *Paracoccidioides brasiliensis*, a dimorphic fungus acquired by inhalation from environmental sources. Acute infection occurs in young or immunocompromised pts and manifests as disseminated infection of the reticuloendothelial system. Chronic infection accounts for 90% of cases and presents primarily as progressive pulmonary disease with occasional ulcerative and nodular mucocutaneous lesions in the nose and mouth. Diagnosis relies on culture of the organism. Itraconazole (100–200 mg/d for 6–12 months) is effective, but AmB may be required for seriously ill pts.

TALAROMYCOSIS (PENICILLIOSIS)

Talaromyces marneffeii (formerly *Penicillium marneffeii*) is a leading cause of opportunistic infection in pts with immunocompromise (e.g., due to AIDS) in Southeast Asia and is acquired by spore inhalation. Clinical manifestations are similar to those of disseminated histoplasmosis, with fever, fatigue, weight loss, lymphadenopathy, hepatomegaly, and skin lesions resembling molluscum contagiosum. The organism grows readily in culture and produces a distinctive red pigment. AmB is the initial treatment of choice for severely ill pts; less severe disease may be treated with itraconazole (200 mg bid for 12 weeks). Suppressing therapy with itraconazole (200 mg/d) may be indicated for pts with HIV infection or AIDS until the CD4+ T cell count is >100 cells/ μL for ≥ 6 months.

FUSARIOSIS

Fusarium species are found worldwide in soil and on plants; inhalation, ingestion, and direct inoculation of spores can cause disease, particularly disseminated disease in immunocompromised pts. Fusariosis is angioinvasive and has clinical manifestations similar to those of aspergillosis. One difference is that painful nodular or necrotic skin lesions are extremely common with disseminated fusariosis. Blood cultures are positive in 50% of cases; the organism is difficult to differentiate from *Aspergillus* in tissue. *Fusarium* species are often resistant to antifungal agents; liposomal AmB (≥ 5 mg/kg qd), voriconazole (200–400 mg bid), or posaconazole (300 mg/d) is recommended. Even with treatment, mortality rates are $\sim 50\%$.

SCEDOSPORIOSIS

Scedosporium apiospermum and *Lomentospora prolificans* (formerly *S. prolificans*) are molds that are angioinvasive, causing pneumonia and widespread dissemination with abscesses (including brain abscess) in immunocompromised hosts. Most disseminated infections are fatal. These organisms are resistant to AmB, echinocandins, and some azoles. Voriconazole is the agent of choice for *S. apiospermum* infection, which has a mortality rate of $\sim 50\%$; invasive disease caused by *L. prolificans*, which is resistant in vitro to every available antifungal agent, has a mortality rate of 85–100%.

DERMATOPHYTOSIS

See Chap. 61.

109 Overview of Parasitic Infections



Parasites have a eukaryotic cell structure similar to that of human cells and are divided into two types: helminths and protozoa.

- *Helminths* are flatworms and roundworms that can be seen with the naked eye. Some helminths mature from larvae into adults in the GI tract (making humans the definitive host) and usually cause mild disease. In contrast, the larval stage of some helminths penetrates the intestine; migrates through tissue; invades organs, where larvae mature into adults (making humans an intermediate host); and may cause severe disease.
 - Except for *Strongyloides* and *Capillaria*, all helminths require stages in other hosts to complete their life cycle. Thus increases in the burden of infection require repeated exogenous infections (e.g., residence in an endemic region).
- *Protozoa* are microscopic single-celled organisms that, similar to bacteria, multiply within the human body and cause overwhelming infections.
 - Naïve pts with their first protozoal infection usually are the most severely affected because partial immunity often limits the number of parasites during recurrent infections.
- **Table 109-1** breaks down the symptoms of major parasitic infections by organ system and geographic distribution, with comments on clinical and epidemiologic associations.

TABLE 109-1 Parasitic Infections, by Organ System and Signs/Symptoms

ORGAN SYSTEM, MAJOR SIGN(S)/SYMPTOM(S)	PARASITE(S)	GEOGRAPHIC DISTRIBUTION	COMMENTS
Skin			
Serpentine rash	Hookworm	Worldwide	Can cause anemia in heavy infections
	<i>Strongyloides</i>	Moist tropics and subtropics	Disseminated infection in immunocompromise
	<i>Toxocara</i> (animal roundworm)	Tropical and temperate zones	Cutaneous or visceral larva migrans
Itchy skin rash	<i>Onchocerca</i>	Mexico, Central/South America, Africa	Larvae detectable in skin snips and nodules
Painless ulcers	<i>Leishmania</i>	Tropics and subtropics	Amastigotes detectable in biopsies; may cause destructive mucocutaneous infection; AIDS-defining infection
Skin nodules	<i>Onchocerca</i>	Mexico, South America, Africa	Large nodules of adult worms
	<i>Loa loa</i> (African eye worm)	Western and central Africa	Migratory nodules
	<i>Gnathostoma</i>	Southeast Asia and China	Migratory nodules with eosinophilia

(Continued)

TABLE 109-1 Parasitic Infections, by Organ System and Signs/Symptoms (Continued)

ORGAN SYSTEM, MAJOR SIGN(S)/ SYMPTOM(S)	PARASITE(S)	GEOGRAPHIC DISTRIBUTION	COMMENTS
Painful nodules, especially involving feet	<i>Dracunculus</i> (Guinea worm)	Africa	Nearly eradicated
Central nervous system			
Somnolence, seizures, coma	<i>Plasmodium falciparum</i>	Subtropics and tropics	Cerebral malaria, especially in children
	<i>Trypanosoma brucei rhodesiense</i>	Sub-Saharan eastern Africa	Painful chancre from tsetse fly bite; death in weeks to months
Space-occupying lesions, seizures	<i>Acanthamoeba</i>	Worldwide	Immunocompromised individuals
	<i>Balamuthia</i>	Americas	Indolent meningoencephalitis with brain mass
	<i>Toxoplasma</i>	Worldwide	Reactivation disease in immunocompromise; ring-enhancing lesions; AIDS-defining infection
	<i>Taenia solium</i>	Mexico, Central/South America, Africa	Cysticercosis; variable sized or calcified larval cysts on CT
	<i>Schistosoma japonicum</i>	Far East	Aberrant eggs can form brain or spinal cord masses.
	<i>Schistosoma mansoni</i>	Africa, Central/South America	Aberrant eggs can form brain or spinal cord masses.
Pyogenic meningitis	<i>Naegleria</i>	Worldwide	Motile trophozoites in fresh cerebrospinal fluid; rapid death
Eosinophilic meningitis	<i>Angiostrongylus</i> (rat lung worm)	Southeast Asia, Pacific, Caribbean	Most common cause globally; spontaneous resolution
	<i>Gnathostoma</i>	Southeast Asia and China	Migratory nodules
Eyes			
Painful corneal ulcers	<i>Acanthamoeba</i>	Worldwide	Freshwater and brackish water; corneal trauma; long-wear contact lenses
Corneal opacification	<i>Onchocerca</i>	Mexico, Central/South America, Africa	Immune response to microfilaria in cornea

(Continued)

TABLE 109-1 Parasitic Infections, by Organ System and Signs/Symptoms (Continued)

ORGAN SYSTEM, MAJOR SIGN(S)/SYMPTOM(S)	PARASITE(S)	GEOGRAPHIC DISTRIBUTION	COMMENTS
Congenital or adult visual loss	<i>Toxoplasma</i>	Worldwide	Primary infection in pregnancy and subsequent primary or reactivation infection
Retinal mass	<i>Toxocara</i>	Worldwide	Ocular larva migrans
Visible roundworm in eye	<i>Onchocerca</i>	Mexico, Central/South America, Africa	Worms may cross eye during migration.
	<i>L. loa</i>	Western and central Africa	Worms may cross eye during migration.
Pain, possible vision loss	<i>Gnathostoma</i>	Southeast Asia and China	Migratory skin nodules, eosinophilia
Lungs			
Pulmonary nodule/abscess	<i>Paragonimus</i>	Far East, Africa, Americas	Ectopic migration to abdomen or central nervous system
Cough, transient infiltrates, eosinophilia	Migrating helminths	Worldwide	Loeffler's syndrome from migrating <i>Ascaris</i> , hookworm, <i>Strongyloides</i>
Heart			
Pulmonary edema	<i>P. falciparum</i> (complication)	Tropics and subtropics	End-organ damage from severe malaria
Cardiomegaly, arrhythmias	<i>Trypanosoma cruzi</i>	Mexico, Central/South America	Late amastigote infection of myocardium; AIDS-defining infection
Gastrointestinal tract			
Hepatosplenomegaly	Malaria (multiple episodes)	Tropics and subtropics	Splenomegaly with anemia and recurrent fever are hallmarks of malaria.
	<i>S. mansoni</i>	Africa, Central/South America	Portal obstruction with cirrhosis and late varices
	<i>Leishmania donovani</i> complex	Tropics and subtropics	Visceral leishmaniasis; AIDS-defining infection
Hepatomegaly	<i>Entamoeba histolytica</i>	Tropics	Acute with fever, right-upper-quadrant pain; or chronic with enlarged liver; hypochoic abscess(es) on ultrasound or CT
	<i>Echinococcus</i>	Sheep-raising areas	Characteristic cysts of liver > lung

(Continued)

TABLE 109-1 Parasitic Infections, by Organ System and Signs/Symptoms (Continued)

ORGAN SYSTEM, MAJOR SIGN(S)/SYMPTOM(S)	PARASITE(S)	GEOGRAPHIC DISTRIBUTION	COMMENTS
	<i>Fasciola</i>	Sheep-raising areas	Eosinophilia
Cholangitis	<i>Clonorchis</i>	China, Southeast Asia	Recurrent cholangitis and late cholangiocarcinoma
	Microsporidia	Worldwide	AIDS
	<i>Cryptosporidium</i>	Worldwide	AIDS-defining infection
Bloody diarrhea	<i>E. histolytica</i>	Tropics	Less fever than in diarrhea of bacterial etiology
	<i>S. mansoni</i>	Africa, Central/South America	Only in heavy, acute infection with fever and eosinophilia
	<i>S. japonicum</i>	Far East	Only in heavy, acute infection
Watery diarrhea	<i>Cryptosporidium</i>	Worldwide	Severe in immunocompromised pts
	<i>Giardia</i>	Worldwide	Foul-smelling stool with steatorrhea
	<i>Isospora belli</i>	Worldwide	Fever, abdominal pain, chronic diarrhea
	Microsporidia	Worldwide	Chronic diarrhea with AIDS
	<i>Capillaria</i>	Southeast Asia, Egypt	Malabsorption, wasting
Passage of large roundworm (>6 cm)	<i>Ascaris</i>	Worldwide	Pts may confuse the roundworm with an earthworm.
Small roundworms visible around anus	Pinworm	Worldwide	Anal itching; eggs rarely detected by ova and parasite (O&P) exam
	<i>Trichuris</i>	Worldwide	Rectal prolapse with heavy infection in children
Passage of tapeworm segments	<i>T. solium</i> or <i>Taenia saginata</i>	Worldwide	Usual reason for seeking medical care
	<i>Diphyllobothrium latum</i>	Worldwide	Pernicious anemia in genetically predisposed Scandinavians
Genitourinary system			
Itchy discharge	<i>Trichomonas vaginalis</i>	Worldwide	Common sexually transmitted disease of both sexes

(Continued)

TABLE 109-1 Parasitic Infections, by Organ System and Signs/Symptoms (Continued)

ORGAN SYSTEM, MAJOR SIGN(S)/SYMPTOM(S)	PARASITE(S)	GEOGRAPHIC DISTRIBUTION	COMMENTS
Hematuria	<i>Schistosoma haematobium</i>	Africa	Hematuria with negative cultures, urinary tract infections, and late bladder cancer
Muscular system			
Myalgias, myositis	<i>Trichinella</i>	Worldwide	Palpebral swelling; high-level eosinophilia
Bloodstream			
Fever without localizing symptoms	<i>Plasmodium</i>	Tropics and subtropics	Consider in any pt from a malarious area.
	<i>Babesia</i>	New England, United States	Geographically limited; worse with splenectomy
	<i>T. brucei rhodesiense</i> , <i>T. brucei gambiense</i>	Sub-Saharan Africa	Limited to tsetse fly range; painful chancre; adenopathy and cyclical fevers; early (<i>rhodesiense</i>) or late (<i>gambiense</i>) central nervous system involvement
	Filariae	Asia, India	Periodic fever with eosinophilia, adenolymphangitis, chronic lymphangitis
	<i>L. donovani</i> complex	Tropics and subtropics	Hepatosplenomegaly, fever, wasting; AIDS-defining infection

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Malaria, Toxoplasmosis, Babesiosis, and Other Protozoal Infections



MALARIA

■ MICROBIOLOGY AND EPIDEMIOLOGY

Six major species of *Plasmodium* cause nearly all cases of human disease: *P. falciparum*, *P. vivax*, two morphologically identical sympatric species of *P. ovale*, *P. malariae*, and *P. knowlesi*.

- *P. falciparum*, the cause of most cases of severe disease and most deaths, predominates in Africa, New Guinea, and Hispaniola.

- *P. vivax* is more common in Central America.
- *P. falciparum* and *P. vivax* are equally prevalent in South America, the Indian subcontinent, eastern Asia, and Oceania.
- *P. ovale* makes up <1% of isolates outside Africa.
- *P. malariae* is found in most areas (especially throughout sub-Saharan Africa) but is less common.
- *P. knowlesi* (the monkey malaria parasite) can reliably be identified only by molecular techniques and is present in Borneo and Southeast Asia.
- Malaria is the most important parasitic disease in humans, causing ~1200 deaths each day.

■ PATHOGENESIS

After introduction of *sporozoites* into the bloodstream by female anopheline mosquitoes, the parasite travels to the liver and reproduces asexually to form *merozoites* that infect RBCs. The merozoites transform into *trophozoites*, feed on intracellular proteins (principally hemoglobin), multiply 6- to 20-fold every 48 h (*P. knowlesi*, 24 h; *P. malariae*, 72 h), and cause the RBCs to rupture, releasing daughter merozoites. The process then repeats.

- Some parasites develop into long-lived sexual forms called *gametocytes*, whose uptake by another female anopheline mosquito allows transmission.
- In *P. vivax* or *P. ovale* infection, dormant forms called *hypnozoites* remain in liver cells and may cause disease 2 weeks to >1 year later.
- RBCs infected with *P. falciparum* may exhibit *cytoadherence* (attachment to venular and capillary endothelium), *rosetting* (adherence to uninfected RBCs), and *agglutination* (adherence to other infected RBCs). The result is sequestration of *P. falciparum* in vital organs, with consequent underestimation (through parasitemia determinations) of parasite numbers in the body. Sequestration is central to the pathogenesis of falciparum malaria but is not evident in the other human malarias.
- In nonimmune individuals, infection triggers nonspecific host defense mechanisms such as increased splenic filtration.
 - With repeated exposure to malaria, pts develop resistance to high-level parasitemia and disease but not to infection.
 - Hemoglobinopathies (e.g., sickle cell disease, ovalocytosis, thalassemia) and G6PD deficiency are more common in endemic areas and protect against death from malaria.

■ CLINICAL MANIFESTATIONS

Pts initially develop nonspecific symptoms (e.g., headache, fatigue, myalgias) that are followed by fever.

- Febrile paroxysms at regular intervals are unusual and suggest infection with *P. vivax* or *P. ovale*.
- Splenomegaly, hepatomegaly, mild anemia, and jaundice may develop.
- The diagnosis of severe falciparum malaria requires one or more of the following: impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, ARDS, circulatory shock, DIC, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and a parasitemia level of >5%.
 - Cerebral malaria manifests as diffuse symmetric encephalopathy, typically without focal neurologic signs.
 - Coma is an ominous sign associated with mortality rates of ~20%.
- Pregnant women have unusually severe illness. Premature labor, fetal distress, stillbirth, and delivery of low-birth-weight infants are common.

- Tropical splenomegaly (hyperreactive malarial splenomegaly) may result as a chronic complication of malaria and is characterized by massive splenomegaly, hepatomegaly, and an abnormal immunologic response to infection.

■ DIAGNOSIS

Although antibody-based diagnostic tests are being used with increasing frequency, demonstration of asexual forms of the parasite on peripheral-blood smears is required for diagnosis.

- Thick and thin smears should be examined; thick smears offer higher diagnostic sensitivity, and thin smears enable identification of the specific *Plasmodium* species.
- If the level of clinical suspicion is high and smears are initially negative, smear examination should be repeated daily for 2 days.
- Other laboratory findings generally include normochromic, normocytic anemia; elevated inflammatory markers; and thrombocytopenia ($\sim 10^5/\mu\text{L}$).

TREATMENT

Malaria

- See [Table 110-1](#) for treatment regimens. IV artesunate is approved by the U.S. Food and Drug Administration for emergency use against severe malaria through the Centers for Disease Control and Prevention (CDC) (Malaria Hotline: 855-856-4713; Emergency Operations Center [after hours]: 770-488-7100).

TABLE 110-1 Regimens for the Treatment of Malaria^a

TYPE OF DISEASE OR TREATMENT	REGIMEN(S)
Uncomplicated malaria	
Known chloroquine-sensitive strains of <i>Plasmodium vivax</i> , <i>P. malariae</i> , <i>P. ovale</i> , <i>P. falciparum</i> ^b	Chloroquine (10 mg of base/kg stat followed by 5 mg/kg at 12, 24, and 36 h or by 10 mg/kg at 24 h and 5 mg/kg at 48 h) or Amodiaquine (10–12 mg of base/kg qd for 3 days)
Radical treatment for <i>P. vivax</i> or <i>P. ovale</i> infection	In addition to chloroquine or amodiaquine as detailed earlier or ACT as detailed next, primaquine (0.5 mg of base/kg qd in Southeast Asia and Oceania and 0.25 mg/kg elsewhere) should be given for 14 days to prevent relapse. In mild G6PD deficiency, 0.75 mg of base/kg should be given once weekly for 8 weeks. Primaquine should not be given in severe G6PD deficiency.
<i>P. falciparum</i> malaria ^c	Artesunate ^d (4 mg/kg qd for 3 days) <i>plus</i> sulfadoxine (25 mg/kg)/pyrimethamine (1.25 mg/kg) as a single dose or Artesunate ^d (4 mg/kg qd for 3 days) <i>plus</i> amodiaquine (10 mg of base/kg qd for 3 days) ^e or Artemether-lumefantrine ^d (1.5/9 mg/kg bid for 3 days with food) or

(Continued)

TABLE 110-1 Regimens for the Treatment of Malaria^a (Continued)

TYPE OF DISEASE OR TREATMENT	REGIMEN(S)
	Artesunate ^d (4 mg/kg qd for 3 days) <i>plus</i> mefloquine (24–25 mg of base/kg—either 8 mg/kg qd for 3 days or 15 mg/kg on day 2 and then 10 mg/kg on day 3) ^e or DHA-piperaquine ^d (target dose: 4/24 mg/kg qd for 3 days in children weighing <25 kg and 4/18 mg/kg qd for 3 days in persons weighing ≥25 kg)
Second-line treatment/treatment of imported malaria	Artesunate ^d (2 mg/kg qd for 7 days) <i>or</i> quinine (10 mg of salt/kg tid for 7 days) <i>plus 1 of the following 3</i> : 1. Tetracycline ^f (4 mg/kg qid for 7 days) 2. Doxycycline ^f (3 mg/kg qd for 7 days) 3. Clindamycin (10 mg/kg bid for 7 days) or Atovaquone-proguanil (20/8 mg/kg qd for 3 days with food)
Severe falciparum malaria^{g,h}	
	Artesunate ^d (2.4 mg/kg stat IV followed by 2.4 mg/kg at 12 and 24 h and then daily if necessary; for children weighing <20 kg, give 3 mg/kg per dose) ^h or, if unavailable, Artemether ^d (3.2 mg/kg stat IM followed by 1.6 mg/kg qd) or, if unavailable, Quinine dihydrochloride (20 mg of salt/kg ⁱ infused over 4 h, followed by 10 mg of salt/kg infused over 2–8 h q8h) or, if none of the above are available, Quinidine (10 mg of base/kg ⁱ infused over 1–2 h, followed by 1.2 mg of base/kg per hour ^j with electrocardiographic monitoring)

^aIn endemic areas where malaria transmission is low, except in pregnant women and infants, a single dose of primaquine (0.25 mg of base/kg) should be added as a gametocytocide to all falciparum malaria treatments to prevent transmission. This addition is considered safe, even in G6PD deficiency.

^bVery few areas now have chloroquine-sensitive *P. falciparum* malaria.

^cIn areas where the partner drug to artesunate is known to be effective.

^dArtemisinin derivatives are not readily available in some temperate countries.

^eFixed-dose co-formulated combinations are available. The World Health Organization now recommends artemisinin combination regimens as first-line therapy for falciparum malaria in all tropical countries and advocates use of fixed-dose combinations.

^fTetracycline and doxycycline should not be given to pregnant women after 15 weeks of gestation or to children <8 years of age.

^gOral treatment should be substituted as soon as the pt recovers sufficiently to take fluids by mouth.

^hArtesunate is the drug of choice when available. The data from large studies in Southeast Asia showed a 35% lower mortality rate than with quinine, and very large studies in Africa showed a 22.5% reduction in mortality rate compared with quinine. The doses of artesunate in children weighing <20 kg should be 3 mg/kg.

ⁱA loading dose should not be given if therapeutic doses of quinine or quinidine have definitely been administered in the previous 24 h. Some authorities recommend a lower dose of quinidine.

^jInfusions can be given in 0.9% saline and 5–10% dextrose in water. Infusion rates for quinine and quinidine should be carefully controlled.

Abbreviations: ACT, artemisinin combination therapy; DHA, dihydroartemisinin; G6PD, glucose-6-phosphate dehydrogenase.

- Pts receiving quinidine should undergo cardiac monitoring; a total plasma level of $>8 \mu\text{g/mL}$, increased QT_c intervals ($>0.6 \text{ s}$), or QRS widening by $>25\%$ over baseline is an indication for slowing or temporarily stopping the infusion rate.
- Exchange transfusions can be considered for severely ill pts, although indications for their use are not yet agreed upon.
- All pts with severe malaria should receive a continuous infusion of dextrose. Unconscious pts should have blood glucose levels measured q4–6h.
- Parasite counts and hematocrits for pts with severe malaria and pts with uncomplicated disease should be measured q6–12h and q24h, respectively.
- Primaquine (0.5 mg of base/kg for 14 days) eradicates persistent liver stages and prevents relapse in *P. vivax* or *P. ovale* infection. G6PD deficiency must be ruled out before treatment.

■ PERSONAL PROTECTION MEASURES

Measures that can protect persons against infection include avoidance of mosquito exposure, with particular caution at peak feeding times (dusk to dawn); use of insect repellents containing DEET (10–35%) or (if DEET is unacceptable) picaridin (7%); suitable clothing; and insecticide-impregnated bed nets.

■ CHEMOPROPHYLAXIS

See [Table 110-2](#) for prophylaxis options.

- Mefloquine is the only drug advised for pregnant women traveling to areas with drug-resistant malaria and is generally considered safe in the second and third trimesters; data regarding use in the first trimester, although limited, are reassuring.

BABESIOSIS

■ MICROBIOLOGY

Babesiosis is caused by intraerythrocytic protozoa of the genus *Babesia*. *B. microti*, the cause of most cases, is the etiologic agent in the northeastern and upper midwestern United States, *B. duncani* is responsible for disease on the West Coast, and *B. divergens*-like organisms cause disease in Arkansas, Kentucky, Missouri, and Washington. The deer tick (*Ixodes scapularis*) transmits *B. microti*.

■ EPIDEMIOLOGY

In the United States, infections occur most frequently in the Northeast and upper Midwest. In 2016, >1600 cases were reported in the United States, with $\sim 75\%$ of cases presenting between June and August; this number is probably an underestimate, given that most pts experience a mild and self-limiting disease and may not seek medical attention.

■ CLINICAL MANIFESTATIONS

Most pts develop a mild illness, but immunosuppressed pts may have more severe disease. Twenty percent of adults and 40% of children develop asymptomatic infection that may persist for >2 years.

- After an incubation period of 1–4 weeks, pts gradually develop fevers, fatigue, and weakness. Other symptoms may include chills, sweats, myalgias, arthralgias, headache, and—less often—photophobia, shortness of breath, and abdominal pain. Lymphadenopathy is absent. Symptoms typically last 1–2 weeks, although fatigue may persist for months.
- Severe babesiosis is associated with parasitemia levels of $>4\%$.
 - Risk factors include an age of >50 years, neonatal prematurity, asplenia/hyposplenism, HIV infection/AIDS, malignancy, and immunosuppression.

TABLE 110-2 Drugs Used in the Prophylaxis of Malaria

DRUG	USAGE	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
Atovaquone-proguanil (Malarone)	Prophylaxis in areas with chloroquine- or mefloquine-resistant <i>Plasmodium falciparum</i>	1 adult tablet PO ^a	5–8 kg: ½ pediatric tablet ^b daily ≥8–10 kg: ¾ pediatric tablet daily ≥10–20 kg: 1 pediatric tablet daily ≥20–30 kg: 2 pediatric tablets daily ≥30–40 kg: 3 pediatric tablets daily ≥40 kg: 1 adult tablet daily	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 7 days after leaving such areas. Atovaquone-proguanil is contraindicated in persons with severe renal impairment (creatinine clearance rate, <30 mL/min). In the absence of data, it is not recommended for children weighing <5 kg, pregnant women, or women breast-feeding infants weighing <5 kg. Atovaquone-proguanil should be taken with food or a milky drink.
Chloroquine phosphate (Aralen and generic)	Prophylaxis only in areas with chloroquine-sensitive <i>P. falciparum</i> ^c or areas with <i>P. vivax</i> only	300 mg of base (500 mg of salt) PO once weekly	5 mg of base/kg (8.3 mg of salt/kg) PO once weekly, up to maximum adult dose of 300 mg of base	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Chloroquine phosphate may exacerbate psoriasis.
Doxycycline (many brand names and generic)	Prophylaxis in areas with chloroquine- or mefloquine-resistant <i>P. falciparum</i> ^c	100 mg PO qd (except in pregnant women; see Comments)	≥8 years of age: 2 mg/kg, up to adult dose	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 4 weeks after leaving such areas. Doxycycline is contraindicated in children aged <8 years and in pregnant women after 15 weeks of gestation.

(Continued)

TABLE 110-2 Drugs Used in the Prophylaxis of Malaria (Continued)

DRUG	USAGE	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
Hydroxychloroquine sulfate (Plaquenil)	An alternative to chloroquine for primary prophylaxis only in areas with chloroquine-sensitive <i>P. falciparum</i> ^c or areas with <i>P. vivax</i> only	310 mg of base (400 mg of salt) PO once weekly	5 mg of base/kg (6.5 mg of salt/kg) PO once weekly, up to maximum adult dose of 310 mg of base	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Hydroxychloroquine may exacerbate psoriasis.
Mefloquine (Lariam and generic)	Prophylaxis in areas with chloroquine-resistant <i>P. falciparum</i> ^c	228 mg of base (250 mg of salt) PO once weekly	<p>≤9 kg: 4.6 mg of base/kg (5 mg of salt/kg) PO once weekly</p> <p>10–19 kg: ¼ tablet^d once weekly</p> <p>20–30 kg: ½ tablet once weekly</p> <p>31–45 kg: ¾ tablet once weekly</p> <p>≥46 kg: 1 tablet once weekly</p>	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Mefloquine is contraindicated in persons allergic to this drug or related compounds (e.g., quinine and quinidine) and in persons with active or recent depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in persons with psychiatric disturbances or a history of depression. Mefloquine is not recommended for persons with cardiac conduction abnormalities.

Primaquine	For prevention of malaria in areas with mainly <i>P. vivax</i>	30 mg of base (52.6 mg of salt) PO qd	0.5 mg of base/kg (0.8 mg of salt/kg) PO qd, up to adult dose; should be taken with food	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 7 days after leaving such areas. Primaquine is contraindicated in persons with G6PD deficiency. It is also contraindicated during pregnancy.
Primaquine	Used for presumptive anti-relapse therapy (terminal prophylaxis) to decrease risk of relapses of <i>P. vivax</i> and <i>P. ovale</i>	30 mg of base (52.6 mg of salt) PO qd for 14 days after departure from the malarious area	0.5 mg of base/kg (0.8 mg of salt/kg), up to adult dose, PO qd for 14 days after departure from the malarious area	This therapy is indicated for persons who have had prolonged exposure to <i>P. vivax</i> and/or <i>P. ovale</i> . It is contraindicated in persons with G6PD deficiency as well as during pregnancy.

^aAn adult tablet contains 250 mg of atovaquone and 100 mg of proguanil hydrochloride.

^bA pediatric tablet contains 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride.

^cVery few areas now have chloroquine-sensitive malaria.

^dOne tablet contains 228 mg of base (250 mg of salt).

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.

Source: CDC: Choosing a drug to prevent malaria. Available from www.cdc.gov/malaria/travelers/drugs.html.

- Complications include ARDS, DIC, CHF, renal failure, hemophagocytic lymphohistiocytosis, and splenic infarcts and rupture.
- The fatality rate is 3–9% among all hospitalized pts and 20% among immunocompromised pts and those who acquire the infection through blood transfusion.

■ DIAGNOSIS

Giemsa-stained thin smears identify intraerythrocytic *Babesia* parasites, which appear round, pear-shaped, or ameboid.

- Ring forms resembling *P. falciparum* but without pigment are most common.
- Tetrad (“Maltese crosses”)—formed by four budding merozoites—are pathognomonic for *B. microti* and other small *Babesia* species.
- PCR and serology can also be used for diagnostic purposes.

TREATMENT

Babesiosis

- Mild to moderate illness should be treated with atovaquone (750 mg PO q12h) plus azithromycin (500 mg PO on day 1 followed by 250 mg/d PO) for 7–10 days.
 - Clindamycin plus quinine is equally effective but not as well tolerated.
- Severe disease should be treated with azithromycin (500 mg IV q24h) and atovaquone (750 mg PO q12h) for 7–10 days.
 - Clindamycin (300–600 mg q6h IV or 600 mg q8h PO) plus quinine (650 mg q6–8h PO) is an alternative.
 - Consider exchange transfusion in pts with high-level parasitemia (>10%); hemoglobin levels of ≤ 10 g/dL; or pulmonary, hepatic, or renal compromise.
 - Immunocompromised pts generally need longer courses of treatment (e.g., 6 weeks), with at least 2 weeks of therapy after parasites are no longer detected on blood smear.
- *B. duncani* and *B. divergens* infections can be treated with IV clindamycin and quinine for 7–10 days.

TOXOPLASMOSIS

■ MICROBIOLOGY AND EPIDEMIOLOGY

Toxoplasmosis is caused by the intracellular parasite *Toxoplasma gondii*; cats and their prey are the definitive hosts. The primary route of transmission to humans is ingestion of tissue cysts from soil, food (e.g., undercooked meat), or water contaminated by cat feces.

- Roughly one-third of women who contract *T. gondii* during pregnancy transmit the parasite to the fetus, with a 65% risk of transmission if maternal infection is acquired in the third trimester.
- In the United States and most European countries, seroconversion rates increase with age and exposure. In the United States in 2009–2010, 13.2% of individuals >6 years old had serologic evidence of exposure; rates are higher in most other regions of the world.

■ PATHOGENESIS

Both humoral and cellular immunity are important, but subclinical infection commonly persists for the pt's lifetime. Immunocompromised hosts lack factors required to control infection; the consequences are progressive focal destruction and organ failure.

■ CLINICAL MANIFESTATIONS

Disease in immunocompetent hosts is usually asymptomatic (80–90% of cases) and self-limited and does not require therapy. In contrast, immunocompromised pts, including newborns, can develop severe infections typically involving the CNS.

- In the minority of immunocompetent pts who develop symptoms of acute infection, cervical lymphadenopathy is the most common finding; nodes are nontender and discrete. Generalized lymphadenopathy, fever $<40^{\circ}\text{C}$ ($<104^{\circ}\text{F}$), headache, malaise, and fatigue occur in 20–40% of pts. Clinical disease usually resolves within several weeks, although lymphadenopathy may persist for several months.
- Immunocompromised pts develop acute toxoplasmosis through reactivation of latent infection in 95% of cases; the remainder of cases are due to new acquisition of parasites.
 - CNS findings include encephalopathy, meningoencephalitis, and mass lesions. Pts may develop changes in mental status (75%), fever (10–72%), seizures (33%), headaches (56%), and focal neurologic findings (60%). The brainstem, basal ganglia, pituitary gland, and corticomedullary junction are most often involved.
- Multiple organs (e.g., lungs, GI tract, skin, eyes, heart, liver) can be affected.
 - *Toxoplasma* pneumonia is often confused with *Pneumocystis* pneumonia because of an overlapping pt population and similar clinical presentations (i.e., fever, dyspnea, and nonproductive cough rapidly progressing to respiratory failure).
- Congenital infection, which affects 400–4000 infants each year in the United States, may initially be asymptomatic but can result in reactivation and clinical disease (e.g., chorioretinitis) decades later.
- *Toxoplasma* causes ~35% of all cases of chorioretinitis in the United States and Europe. Blurred vision, macular involvement with loss of central vision, scotoma, photophobia, and eye pain are manifestations of infection. On examination, yellow-white cotton-like patches with indistinct margins of hyperemia are seen. Older lesions appear as white plaques with distinct borders and black spots.

■ DIAGNOSIS

Culture of the parasite is difficult and can be done only at specialized laboratories. Serology is the primary method of diagnosis.

- Results of IgM, IgG, and antibody avidity assays can be combined to help determine when infection may have occurred. (Of note, IgM can persist for >1 year.) These tests, along with a more extensive panel of serologic tests, can be performed at the *Toxoplasma* Serology Laboratory at the Palo Alto Medical Foundation (www.pamf.org/serology/clinicianguide.html).
- In immunocompromised pts, a presumptive clinical diagnosis can be based on clinical presentation, history of exposure (e.g., a positive IgG result), and radiologic evaluation. Radiologic studies demonstrate bilateral contrast-enhancing lesions, typically in the basal ganglia and corticomedullary junction. These lesions can be difficult to distinguish from CNS lymphoma, although the

latter more frequently consists of only a single lesion. A brain biopsy may be required for definitive diagnosis.

- Congenital toxoplasmosis is diagnosed by PCR of amniotic fluid (to detect the B1 gene of the parasite) and by the persistence of IgG antibody or a positive IgM titer after the first week of life; IgG antibody determinations should be repeated every 2 months.
- Ocular toxoplasmosis is diagnosed by the detection of typical lesions on ophthalmologic examination and the demonstration of a positive IgG titer in serum.

TREATMENT

Toxoplasmosis

- Immunocompetent pts with only lymphadenopathy do not require treatment unless they have persistent, severe symptoms.
- Immunocompromised pts should receive pyrimethamine plus sulfadiazine.
 - In resource-poor settings, trimethoprim-sulfamethoxazole (TMP-SMX; one double-strength tablet daily) is an effective alternative.
 - Either dapsone plus pyrimethamine or atovaquone with or without pyrimethamine is an alternative for pts who cannot take TMP-SMX.
- Congenital infection is treated daily for 1 year with oral pyrimethamine (1 mg/kg), sulfadiazine (100 mg/kg), and folinic acid.
- Ocular toxoplasmosis is treated with pyrimethamine and either sulfadiazine or clindamycin (and sometimes with prednisone) for 1 month.

■ CHEMOPROPHYLAXIS

The risk of disease is very high among AIDS pts who are seropositive for *T. gondii* and have a CD4+ T lymphocyte count of $<100/\mu\text{L}$. TMP-SMX (one double-strength tablet daily) should be given to these pts as prophylaxis against both *Pneumocystis* pneumonia and toxoplasmosis. Primary or secondary prophylaxis can be stopped if, after institution of antiretroviral treatment, the CD4+ T lymphocyte count remains $>200/\mu\text{L}$ for 3 months.

■ PERSONAL PROTECTION MEASURES

Toxoplasma infection can be prevented by the avoidance of undercooked meats and oocyst-contaminated materials (e.g., a cat's litter box).

LEISHMANIASIS

■ MICROBIOLOGY

Leishmania species are extracellular, flagellated promastigotes while dwelling in their sandfly vector, but are obligate intracellular, nonflagellated amastigotes while living in vertebrate hosts, including humans.

- Organisms of the *L. donovani* complex usually cause visceral leishmaniasis and are present in Asia, the Middle East, the horn of Africa, the Mediterranean, and Central and South America.
- *L. tropica*, *L. major*, and *L. aethiopica* cause Old World cutaneous leishmaniasis and are present in Asia and in northern and sub-Saharan Africa.
- The *L. mexicana* complex causes New World cutaneous leishmaniasis and is present in Central America and northern South America.

■ EPIDEMIOLOGY

More than 1.5 million cases of leishmaniasis occur annually worldwide, of which 0.7–1.2 million are cutaneous and 200,000–400,000 are visceral.

■ CLINICAL MANIFESTATIONS

Visceral leishmaniasis (kala-azar): Pts most commonly present with an abrupt onset of moderate- to high-grade fever associated with rigor and chills.

- Splenomegaly, hepatomegaly, and (except in the Indian subcontinent) lymphadenopathy are common.
- Leukopenia, anemia, thrombocytopenia, a polyclonal increase in serum immunoglobulins, and hepatic transaminitis are also common.
- Up to 50% of pts in India, East Africa, and the Sudan may develop hypopigmented skin lesions (post-kala-azar dermal leishmaniasis) concurrent with or after cure of visceral leishmaniasis. In some cases, these pts may require unusually long treatment courses.

Cutaneous leishmaniasis: After an incubation period of days or weeks, papular lesions progress to nodules that ulcerate over weeks or months. Lesions usually heal spontaneously after 2–15 months.

- The margins of the ulcer are raised and indurated, and the base of the ulcer is usually painless.
- Disease due to *L. tropica* may involve *leishmaniasis recidivans*: development of new scaly, erythematous papules in the area of a healed sore.

Mucosal leishmaniasis: This disfiguring sequela of New World cutaneous leishmaniasis results from dissemination of parasites from the skin to the nasopharyngeal mucosa.

- Disease may occur 1–5 years after the initial cutaneous episode.
- Persistent nasal congestion and bleeding are followed by progressive ulcerative destruction.
- These lesions do not resolve spontaneously.

■ DIAGNOSIS

- *Visceral leishmaniasis*: Identification of amastigotes in smears of tissue aspirates is the gold standard for diagnosis.
 - The sensitivity of splenic smears is >95%, but splenic aspiration may be very dangerous; smears of bone marrow and lymph node aspirates have sensitivities of 60–85% and 50%, respectively.
 - Several serologic techniques, including a rapid test, are available and offer good sensitivity and specificity.
- *Cutaneous and mucosal leishmaniasis*: Diagnosis is made by microscopy, culture, or PCR examination of aspirates and biopsy specimens from skin lesions and lymph nodes.

TREATMENT

Leishmaniasis

- *Visceral leishmaniasis*: The pentavalent antimonial (Sb^V) compounds sodium stibogluconate and meglumine antimoniate (20 mg/kg per day IV or IM for 28–30 days) are the first-line therapeutic agents and provide cure rates >90%.
 - Amphotericin B (AmB; either deoxycholate or a lipid formulation) is recommended in areas with Sb^V resistance (e.g., northeastern India) or if initial Sb^V therapy fails.

- Paromomycin and the oral agent miltefosine have been approved for the treatment of visceral leishmaniasis in India.
 - Liposomal AmB is the drug of choice for HIV-infected pts.
 - *Cutaneous leishmaniasis*: Although lesions generally resolve spontaneously, treatment may be needed if lesions spread or persist.
 - Topical agents can be effective for a few small lesions. Systemic treatment is needed for multiple lesions; lesions on the face, hands, or joints; and lesions of New World cutaneous leishmaniasis.
 - Administration of Sb^v (20 mg/kg daily for 20 days) constitutes the most effective treatment. Exceptions include disease due to *L. guyanensis* (pentamidine isethionate preferred) or *L. aethiopica* (paromomycin preferred).
 - *Mucosal leishmaniasis*: Sb^v (20 mg/kg for 30 days) is recommended.
 - Pts require long-term follow-up, and neither relapse nor failure of therapy is uncommon.
 - AmB and potentially miltefosine can be used in cases of relapse or therapy failure.
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TRYPANOSOMIASIS

■ CHAGAS DISEASE

Microbiology and Pathology

Trypanosoma cruzi causes Chagas disease (American trypanosomiasis) and is transmitted among mammalian hosts by blood-sucking triatomine bugs. Organisms disseminate through the bloodstream, preferentially infecting cardiac, skeletal, and smooth-muscle cells.

Epidemiology

T. cruzi is found exclusively in the Americas and causes disease mostly among the poor in rural areas of Mexico and Central and South America; however, given rapid urbanization and migration, the distribution of cases is extending to cities. An estimated 5.7 million people are infected, including >1 million individuals with chronic cardiomyopathy.

Clinical Manifestations

Acute infection resolves spontaneously—without treatment—in 5–10% of pts infected with *T. cruzi*; otherwise, pts develop chronic infection, with 30–40% sustaining detectable organ damage of variable severity.

- Acute disease develops 1–2 weeks after a bite by the triatomine bug, with >90% of individuals remaining asymptomatic or having a mild febrile illness. Local swelling develops at the inoculation site and is referred to as a *chagoma* if on the skin or as *Romana's sign* if on the eyelid. Disease resolves spontaneously within 4–8 weeks.
- Chronic disease is *indeterminate* until there are clinically apparent complications (the *determinate* form of chronic disease), which generally present as cardiac and/or digestive disorders years to decades after the initial infection. Symptoms include dyspnea, chest pain, palpitations, syncope, sudden death, stroke, dysphagia, regurgitation, constipation, fecaloma, volvulus, and peripheral neuropathy. The 5-year mortality rate is as high as 63% and is typically related to cardiac issues.

- Immunosuppressed pts may develop reactivation of acute disease, which can present as myocarditis, erythema nodosum, panniculitis, *Toxoplasma*-like focal brain lesion, or meningoencephalitis.

Diagnosis

Microscopic or PCR examination of peripheral blood, CSF, or other body fluids may reveal organisms in cases of acute Chagas disease. Chronic Chagas disease is diagnosed by detection of specific IgG antibodies. Given the frequency of false-positive results, diagnosis requires confirmation by at least two serologic assays.

TREATMENT

Chagas Disease

- Treatment is effective during the acute and early chronic phases (i.e., in pts <18 years of age), but its efficacy in pts >18 years of age is not known.
 - Treatment may protect against the development of later cardiac damage, but it is ineffective against digestive complications or preexisting chronic cardiomyopathy.
- Only two drugs—nifurtimox and benznidazole—are available to treat Chagas disease.
 - Benznidazole (5 mg/kg qd in two divided doses for 30–60 days) is the recommended first-line drug.
 - Nifurtimox (15 mg/kg qd in 3–4 divided oral doses for 60–90 days) reduces symptom duration, parasitemia level, and mortality rate but offers a parasitologic cure in only ~70% of cases.
 - Both drugs have a number of side effects. Benznidazole is better tolerated in adults.

■ SLEEPING SICKNESS

Microbiology and Epidemiology

Sleeping sickness (human African trypanosomiasis, HAT) is caused by parasites of the *T. brucei* complex and is transmitted via tsetse flies.

- *T. b. rhodesiense* causes the East African form and *T. b. gambiense* the West African form; these two forms are epidemiologically and clinically distinct illnesses.
- Humans are the only reservoir for *T. b. gambiense*; infection occurs primarily in rural populations and rarely develops in tourists. *T. b. rhodesiense* has reservoirs in antelope and cattle; tourists can be infected when visiting game parks.
- The incidence of HAT due to either subspecies decreased by ~90% between 1999 and 2015, with fewer than 3000 cases in 2015.

Pathogenesis and Clinical Manifestations

Following the bite of an infected tsetse fly, a trypanosomal chancre develops; trypanosomes disseminate into the hematolymphatic system; lymphadenopathy develops; and organisms multiply in the skin, skeletal muscles, serous membranes, and heart. The second stage of disease is marked by invasion of the CNS, which occurs weeks to months (*T. b. rhodesiense*) or months to years (*T. b. gambiense*) after initial infection.

- *T. b. gambiense*: After an incubation period of weeks to months, pts develop irregular and remittent fever, fatigue, malaise, myalgia, and painless edema of

the face. Serpiginous rashes (*trypanids*) can occur on the trunk and proximal parts of the extremities.

- Lymphadenopathy with discrete, rubbery, nontender nodes is prominent in *T. b. gambiense* disease. Enlargement of nodes of the lateroposterior cervical triangle (*Winterbottom's sign*) is a classic manifestation.
- *T. b. rhodesiense*: The incubation period is <3 weeks, after which high fever, headaches, diffuse myalgia, and arthralgia occur. Lymphadenopathy is less common than with *T. b. gambiense* and occurs in submandibular, axillary, and inguinal regions. Myocarditis and pericarditis influence clinical course and outcome.
- With second-stage disease, pts develop various sleep disturbances (daytime somnolence, nocturnal insomnia), with dysregulation of the daily sleep/wake cycle and fragmented sleep patterns. Other neurologic and psychiatric syndromes (e.g., motor weakness, rigidity, abnormal movements, ataxia, mood disorders, psychosis, apathy) can develop. Disease due to *T. b. rhodesiense* has a more rapid evolution toward coma and death.

Diagnosis

Examination of fluid from the chancre, thin or thick blood smears, buffy coats, lymph node aspirates, bone marrow biopsy specimens, or CSF can reveal the parasite. Serologic screening tests are available for *T. b. gambiense* but not *T. b. rhodesiense*.

- Parasitemia is more likely in stage 1 than in stage 2 disease and in pts infected with *T. b. rhodesiense* rather than *T. b. gambiense*.
- CSF should be examined for staging of the disease; >5 leukocytes/ μL and/or the presence of trypanosomes confirms second-stage HAT.

TREATMENT

Sleeping Sickness

Stage 1 disease

- *T. b. rhodesiense*: suramin (4–5 mg/kg on day 1 followed by 20 mg/kg on days 3, 10, 17, 24, and 31)
 - Pyrexia and nephrotoxicity are the most important adverse effects.
 - Albuminuria and renal function should be assessed before each dose.
- *T. b. gambiense*: pentamidine isethionate (4 mg/kg daily IM or IV for 7 days)
Hypotension after injection is common but generally mild.
Suramin is an alternative agent.

Stage 2 disease

- *T. b. rhodesiense*: melarsoprol (2.2 mg/kg IV daily for 10 days)
 - Reactive encephalopathy is a life-threatening adverse event that occurs in 5–18% of pts, with an associated mortality rate of 10–70%. The efficacy of concomitant high-dose prednisolone to prevent reactive encephalopathy in pts with *T. b. rhodesiense* HAT is not known.
- *T. b. gambiense*: eflornithine (200 mg/kg IV bid for 7 days) plus nifurtimox (5 mg/kg PO tid for 10 days)
 - Common adverse reactions include nausea, vomiting, abdominal pain, headaches, anorexia, and reversible bone-marrow toxicity.

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Helminthic Infections and Ectoparasite Infestations

**HELMINTHS****■ NEMATODES**

The nematodes, or roundworms, that are of medical significance can be broadly classified as either tissue or intestinal parasites.

Tissue Nematode Infections

With the exception of trichinellosis, these infections are due to invasive larval stages that do not reach maturity in humans.

TRICHINELLOSIS

MICROBIOLOGY AND EPIDEMIOLOGY Eight species of *Trichinella* cause human infection; two—*T. spiralis* and *T. pseudospiralis*—are found worldwide.

- Infection results when humans ingest meat (usually pork) that contains encysted *Trichinella* larvae.
 - The larvae invade the small-bowel mucosa.
 - After 1 week, female worms release new larvae that migrate to striated muscle via the circulation and encyst.
- The host immune response has few deleterious effects on muscle-dwelling larvae.
- About 12 cases of trichinellosis are reported annually in the United States.

CLINICAL MANIFESTATIONS Most light infections (<10 larvae per gram of muscle) are asymptomatic. A burden of >50 larvae per gram can cause fatal disease.

- In the first week of infection, large numbers of parasites invading the gut usually cause diarrhea, abdominal pain, constipation, nausea, and/or vomiting.
- In the second week of infection, pts develop symptoms related to larval migration and muscle invasion: hypersensitivity reactions with fever and hypereosinophilia; periorbital and facial edema; and hemorrhages in conjunctivae, retina, and nail beds. Deaths are usually due to myocarditis with arrhythmias or heart failure.
- Approximately 2–3 weeks after infection, larval encystment in muscle causes myositis, myalgias, muscle edema, and weakness (especially in extraocular muscles; the biceps; and muscles of the jaw, neck, lower back, and diaphragm).
- Symptoms peak at 3 weeks; convalescence is prolonged.

DIAGNOSIS Eosinophilia develops in >90% of pts, peaking at a level of >50% at 2–4 weeks after infection.

- An increase in parasite-specific antibody titers after the third week of infection confirms the diagnosis.
- Detection of larvae by microscopic examination of ≥1 g of fresh muscle tissue (i.e., not routine histopathologic sections) also confirms the diagnosis. Yields are highest near tendon insertions.

TREATMENT**Trichinellosis**

- Mebendazole (200–400 mg tid for 3 days; then 400 mg tid for 8–14 days) or albendazole (400 mg bid for 8–14 days) is active against enteric-stage parasites; the efficacy of these drugs against encysted larvae is inconclusive.

- Glucocorticoids (e.g., prednisone at 1 mg/kg daily for 5 days) may reduce severe myositis and myocarditis.

PREVENTION Cooking pork until it is no longer pink or freezing it at -15°C (5°F) for 3 weeks kills larvae and prevents infection by most *Trichinella* spp.

VISCERAL AND OCULAR LARVA MIGRANS

MICROBIOLOGY AND EPIDEMIOLOGY Humans are incidental hosts for nematodes that cause visceral larva migrans. Most cases are caused by the canine ascarid *Toxocara canis*. Infection results when humans—most often preschool children—ingest soil contaminated by puppy feces that contains infective *T. canis* eggs. Larvae penetrate the intestinal mucosa and disseminate hematogenously to a wide variety of organs (e.g., liver, lungs, CNS), provoking intense eosinophilic granulomatous responses.

CLINICAL MANIFESTATIONS Symptomatic infections result in fever, malaise, anorexia, weight loss, cough, wheezing, rashes, hepatosplenomegaly, and occasional profound eosinophilia (up to 90%). Ocular disease usually develops in older children or young adults and includes an eosinophilic mass that mimics retinoblastoma, endophthalmitis, uveitis, and/or chorioretinitis.

DIAGNOSIS The clinical diagnosis can be confirmed by an ELISA for toxocaral antibodies. Stool examination for eggs is ineffective because larvae do not develop into adult worms in humans.

TREATMENT

Visceral and Ocular Larva Migrans

- The vast majority of *Toxocara* infections are self-limited and resolve without specific therapy.
- For pts with severe disease, glucocorticoids can reduce inflammatory complications.
- Anthelmintic drugs, including mebendazole and albendazole, have not been shown to alter the course of larva migrans.
- Ocular disease can be treated with albendazole (800 mg bid) and glucocorticoids for 5–20 days.

CUTANEOUS LARVA MIGRANS

This disease is caused by larvae of animal hookworms, usually the dog and cat hookworm *Ancylostoma braziliense*. Larvae in contaminated soil penetrate human skin; intensely pruritic, erythematous lesions form along the tracks of larval migration and advance several centimeters each day. Ivermectin (a single dose of 200 $\mu\text{g}/\text{kg}$) or albendazole (200 mg bid for 3 days) can relieve the symptoms of this self-limited infestation.

Intestinal Nematode Infections

Intestinal nematodes infect >1 billion persons worldwide, most commonly in regions with poor sanitation and particularly in developing countries in the tropics or subtropics. Because most helminthic parasites do not self-replicate, clinical disease (as opposed to asymptomatic infection) generally develops only with prolonged residence in an endemic area and is typically related to infection intensity.

ASCARIASIS

MICROBIOLOGY Ascariasis is caused by *Ascaris lumbricoides*, the largest intestinal nematode, which reaches lengths up to 40 cm.

- Humans—primarily younger children—are infected by ingestion of fecally contaminated soil that contains ascarid eggs.
- Larvae hatch in the intestine, invade the mucosa, migrate to the lungs, break into the alveoli, ascend the bronchial tree, are swallowed, mature in the small intestine, and produce up to 240,000 eggs per day that pass in the feces.

CLINICAL MANIFESTATIONS Most infections have a low worm burden and are asymptomatic. During lung migration of the parasite (~9–12 days after egg ingestion), pts may develop a cough and substernal discomfort, occasionally with dyspnea or blood-tinged sputum, fever, and eosinophilia.

- Eosinophilic pneumonitis (Löffler's syndrome) may be evident.
- Heavy infections with numerous entangled worms can occasionally cause pain, small-bowel obstruction, perforation, volvulus, biliary obstruction and colic, or pancreatitis.

LABORATORY FINDINGS *Ascaris* eggs (65 by 45 μm) can be found in fecal samples. Adult worms can pass in the stool or, much less commonly, through the mouth or nose.

TREATMENT

Ascariasis

A single dose of albendazole (400 mg), mebendazole (500 mg), or ivermectin (150–200 $\mu\text{g}/\text{kg}$) is effective; these medications are contraindicated in pregnancy.

HOOKWORM

MICROBIOLOGY Two hookworm species, *Ancylostoma duodenale* and *Necator americanus*, cause most human infections, although *A. ceylanicum* is being recognized as a major hookworm pathogen in Asia. Infectious larvae present in soil penetrate the skin, reach the lungs via the bloodstream, invade the alveoli, ascend the airways, are swallowed, reach the small intestine, mature into adult worms, attach to the mucosa, and suck blood (0.2 mL/d per *Ancylostoma* adult) and interstitial fluid.

CLINICAL MANIFESTATIONS Most infections are asymptomatic. Chronic infection causes iron deficiency and—in marginally nourished persons—progressive anemia and hypoproteinemia, weakness, and shortness of breath. Larvae may cause pruritic rash (“ground itch”) at the site of skin penetration as well as serpiginous tracks of SC migration (similar to those of cutaneous larva migrans).

LABORATORY FINDINGS Hookworm eggs (40 by 60 μm) can be found in the feces. Stool concentration may be needed for the diagnosis of light infections. PCR can provide a species-specific diagnosis.

TREATMENT

Hookworm

- Albendazole (400 mg once) or mebendazole (500 mg once) is effective, although there is significant concern that these agents are becoming much less effective. Nutritional support, iron replacement, and deworming are undertaken as needed.

STRONGYLOIDIASIS

MICROBIOLOGY AND EPIDEMIOLOGY Unlike other helminths, *Strongyloides stercoralis* can replicate in the human host, permitting ongoing cycles of autoinfection from endogenously produced larvae.

- Infection results when filariform larvae in fecally contaminated soil penetrate the skin or mucous membranes.
 - Larvae travel through the bloodstream to the lungs, break through into alveolar spaces, ascend the bronchial tree, are swallowed, reach the small intestine, mature into adult worms, and penetrate the mucosa of the proximal small bowel; eggs hatch in the intestinal mucosa.
 - Rhabditiform larvae can pass with the feces into the soil or can develop into filariform larvae that penetrate the colonic wall or perianal skin and enter the circulation to establish ongoing autoinfection.
- Autoinfection is constrained by unknown factors of the host immune system, disruption of which (e.g., by glucocorticoid therapy) can lead to hyperinfection.

CLINICAL FEATURES Uncomplicated disease is associated with mild cutaneous and/or abdominal manifestations such as recurrent urticaria, larva currens (a pathognomonic serpiginous, pruritic, erythematous eruption along the course of larval migration that may advance up to 10 cm/h), abdominal pain, nausea, diarrhea, bleeding, and weight loss.

- Disseminated disease involves tissues outside the GI tract and lungs, including the CNS, peritoneum, liver, and kidney.
 - Gram-negative sepsis, pneumonia, or meningitis can complicate or dominate the clinical course.
 - Disease can be fatal in pts given glucocorticoids; disseminated infection is uncommon among pts with HIV-1 infection.
- Fluctuating eosinophilia is common in uncomplicated disease but is uncommon in disseminated disease.

DIAGNOSIS A single stool examination detects rhabditiform larvae (~250 µm long) in about one-third of uncomplicated infections. PCR is available and provides increased diagnostic specificity.

- Duodenojejunal contents can be sampled if stool examinations are repeatedly negative.
- Antibodies can be detected by ELISA.
- In disseminated infection, filariform larvae can be found in stool or at sites of larval migration (e.g., sputum, bronchoalveolar lavage fluid, surgical drainage fluid).

TREATMENT**Strongyloidiasis**

- Ivermectin (200 µg/kg daily for 2 days) is more effective than albendazole (400 mg daily for 3 days). Asymptomatic pts should be treated, given the potential for later fatal hyperinfection.
- Disseminated disease should be treated with ivermectin for at least 5–7 days (or until the parasites are eradicated).
- In immunocompromised hosts, the course of ivermectin should be repeated 2 weeks after initial treatment.

ENTEROBIASIS

MICROBIOLOGY AND EPIDEMIOLOGY Enterobiasis (pinworm) is caused by *Enterobius vermicularis* and affects ~40 million people in the United States (primarily children).

- Gravid female worms migrate nocturnally from the cecum to the perianal region, each releasing up to 2000 immature eggs that become infective within hours.
- Autoinfection and person-to-person transmission result from perianal scratching and transport of infective eggs to the mouth.

CLINICAL MANIFESTATIONS Perianal pruritus is the cardinal symptom and is often worst at night. Eosinophilia is uncommon.

DIAGNOSIS Eggs (55 by 25 μm and flattened on one side) are detected by microscopic examination of cellulose acetate tape applied to the perianal region in the morning.

TREATMENT**Enterobiasis**

- One dose of mebendazole (100 mg) or albendazole (400 mg) is given, with the same treatment repeated after 2 weeks. Household members should also be treated to avoid reservoirs of potential reinfection.

Filarial and Related Infections

Filarial worms, which infect >170 million people worldwide, are nematodes that dwell in the SC tissue and lymphatics. Usually, infection is established only with repeated and prolonged exposures to infective larvae; however, filarial disease is characteristically more intense and acute in newly exposed individuals than in natives of endemic areas.

- Filarial parasites have a complex life cycle, including infective larval stages carried by insects and adult worms that reside in humans.
 - The offspring of adults are microfilariae (200–250 μm long, 5–7 μm wide) that either circulate in the blood or migrate through the skin.
 - Microfilariae are ingested by the arthropod vector and develop over 1–2 weeks into new infective larvae.
- A bacterial endosymbiont, *Wolbachia*, is found in all stages of *Brugia*, *Wuchereria*, *Mansonella*, and *Onchocerca* spp. and has become a target for antifilarial chemotherapy.

LYMPHATIC FILARIASIS

MICROBIOLOGY Lymphatic filariasis is caused by *Wuchereria bancrofti* (most commonly), *Brugia malayi*, or *B. timori*, which can reside in and cause inflammatory damage to lymphatic channels or lymph nodes.

CLINICAL MANIFESTATIONS Subclinical microfilaremia, hydrocele, acute adenolymphangitis (ADL), and chronic lymphatic disease are the main clinical presentations.

- ADL is associated with high fever, lymphatic inflammation, and transient local edema. Both the upper and lower extremities can be involved in both bancroftian and brugian filariasis, but *W. bancrofti* almost exclusively affects genital lymphatics.

- ADL may progress to more chronic lymphatic obstruction and elephantiasis with brawny edema, thickening of the SC tissues, and hyperkeratosis. Superinfection is a problem.

DIAGNOSIS Detection of the parasite is difficult, but microfilariae can be found in peripheral blood, hydrocele fluid, and occasionally other body fluids.

- Timing of blood collection is critical and should be based on the periodicity of the microfilariae in the endemic region involved (primarily nocturnal in many regions).
- Two assays are available to detect *W. bancrofti* circulating antigens, and a PCR has been developed to detect DNA of both *W. bancrofti* and *B. malayi* in the blood.
- High-frequency ultrasound (with Doppler techniques) of the scrotum or the female breast can identify motile adult worms.
- The presence of antifilarial antibody supports the diagnosis, but cross-reactivity with other helminthic infections makes interpretation of this finding difficult.

TREATMENT

Lymphatic Filariasis

- Pts with active lymphatic filariasis (defined by microfilaremia, antigen positivity, or adult worms on ultrasound) should be treated with diethylcarbamazine (DEC, 6 mg/kg daily for 12 days), which has macro- and microfilaricidal properties. Albendazole (400 mg bid for 21 days), albendazole and DEC both given daily for 7 days, doxycycline (100 mg bid for 4–6 weeks), and the addition of DEC to a 3-week course of doxycycline are alternative regimens with macrofilaricidal efficacy.
- A single dose of albendazole (400 mg) combined with DEC (6 mg/kg) or ivermectin (200 µg/kg) has sustained (≥2 years) microfilaricidal activity and is used in lymphatic filariasis eradication campaigns.
- For pts with chronic lymphatic filariasis, treatment regimens should focus on hygiene, prevention of secondary bacterial infections, and physiotherapy. Drug treatment should be reserved for individuals with evidence of active infection, although a 6-week course of doxycycline improves filarial lymphedema irrespective of disease activity.

ONCHOCERCIASIS

MICROBIOLOGY AND EPIDEMIOLOGY Onchocerciasis (“river blindness”) is caused by *Onchocerca volvulus*, which infects 37 million people worldwide and is transmitted by the bite of an infected blackfly near free-flowing rivers and streams.

- Larvae deposited by the blackfly develop into adult worms (females and males are ~40–60 cm and ~3–6 cm in length, respectively) that are found in SC nodules (*onchocercomata*). About 7 months to 3 years after infection, the gravid female releases microfilariae that migrate out of the nodules and concentrate in the dermis.
- In contrast to lymphatic filariasis, onchocerciasis is characterized by microfilarial induction of inflammation.

CLINICAL MANIFESTATIONS Onchocerciasis most commonly presents as dermatologic manifestations (an intensely pruritic papular rash or firm nontender onchocercomata), but visual impairment is the most serious complication in pts with moderate or heavy infections.

- Conjunctivitis with photophobia is an early ocular finding.
- Sclerosing keratitis (the leading cause of onchocercal blindness in Africa, affecting 1–5% of pts), anterior uveitis, iridocyclitis, and secondary glaucoma due to pupillary deformities are more serious ocular complications.

DIAGNOSIS A definitive diagnosis is based on the finding of an adult worm in an excised nodule or of microfilariae in a skin snip.

- Specific antibody assays and PCR to detect onchocercal DNA are available in reference laboratories.
- Eosinophilia and elevated serum IgE levels are common but nonspecific.

TREATMENT

Onchocerciasis

- Ivermectin (a single dose of 150 µg/kg), given yearly or semiannually, is microfilaricidal and is the mainstay of treatment.
 - In African regions where *O. volvulus* is coendemic with *Loa loa*, ivermectin is contraindicated because of the risk of severe posttreatment encephalopathy.
 - Doxycycline therapy for 6 weeks is macrofilaristatic, rendering adult female worms sterile for long periods, and also targets the *Wolbachia* endosymbiont.
- Nodules on the head should be excised to avoid ocular infection.

TREMATODES

- The trematodes, or flatworms, may be classified according to the tissues invaded by the adult stage of the fluke: blood, liver (biliary tree), intestines, or lungs.
- The life cycle involves a definitive mammalian host (e.g., humans), in whom adult worms produce eggs through sexual reproduction, and an intermediate host (e.g., snails), in which miracidial forms undergo asexual reproduction to form cercariae. Worms do not multiply within the definitive host.
- Human infection results from either direct penetration of intact skin or ingestion.
- Infections with trematodes that migrate through or reside in host tissues are associated with a moderate to high degree of peripheral-blood eosinophilia.

SCHISTOSOMIASIS

MICROBIOLOGY AND EPIDEMIOLOGY Five species cause human schistosomiasis: *Schistosoma mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum* cause intestinal and hepatic schistosomiasis, and *S. haematobium* causes urogenital schistosomiasis.

- After infective cercariae penetrate intact skin, they mature into schistosomula and migrate through venous or lymphatic vessels to the lungs and ultimately the liver parenchyma. Sexually mature worms migrate to the veins of the bladder and pelvis (*S. haematobium*) or the mesentery (*S. mansoni*, *S. japonicum*, *S. mekongi*, *S. intercalatum*) and deposit eggs.
 - Some mature ova are extruded into the intestinal or urinary lumina, from which they may be voided and ultimately may reach water and perpetuate the life cycle.
 - The persistence of ova in tissues leads to a granulomatous host response and fibrosis.

- These blood flukes infect ~230 million persons (mostly children and young adults), with >70% of infected people living in sub-Saharan Africa.

CLINICAL MANIFESTATIONS Schistosomiasis occurs in three stages that vary by species, intensity of infection, and host factors (e.g., age, genetics).

- *Cercarial dermatitis* causes a pruritic maculopapular rash (“swimmers’ itch”) that lasts for 1–2 weeks.
- *Acute schistosomiasis* (Katayama fever) presents between 2 weeks and 3 months after parasite exposure with fever, myalgia, general malaise, fatigue, headache, cough, abdominal tenderness, eosinophilia, and transient pulmonary infiltrates.
- *Chronic schistosomiasis* causes manifestations that depend primarily on the schistosome species.
 - Intestinal schistosomiasis involves mucosal granulomatous inflammation with microulcerations, superficial bleeding, and sometimes pseudopolypoidosis. Disease due to *S. mansoni* and *S. japonicum* is generally more severe and may also involve hepatosplenic manifestations that can progress to periportal fibrosis.
 - Urogenital schistosomiasis due to *S. haematobium* consists of an inflammatory active stage (dysuria; hematuria, particularly at the end of voiding; urinary egg excretion; obstructive uropathy) in children and young adults that progresses in later life to a fibrotic chronic stage (nocturia, urine retention, dribbling, and incontinence).
 - Pulmonary disease (e.g., pulmonary hypertension, cor pulmonale) and CNS disease (e.g., seizures, encephalopathy, transverse myelitis) can occur and are due to granulomas and fibrosis.

DIAGNOSIS Diagnosis is based on geographic history, clinical presentation, and presence of schistosome ova in excreta.

- Serologic assays for schistosomal antibodies (available through the CDC in the United States) may yield positive results before eggs are seen in excreta.
- Infection may also be diagnosed by examination of rectal biopsies (*S. mansoni* and *S. haematobium*) and occasionally Pap smears and semen samples (*S. haematobium*).

TREATMENT

Schistosomiasis

- Praziquantel (20 mg/kg bid for *S. mansoni*, *S. intercalatum*, and *S. haematobium* infections; 20 mg/kg tid for *S. japonicum* and *S. mekongi* infections) is the drug of choice. In pts not cured by initial treatment, the same dose can be repeated at weekly intervals for 2 weeks.
 - Since praziquantel is ineffective against the young migrating schistosome stages, treatment may need to be repeated in 6–12 weeks if eosinophilia or symptoms persist.
 - Glucocorticoids can be added in Katayama fever to suppress the hypersensitivity reaction.
 - Late established manifestations, such as severe fibrosis, do not improve with treatment.

PREVENTION Travelers to endemic regions should avoid contact with all fresh-water bodies.

LIVER (BILIARY) FLUKES

- Clonorchiasis (due to *Clonorchis sinensis*) and opisthorchiasis (due to *Opisthorchis viverrini* and *O. felineus*) occur in Southeast Asia and Eastern Europe.
 - Infection is acquired by ingestion of contaminated raw or undercooked freshwater fish; larvae travel through the ampulla of Vater and mature in biliary canaliculi.
 - Most infected individuals are minimally symptomatic; chronic or repeated infection causes cholangitis, cholangiohepatitis, and biliary obstruction and is associated with cholangiocarcinoma.
 - Therapy for acute infection consists of praziquantel administration (25 mg/kg tid for 2 days).
- Fascioliasis is due to *Fasciola hepatica* and *F. gigantica*, which commonly infect sheep and cattle.
 - Infection is acquired by ingestion of contaminated aquatic plants (e.g., watercress).
 - Acute disease develops 1–4 weeks after infection and causes high fever, weight loss, RUQ pain, and sometimes urticaria. Chronic infection is infrequently associated with bile duct obstruction due to fibrosis.
 - For treatment, triclabendazole is given as a single dose of 10 mg/kg.
- Stool ova and parasite (O & P) examination diagnoses infection with liver flukes. Serologic testing is helpful, particularly in lightly infected pts.

LUNG FLUKES

- Infection with *Paragonimus* spp. is acquired by ingestion of contaminated crayfish and freshwater crabs.
- Acute infection presents with fever, cough, hemoptysis, and peripheral eosinophilia, although pts with low parasite burdens may remain relatively asymptomatic for prolonged periods.
- Chronic infection is associated with dyspnea, bloody (“rusty”) sputum, and bronchitis-, asthma-, and tuberculosis-like symptoms. Pts may develop pulmonary cyst formation or ectopic infection in the CNS and other organs.
- The diagnosis is made by O & P examination of sputum or stool; serology can be helpful.
- Praziquantel (25 mg/kg tid for 2 days) is the recommended therapy.

■ CESTODES

The cestodes, or tapeworms, are segmented worms that can be classified into two groups according to whether humans are the definitive or the intermediate host. The tapeworm attaches to intestinal mucosa via sucking cups or hooks located on the scolex. Proglottids (segments) form behind the scolex and constitute the bulk of the tapeworm.

TAENIASIS SAGINATA AND TAENIASIS ASIATICA

MICROBIOLOGY Humans are the definitive host for *Taenia saginata*, the beef tapeworm, and *T. asiatica*, the swine tapeworm, which inhabit the upper jejunum. Eggs are excreted in feces and ingested by cattle or other herbivores (*T. saginata*) or pigs (*T. asiatica*); larvae encyst (cysticerci) in the striated muscles of these animals. When humans ingest raw or undercooked meat, the cysticerci mature into adult worms in ~2 months.

CLINICAL MANIFESTATIONS Pts become aware of the infection by noting passage of motile proglottids in their feces. They may experience perianal discomfort, mild abdominal pain, nausea, change in appetite, weakness, and weight loss.

DIAGNOSIS The diagnosis is made by detection of eggs or proglottids in the stool; eggs may be detected in the perianal area by the cellophane-tape test (as in pinworm infection). Eosinophilia and elevated IgE levels are usually absent.

TREATMENT

Taeniasis Saginata and Taeniasis Asiatica

Praziquantel is given in a single dose of 10 mg/kg.

TAENIASIS SOLIUM AND CYSTICERCOSIS

MICROBIOLOGY AND PATHOGENESIS Humans are the definitive host and pigs the usual intermediate host for *T. solium*, the pork tapeworm.

- The disease has two forms, which depend on the form of parasite ingested.
 - By ingesting undercooked pork containing cysticerci, humans develop intestinal tapeworms and a disease similar to taeniasis saginata.
 - If humans ingest *T. solium* eggs (e.g., as a result of close contact with a tapeworm carrier or via autoinfection), they develop cysticercosis as a result of larval penetration of the intestinal wall and migration to many tissues.

CLINICAL MANIFESTATIONS Intestinal infections are generally asymptomatic except for fecal passage of proglottids. The presentation of cysticercosis depends on the number and location of cysticerci as well as the extent of associated inflammatory responses or scarring.

- Cysticerci can be found anywhere in the body but most often are detected in the brain, skeletal muscle, SC tissue, or eye.
- Neurologic manifestations are most common and include seizures (due to inflammation surrounding cysticerci in the brain), hydrocephalus (from obstruction of CSF flow by cysticerci and accompanying inflammation or by arachnoiditis), and signs of increased intracranial pressure (e.g., headache, nausea, vomiting, changes in vision).

DIAGNOSIS Intestinal infection is diagnosed by detection of eggs or proglottids in stool. A consensus conference has delineated criteria for the diagnosis of neurocysticercosis (Table 111-1). Findings on neuroimaging include cystic lesions with or without enhancement, one or more nodular calcifications, or focal enhancing lesions.

TREATMENT

Taeniasis Solium and Cysticercosis

- Intestinal infections respond to a single dose of praziquantel (10 mg/kg), but this treatment may evoke an inflammatory response in the CNS if there is cryptic cysticercosis.
- Neurocysticercosis can be treated with albendazole (15 mg/kg per day for 8–28 days) or praziquantel (50–100 mg/kg daily in three divided doses for 15–30 days). A combination of albendazole and praziquantel (50 mg/kg in three divided doses per day) is more effective in pts with more than two cystic lesions.
 - Given the potential for an inflammatory response to treatment, pts should be carefully monitored, and high-dose glucocorticoids should be used during treatment.

TABLE 111-1 Revised Diagnostic Criteria for Neurocysticercosis^a**1. Absolute criteria**

- a. Histologic demonstration of the parasite from biopsy of a brain or spinal cord lesion
- b. Visualization of subretinal cysticercus
- c. Conclusive demonstration of a scolex within a cystic lesion on neuroimaging studies

2. Neuroimaging criteria**a. Major neuroimaging criteria**

Cystic lesions without a discernible scolex, typical small enhancing lesions, multilobulated cystic lesions in the subarachnoid space, typical parenchymal brain calcifications

b. Confirmative neuroimaging criteria

Resolution of cystic lesions spontaneously or after cysticidal drug therapy
Migration of ventricular cysts documented on sequential neuroimaging studies

c. Minor neuroimaging criteria

Obstructive hydrocephalus or abnormal enhancement of basal leptomeninges

3. Clinical/exposure criteria**a. Major clinical/exposure criteria**

Detection of specific anticysticercal antibodies (e.g., by enzyme-linked immunoelectrotransfer blot [EITB]) or cysticercal antigens by well-standardized immunodiagnostic tests

Cysticercosis outside the central nervous system

Evidence of a household contact with *T. solium* infection

b. Minor clinical/exposure criteria

Clinical manifestations suggestive of neurocysticercosis

Individuals coming from or living in an area where cysticercosis is endemic

^aDiagnosis is confirmed by one absolute criterion, by two major criteria or one major and one confirmatory neuroimaging criteria plus any clinical/exposure criterion, or by one major neuroimaging criterion plus two clinical/exposure criteria (including at least one major clinical/exposure criterion), together with the exclusion of other pathologies producing similar neuroimaging findings. A probable diagnosis is supported by one major neuroimaging criterion plus any two clinical/exposure criteria or by one minor neuroimaging criterion plus at least one major clinical/exposure criterion.

Source: Modified from Del Brutto OH et al: Revised diagnostic criteria for neurocysticercosis. *J Neurol Sci* 372:202, 2017.

- Since glucocorticoids induce praziquantel metabolism, cimetidine should be given with praziquantel to inhibit this effect.
- Supportive measures include antiepileptic administration and treatment of hydrocephalus as indicated.

ECHINOCOCCOSIS

MICROBIOLOGY AND EPIDEMIOLOGY Humans are an intermediate host for larvae of *Echinococcus granulosus sensu lato*, *E. multilocularis*, and *E. vogeli*. Pts acquire disease due to *E. granulosus sensu lato* by ingesting eggs spread by canine feces.

- After ingestion, embryos escape from the eggs, penetrate the intestinal mucosa, enter the portal circulation, and are carried to many organs but

particularly the liver and lungs. Larvae develop into fluid-filled unilocular hydatid cysts within which daughter cysts develop, as do germinating cystic structures (*brood capsules*). Cysts expand over years.

- Echinococcosis is prevalent on all continents, particularly in areas where livestock is raised in association with dogs.
- *E. multilocularis*, found in Arctic or sub-Arctic regions, is similar to *E. granulosus*, but wild canines (e.g., foxes) are the definitive hosts and rodents are the intermediate hosts. The parasite is multilocular, and vesicles progressively invade host tissue.

CLINICAL MANIFESTATIONS Expanding cysts exert the effects of space-occupying lesions, causing symptoms in the affected organ (usually liver and lung); the liver is involved in two-thirds of *E. granulosus* sensu lato infections and ~100% of *E. multilocularis* infections.

- Pts with hepatic disease most commonly present with abdominal pain or a palpable mass in the RUQ. Compression of a bile duct may mimic biliary disease, and rupture or leakage from a hydatid cyst may cause fever, pruritus, urticaria, eosinophilia, or anaphylaxis.
- Pulmonary cysts may rupture into the bronchial tree or pleural cavity and cause cough, salty phlegm, chest pain, or hemoptysis.
- Rupture of cysts may result in multifocal dissemination.
- *E. multilocularis* disease may present as a hepatic tumor, with destruction of the liver and extension into adjoining (e.g., lungs, kidneys) or distant (e.g., brain, spleen) organs.

DIAGNOSIS Radiographic imaging is important in detecting and evaluating echinococcal cysts.

- Daughter cysts within a larger cyst are pathognomonic of *E. granulosus* sensu lato. Eggshell or mural calcification on CT is also indicative of *E. granulosus* infection.
- Serologic testing yields positive results in ~90% of pts with hepatic disease, but results can be negative in up to half of pts with lung cysts.
- Aspiration of cysts usually is not attempted because leakage of cyst fluid can cause dissemination or anaphylactic reactions.

TREATMENT

Echinococcosis

- Therapy is based on considerations of the size, location, and manifestations of cysts and the overall health of the pt. Ultrasound staging is recommended for cystic echinococcosis infection.
- For some uncomplicated lesions, PAIR (*percutaneous aspiration, infusion of scolicidal agents* [95% ethanol or hypertonic saline], and *reaspiration*) is recommended.
 - Albendazole (7.5 mg/kg bid for 2 days before the procedure and for at least 4 weeks afterward) is given for prophylaxis of secondary peritoneal echinococcosis due to inadvertent spillage of fluid during this treatment.
 - PAIR is contraindicated for superficial cysts, for cysts with multiple thick internal septal divisions, and for cysts communicating with the biliary tree.
- Surgical resection is the treatment of choice for complicated cystic echinococcosis.

- Albendazole should also be given prophylactically, as just described. Praziquantel (50 mg/kg daily for 2 weeks) may hasten the death of protoscolices.
- Medical therapy alone with albendazole for 12 weeks to 6 months results in cure in ~30% of cases and in clinical improvement in another 50%.
- *E. multilocularis* infection is treated surgically, and albendazole is given for at least 2 years after presumptively curative surgery. If surgery is not curative, albendazole should be continued indefinitely.

DIPHYLLOBOTHRIASIS

Diphyllobothrium latum, the longest tapeworm (up to 25 m), attaches to the ileal and occasionally the jejunal mucosa. Humans are infected by consumption of infected raw or smoked fish. Symptoms are rare and usually mild, but infection, particularly in Scandinavia, can cause vitamin B₁₂ deficiency because the tapeworm absorbs large amounts of vitamin B₁₂ and interferes with ileal B₁₂ absorption. Up to 2% of infected pts, especially the elderly, have megaloblastic anemia resembling pernicious anemia and can suffer neurologic sequelae due to B₁₂ deficiency. The diagnosis is made by detection of eggs in the stool. Praziquantel (5–10 mg/kg once) is highly effective.

ECTOPARASITES

Ectoparasites are arthropods or helminths that infest the skin or hair of animals, from which they derive sustenance and shelter. These organisms can inflict direct injury, elicit hypersensitivity, or inoculate toxins or pathogens.

SCABIES

ETIOLOGY AND EPIDEMIOLOGY Scabies is caused by the human itch mite *Sarcoptes scabiei* var. *hominis*, which infests ~300 million people worldwide.

- Gravid female mites burrow within the stratum corneum, deposit eggs that mature in ~8 days, and emerge as adults to reinvade the same or another host.
- Scabies transmission is facilitated by direct skin-to-skin contact with an infested person and by crowding, uncleanliness, or contact with multiple sexual partners.

CLINICAL MANIFESTATIONS Itching, which is due to a sensitization reaction against excreta of the mite, is worst at night and after a hot shower. Burrows appear as dark wavy lines (3–15 mm in length), with most lesions located along the digital web spaces or on the volar wrists, elbows, scrotum, and penis. *Crusted* scabies (formerly termed *Norwegian* scabies)—hyperinfestation with thousands of mites—is associated with glucocorticoid use and immunodeficiency diseases.

DIAGNOSIS Scrapings from unroofed burrows reveal the mite, its eggs, or fecal pellets.

TREATMENT

Scabies

- Permethrin cream (5%) should be applied thinly from the jawline down after bathing and removed 8–14 h later with soap and water. A dose of ivermectin (200 µg/kg) is also effective but has not yet been approved by the FDA for scabies treatment.
- For crusted scabies, first a keratolytic agent (e.g., 6% salicylic acid) and then scabicides are applied to the scalp, face, and ears in addition to the rest of the body.

Two doses of ivermectin, separated by an interval of 1–2 weeks, may be required for pts with crusted scabies.

- Itching and hypersensitivity may persist for weeks or months in scabies and should be managed with symptom-based treatment. Bedding and clothing should be washed in hot water and dried in a heated dryer, and close contacts (regardless of symptoms) should be treated to prevent reinfestations.
- Scabies infestations become noncommunicable within 1 day of effective treatment.

PEDICULIASIS

ETIOLOGY AND EPIDEMIOLOGY Nymph and adult forms of human lice—*Pediculus capitis* (the head louse), *P. humanus* (the body louse), and *Phthirus pubis* (the pubic louse)—feed at least once a day and ingest human blood exclusively. The saliva of these lice produces an irritating rash in sensitized persons. Eggs are cemented firmly to hair or clothing, and empty eggs (nits) remain affixed for months or years after hatching. Lice are generally transmitted from person to person. Head lice are transmitted among schoolchildren and body lice among disaster victims and indigent people; pubic lice are usually transmitted sexually. The body louse is a vector for the transmission of diseases such as louse-borne typhus, relapsing fever, and trench fever.

DIAGNOSIS The diagnosis can be suspected if nits are detected, but confirmatory measures should include the demonstration of a live louse.

TREATMENT

Pediculiasis

- If live lice are found, treatment with 1% permethrin (two 10-min applications 10 days apart) is usually adequate. If this course fails, treatment for ≤ 12 h with 0.5% malathion may be indicated. Eyelid infestations should be treated with petrolatum applied for 3–4 days.
- Body lice usually are eliminated by bathing and by changing to laundered clothes.
 - Pediculicides applied from head to foot may be needed in hirsute pts to remove body lice.
 - Clothes and bedding should be deloused by placement in a hot dryer for 30 min or by heat pressing.

MYIASIS In this infestation, maggots invade living or necrotic tissue or body cavities and produce clinical syndromes that vary with the species of fly. Certain flies are attracted to blood and pus, and newly hatched larvae enter wounds or diseased skin. Treatment consists of maggot removal and tissue debridement.

LEECH INFESTATIONS Medicinal leeches can reduce venous congestion in surgical flaps or replanted body parts. Pts occasionally develop sepsis from *Aeromonas hydrophila*, which colonizes the gullets of commercially available leeches.

112 Physical Examination of the Heart



General examination of a pt with suspected heart disease should include vital signs (respiratory rate, pulse, blood pressure) and observation of skin color (e.g., cyanosis, pallor, jaundice), clubbing, edema, evidence of decreased perfusion (cool and diaphoretic skin), and hypertensive changes in optic fundi. Examine abdomen for evidence of hepatomegaly, ascites, or abdominal aortic aneurysm. An ankle-brachial index (systolic bp at ankle divided by arm systolic bp) <0.9 indicates lower extremity arterial obstructive disease. Important findings on cardiovascular examination include:

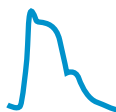
CAROTID ARTERY PULSE (FIG. 112-1)

- *Pulsus parvus*: Weak upstroke due to decreased stroke volume (hypovolemia, LV failure, aortic or mitral stenosis [MS])
- *Pulsus tardus*: Delayed upstroke (aortic stenosis [AS])
- *Bounding (hyperkinetic) pulse*: Hyperkinetic circulation, aortic regurgitation, patent ductus arteriosus, marked vasodilation
- *Pulsus bisferiens*: Double systolic pulsation (aortic regurgitation, hypertrophic cardiomyopathy)
- *Pulsus alternans*: Regular alteration in pulse pressure amplitude (severe LV dysfunction)
- *Pulsus paradoxus*: Exaggerated inspiratory fall (>10 mmHg) in systolic bp (typical of pericardial tamponade; also seen in severe obstructive lung disease, massive pulmonary embolism, tension pneumothorax)

JUGULAR VENOUS PULSATION (JVP)

Jugular venous distention develops in right-sided heart failure, constrictive pericarditis, pericardial tamponade, obstruction of superior vena cava. JVP normally falls with inspiration but may rise (Kussmaul sign) in constrictive pericarditis. Abnormalities in examination include:

A. Hypokinetic Pulse B. Parvus et Tardus Pulse C. Hyperkinetic Pulse



D. Bisferiens Pulse

E. Dicrotic Pulse + Alternans

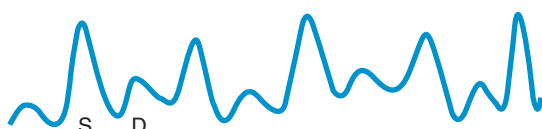
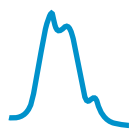


FIGURE 112-1 Carotid artery pulse patterns.

- *Large "a" wave:* Tricuspid stenosis (TS), pulmonic stenosis (PS), atrioventricular (AV) dissociation (right atrium contracts against closed tricuspid valve)
- *Absent "a" wave:* Atrial fibrillation
- *Large "v" wave:* Tricuspid regurgitation, atrial septal defect
- *Steep "y" descent:* Constrictive pericarditis
- *Slow "y" descent:* TS

PRECORDIAL PALPATION

Cardiac apical impulse is normally localized at the fifth intercostal space, midclavicular line. Abnormalities include:

- *Forceful apical thrust:* Left ventricular hypertrophy
- *Lateral and downward displacement of apex impulse:* Left ventricular dilatation
- *Prominent presystolic impulse:* Hypertension, AS, hypertrophic cardiomyopathy
- *Double systolic apical impulse:* Hypertrophic cardiomyopathy
- *Sustained "lift" at lower left sternal border:* Right ventricular hypertrophy
- *Dyskinetic (outward bulge) impulse:* Ventricular aneurysm, large dyskinetic area post MI, cardiomyopathy

AUSCULTATION

■ HEART SOUNDS (FIG. 112-2)

S₁

Loud: MS, short PR interval, hyperkinetic heart, thin chest wall. *Soft:* Long PR interval, heart failure, mitral regurgitation, thick chest wall, pulmonary emphysema.

S₂

Normally A₂ precedes P₂ and splitting increases with inspiration; abnormalities include:

- *Widened splitting:* Right bundle branch block, PS, mitral regurgitation
- *Fixed splitting (no respiratory change in splitting):* Atrial septal defect
- *Narrow splitting:* Pulmonary hypertension
- *Paradoxical splitting (splitting narrows with inspiration):* Left bundle branch block, heart failure, AS
- *Loud A₂:* Systemic hypertension
- *Soft A₂:* Aortic stenosis
- *Loud P₂:* Pulmonary arterial hypertension
- *Soft P₂:* Pulmonic stenosis

S₃

Low-pitched, heard best with bell of stethoscope at apex, following S₂; normal in children; after age 30–35, indicates LV failure or volume overload.

S₄

Low-pitched, heard best with bell at apex, preceding S₁; reflects atrial contraction into a noncompliant ventricle; found in AS, hypertension, hypertrophic cardiomyopathy, and coronary artery disease (CAD).

Opening Snap (OS)

High-pitched; follows S₂ (by 0.06–0.12 s), heard at lower left sternal border and apex in MS; the more severe the MS, the shorter the S₂–OS interval.

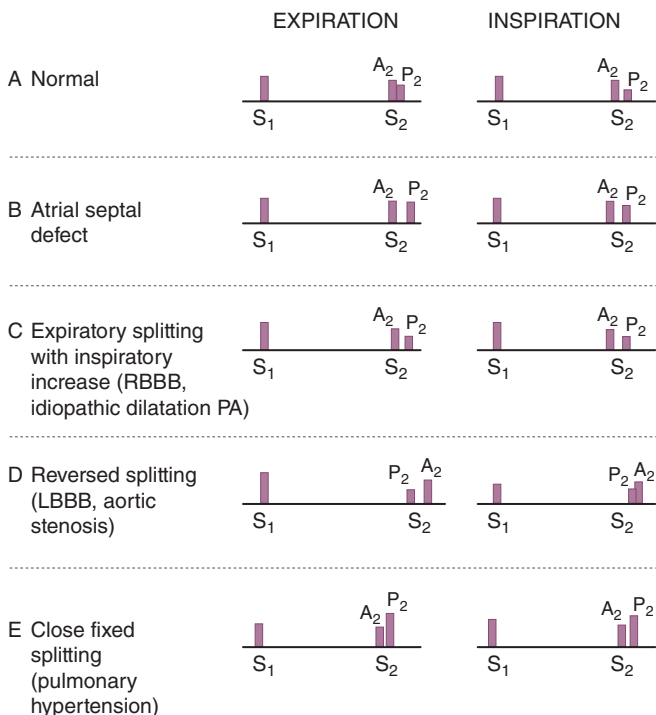


FIGURE 112-2 Heart sounds. **A.** Normal. S_1 , first heart sound; S_2 , second heart sound; A_2 , aortic component of the second heart sound; P_2 , pulmonic component of the second heart sound. **B.** Atrial septal defect with fixed splitting of S_2 . **C.** Physiologic but wide splitting of S_2 with right bundle branch block. **D.** Reversed or paradoxical splitting of S_2 with left bundle branch block. **E.** Narrow splitting of S_2 with pulmonary hypertension. (From Fowler NO: *Diagnosis of Heart Disease*. New York, Springer-Verlag, 1991, p 31. Reproduced with permission from Springer.)

Ejection Clicks

High-pitched sounds following S_1 typically loudest at left sternal border; observed in dilation of aortic root or pulmonary artery, congenital AS or PS; when due to the latter, click decreases with inspiration.

Midsystolic Clicks

At lower left sternal border and apex, often followed by late systolic murmur in mitral valve prolapse.

HEART MURMURS (FIG. 112-3; TABLES 112-1 AND 112-2)

Systolic Murmurs

May be “crescendo-decrescendo” ejection type, pansystolic, or late systolic; right-sided murmurs (e.g., tricuspid regurgitation) typically increase with inspiration.

Diastolic Murmurs

- *Early diastolic murmurs:* Begin immediately after S_2 , are high-pitched, and are usually caused by aortic or pulmonary regurgitation.
- *Mid-to-late diastolic murmurs:* Low-pitched, heard best with bell of stethoscope; observed in MS or TS; less commonly due to atrial myxoma.

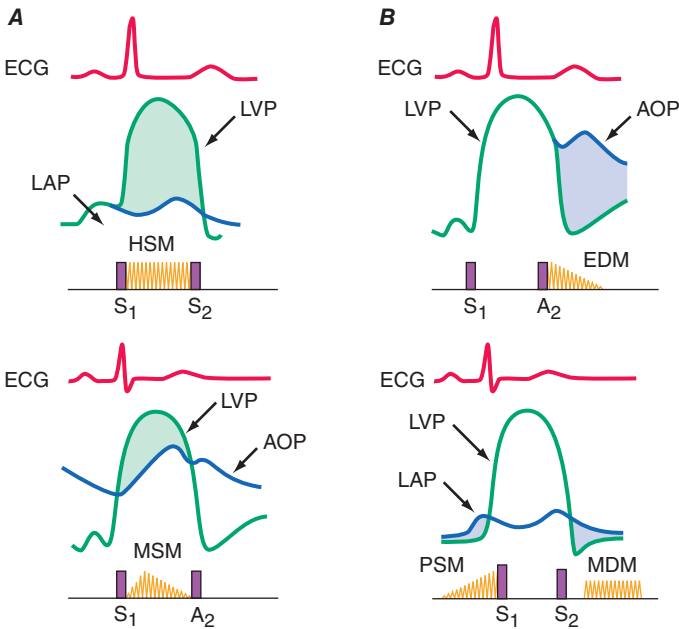


FIGURE 112-3 A. Top. Graphic representation of the systolic pressure difference (green shaded area) between left ventricle and left atrium with phonocardiographic recording of a holosystolic murmur (HSM) indicative of mitral regurgitation. ECG, electrocardiogram; LAP, left atrial pressure; LVP, left ventricular pressure; S₁, first heart sound; S₂, second heart sound. **Bottom.** Graphic representation of the systolic pressure gradient (green shaded area) between left ventricle and aorta in pt with aortic stenosis. A mid-systolic murmur (MSM) with a crescendo-decrescendo configuration is recorded. AOP, aortic pressure. **B. Top.** Graphic representation of the diastolic pressure difference between the aorta and left ventricle (blue shaded area) in a pt with aortic regurgitation, resulting in a decrescendo, early diastolic murmur (EDM) beginning with A₂. **Bottom.** Graphic representation of the diastolic left atrial–left ventricular gradient (blue areas) in a pt with mitral stenosis with a mid-diastolic murmur (MDM) and late presystolic murmurs (PSM).

TABLE 112-1 Heart Murmurs

Systolic murmurs	
Ejection-type	Aortic outflow tract Aortic valve stenosis Hypertrophic obstructive cardiomyopathy Aortic flow murmur Pulmonary outflow tract Pulmonic valve stenosis Pulmonic flow murmur
Holosystolic	Mitral regurgitation Tricuspid regurgitation Ventricular septal defect
Late-systolic	Mitral or tricuspid valve prolapse

(Continued)

TABLE 112-1 Heart Murmurs (Continued)

Diastolic murmurs	
Early diastolic	Aortic valve regurgitation Pulmonic valve regurgitation
Mid-to-late diastolic	Mitral or tricuspid stenosis Flow murmur across mitral or tricuspid valves
Continuous	Patent ductus arteriosus Coronary AV fistula Ruptured sinus of Valsalva aneurysm

Abbreviation: AV, atrioventricular.

- *Continuous murmurs:* Present in systole and diastole (envelops S_2); found in patent ductus arteriosus and sometimes in coarctation of aorta; less common causes are systemic or coronary AV fistula, aortopulmonary septal defect, ruptured aneurysm of sinus of Valsalva.

TABLE 112-2 Effects of Physiologic and Pharmacologic Interventions on the Intensity of Heart Murmurs and Sounds**Respiration**

Systolic murmurs due to TR or pulmonic blood flow through a normal or stenotic valve and diastolic murmurs of TS or PR generally increase with inspiration, as do right-sided S_3 and S_4 . Left-sided murmurs and sounds usually are louder during expiration, as is the pulmonic ejection sound.

Valsalva Maneuver

Most murmurs decrease in length and intensity. Two exceptions are the systolic murmur of HCM, which usually becomes much louder, and that of MVP, which becomes longer and often louder. Following release of the Valsalva maneuver, right-sided murmurs tend to return to control intensity earlier than left-sided murmurs.

After VPB or AF

Murmurs originating at normal or stenotic semilunar valves increase in the cardiac cycle following a VPB or in the cycle after a long cycle length in AF. By contrast, systolic murmurs due to AV valve regurgitation either do not change, diminish (papillary muscle dysfunction), or become shorter (MVP).

Positional Changes

With *standing*, most murmurs diminish, two exceptions being the murmur of HCM, which becomes louder, and that of MVP, which lengthens and often is intensified. With *squatting*, most murmurs become louder, but those of HCM and MVP usually soften and may disappear. Passive leg raising usually produces the same results.

Exercise

Murmurs due to blood flow across normal or obstructed valves (e.g., PS, MS) become louder with both isotonic and submaximal isometric (handgrip) exercise. Murmurs of MR, VSD, and AR also increase with handgrip exercise. However, the murmur of HCM often decreases with near maximum handgrip exercise. Left-sided S_4 and S_3 are often accentuated by exercise, particularly when due to ischemic heart disease.

Abbreviations: AR, aortic regurgitation; HCM, hypertrophic cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; PR, pulmonic regurgitation; PS, pulmonic stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis; VPB, ventricular premature beat; VSD, ventricular septal defect.

113 Electrocardiography



STANDARD APPROACH TO THE ECG

Normally, voltage standardization is 1.0 mV per 10 mm, and paper speed is 25 mm/s (each horizontal small box = 0.04 s).

Heart Rate

Beats/min = 300 divided by the number of *large* boxes (each 5 mm apart) between consecutive QRS complexes. For faster heart rates, divide 1500 by number of *small* boxes (1 mm apart) between each QRS.

Rhythm

Sinus rhythm is present if every P wave is followed by a QRS, PR interval ≥ 0.12 s, every QRS is preceded by a P wave, and the P wave is upright in leads I, II, and III. Arrhythmias are discussed in [Chaps. 124](#) and [125](#).

Mean Axis

If QRS is primarily positive in limb leads I and II, then axis is *normal*. Otherwise, find limb lead in which QRS is most isoelectric (R = S). The mean axis is perpendicular to that lead ([Fig. 113-1](#)). If the QRS complex is *positive* in that perpendicular lead, then mean axis is in the direction of that lead; if *negative*, then mean axis points directly away from that lead.

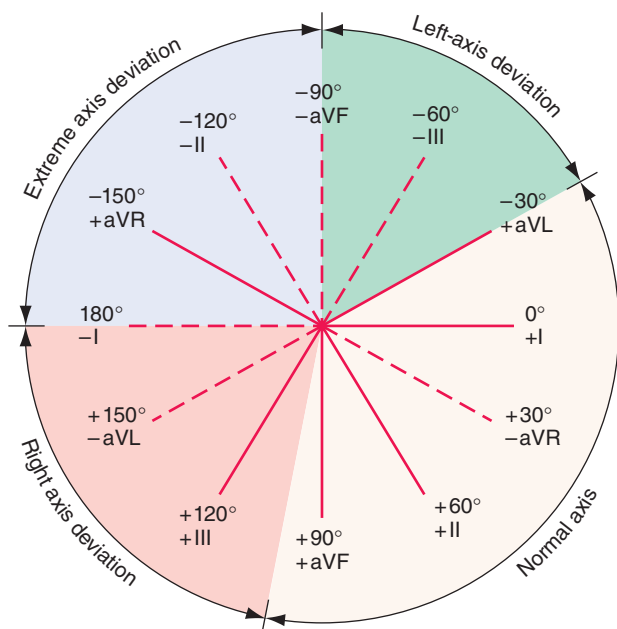


FIGURE 113-1 Electrocardiographic lead systems: The hexaxial frontal plane reference system to estimate electrical axis. Determine leads in which QRS deflections are maximum and minimum. For example, a maximum positive QRS in I which is isoelectric in aVF is oriented to 0°. Normal axis ranges from -30° to $+90^\circ$. An axis $>+90^\circ$ is right-axis deviation and $<-30^\circ$ is left-axis deviation.

Left-axis deviation (more negative than -30°) occurs in diffuse left ventricular disease, inferior MI, and in left anterior hemiblock (small R, deep S in leads II, III, and aVF).

Right-axis deviation ($>90^\circ$) occurs in right ventricular hypertrophy ($R > S$ in V_1) and left posterior hemiblock (small Q and tall R in leads II, III, and aVF). Mild right-axis deviation is common in thin, healthy individuals (up to 110°).

■ INTERVALS (NORMAL VALUES IN PARENTHESES)

PR (0.12–0.20 s)

- *Short:* (1) preexcitation syndrome (look for slurred QRS upstroke due to “delta” wave), (2) nodal rhythm (inverted P in aVF).
- *Long:* first-degree atrioventricular (AV) block (**Chap. 124**).

QRS (0.06–0.10 s)

Widened: (1) ventricular premature beats, (2) bundle branch blocks: *right* (RsR' in V_1 , deep S in V_6) and *left* (RR' in V_6 [**Fig. 113-2**]), (3) toxic levels of certain drugs (e.g., flecainide, propafenone, quinidine), (4) severe hypokalemia.

QT (<50% of RR interval; corrected QT ≤ 0.45 s in men, ≤ 0.46 s in women)

Prolonged: congenital, hypokalemia, hypocalcemia, drugs (e.g., class IA and class III antiarrhythmics, tricyclics).

■ HYPERTROPHY

- *Right atrium:* P wave ≥ 2.5 mm in lead II.
- *Left atrium:* P biphasic (positive, then negative) in V_1 , with terminal negative force wider than 0.04 s.
- *Right ventricle:* $R > S$ in V_1 and R in $V_1 > 5$ mm; deep S in V_6 ; right-axis deviation (**Fig. 113-3**).
- *Left ventricle:* S in V_1 plus R in V_5 or $V_6 \geq 35$ mm or R in aVL > 11 mm (**Fig. 113-3**).

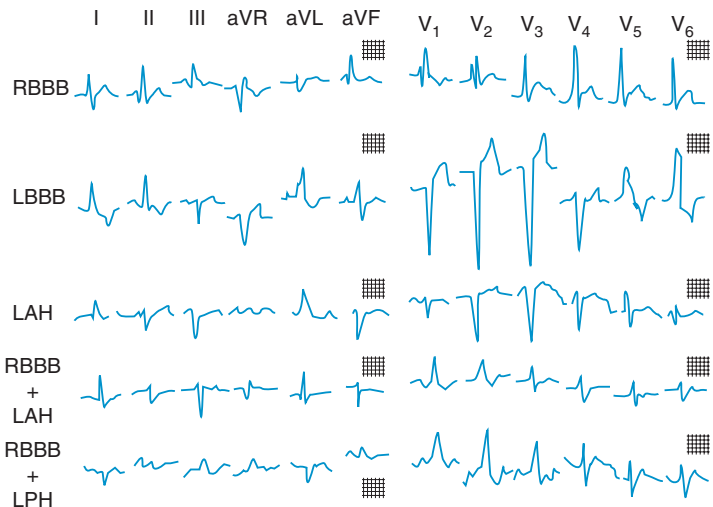


FIGURE 113-2 Intraventricular conduction abnormalities. Illustrated are right bundle branch block (RBBB); left bundle branch block (LBBB); left anterior hemiblock (LAH); right bundle branch block with left anterior hemiblock (RBBB + LAH); and right bundle branch block with left posterior hemiblock (RBBB + LPH).

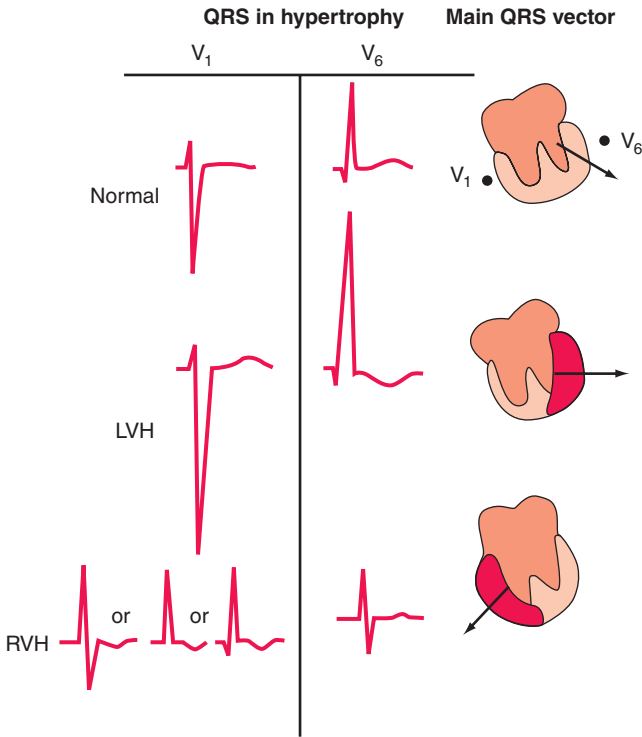


FIGURE 113-3 Left ventricular hypertrophy (LVH) increases the amplitude of electrical forces directed to the left and posteriorly. In addition, repolarization abnormalities may cause ST-segment depression and T-wave inversion in leads with a prominent R wave. Right ventricular hypertrophy (RVH) may shift the QRS vector to the right; this effect usually is associated with an R, RS, or qR complex in lead V_1 . T-wave inversions may be present in the right precordial leads.

Infarction (Fig. 113-4)

Following acute ST-segment elevation MI without successful reperfusion: *Pathologic Q waves* (≥ 0.04 s and $\geq 25\%$ of total QRS height) in leads shown in [Table 113-1](#); acute *non-ST-segment elevation MI* shows ST-T changes in these leads without Q-wave development. A number of conditions (other than acute MI) can cause Q waves ([Table 113-2](#)).

■ ST-T WAVES

- *ST elevation*: Acute MI, coronary spasm, pericarditis (concave upward) (see [Fig. 118-1](#) and [Table 118-2](#)), LV aneurysm, Brugada pattern (RBBB with ST elevation in V_1 - V_2).
- *ST depression*: Digitalis effect, “strain” (due to ventricular hypertrophy), ischemia, or nontransmural MI.
- *Tall peaked T*: Hyperkalemia; acute MI (“hyperacute T”).
- *Inverted T*: Non-Q-wave MI, ventricular “strain” pattern, drug effect (e.g., digitalis), hypokalemia, hypocalcemia, increased intracranial pressure (e.g., subarachnoid bleed).

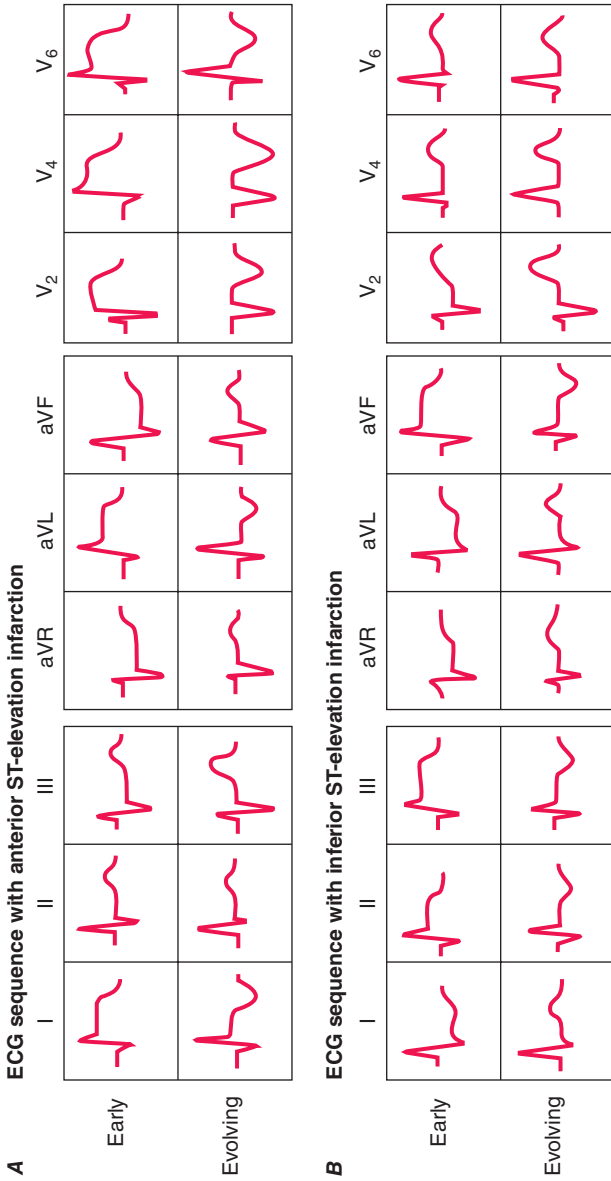


FIGURE 113-4 Sequence of depolarization and repolarization changes with **A**, acute anterior and **B**, acute inferior ST-elevation infarctions (in the absence of successful early reperfusion). With anterior infarcts, ST elevation in leads I, aVL, and the precordial leads may be accompanied by reciprocal ST depressions in leads II, III, and aVF. Conversely, acute inferior (or posterior) infarcts may be associated with reciprocal ST depressions in leads V₁-V₃. (Modified from Goldberger AL et al: *Goldberger's Clinical Electrocardiography: A Simplified Approach*, 9th ed. Philadelphia, Elsevier/Saunders, 2017.)

TABLE 113-1 Leads with Abnormal Q Waves in MI

LEADS WITH ABNORMAL Q WAVES	SITE OF INFARCTION
V ₁ -V ₂	Anteroseptal
V ₃ -V ₄	Apical
I, aVL, V ₅ -V ₆	Anterolateral
II, III, aVF	Inferior
V ₁ -V ₂ (tall R, not deep Q)	True posterior

TABLE 113-2 Differential Diagnosis of Q Waves (with Selected Examples)

Physiologic or positional factors
1. Normal “septal” Q waves
2. Left pneumothorax or dextrocardia
Myocardial injury or infiltration
1. Acute processes: myocardial infarction, myocarditis, hyperkalemia
2. Chronic processes: cardiomyopathy, amyloid, sarcoid, scleroderma, myocardial tumor
Ventricular hypertrophy/enlargement
1. Left ventricular (poor R-wave progression) ^a
2. Right ventricular (reversed R-wave progression)
3. Hypertrophic cardiomyopathy
Conduction abnormalities
1. Left bundle branch block
2. Wolff-Parkinson-White patterns

^aSmall or absent R waves in the right to midprecordial leads.

Source: Modified from Goldberger AL: *Myocardial Infarction: Electrocardiographic Differential Diagnosis*, 4th ed. St. Louis, Mosby-Year Book, 1991.

114 Noninvasive Examination of the Heart



ECHOCARDIOGRAPHY (TABLE 114-1 AND FIG. 114-1)

Visualizes heart in real time with ultrasound; Doppler recordings non-invasively assess hemodynamics and abnormal flow patterns. Imaging may be compromised in pts with chronic obstructive lung disease, thick chest wall, or narrow intercostal spaces. Transesophageal echocardiography (TEE) is performed when higher resolution images of cardiac structures is required.

■ CHAMBER SIZE AND VENTRICULAR PERFORMANCE

Assessment of atrial and ventricular dimensions, global and regional systolic wall motion abnormalities (administration of IV echo contrast enhances myocardial border detection when needed), ventricular hypertrophy/infiltration, evaluation for pulmonary hypertension: RV systolic pressure (RVSP) is calculated from maximum velocity of tricuspid regurgitation (TR):

$$RVSP = 4 \times (TR \text{ velocity})^2 + RA \text{ pressure}$$

TABLE 114-1 Clinical Uses of Echocardiography**2-D Echo**

Cardiac chambers: size, hypertrophy, wall motion abnormalities

Valves: morphology and motion

Pericardium: effusion, tamponade

Aorta: aneurysm, dissection

Assess intracardiac masses

Doppler Echocardiography

Valvular stenosis and regurgitation

Intracardiac shunts

Diastolic filling/dysfunction

Approximate intracardiac pressures

Transesophageal Echocardiography

Superior to 2-D echo to identify:

Infective endocarditis

Cardiac source of embolism

Prosthetic valve dysfunction

Aortic dissection

Stress Echocardiography

Assess myocardial ischemia and viability

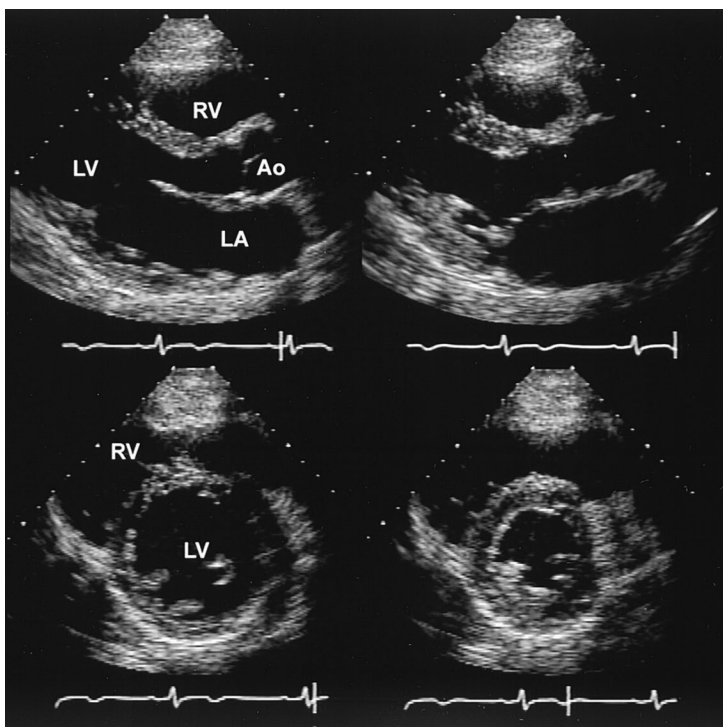


FIGURE 114-1 Two-dimensional echocardiographic still-frame images of a normal heart. *Upper:* Parasternal long axis view during systole and diastole (*left*) and systole (*right*). During systole, there is thickening of the myocardium and reduction in the size of the left ventricle (LV). The valve leaflets are thin and open widely. *Lower:* Parasternal short axis view during diastole (*left*) and systole (*right*) demonstrating a decrease in the left ventricular cavity size during systole as well as an increase in wall thickness. Ao, aorta. (Reproduced from Myerburg RJ: *Harrison's Principles of Internal Medicine*, 12th ed, 1991.)

(RA pressure is same as JVP estimated by physical examination.) In absence of RV outflow obstruction, RVSP = pulmonary artery systolic pressure.

LV diastolic function is assessed by transmitral spectral Doppler and Doppler tissue imaging, which measures velocity of myocardial relaxation (see Fig. 236-8, in HPIM-20).

■ VALVULAR ABNORMALITIES

Thickness, mobility, calcification, and regurgitation of each cardiac valve can be assessed. Severity of valvular stenosis is measured by Doppler (peak pressure gradient = $4 \times [\text{peak velocity}]^2$); valve areas are calculated using additional Doppler techniques. Dobutamine echocardiography can clarify degree of aortic stenosis in pts who have poor contractile function or low-flow states. Structural lesions (e.g., flail leaflet, vegetation) resulting in regurgitation may be identified, and color flow and spectral Doppler (Fig. 114-2) estimate severity of regurgitation.

■ PERICARDIAL DISEASE

Echo is noninvasive modality of choice to rapidly identify pericardial effusion and assess its hemodynamic significance; in tamponade there is diastolic RA and

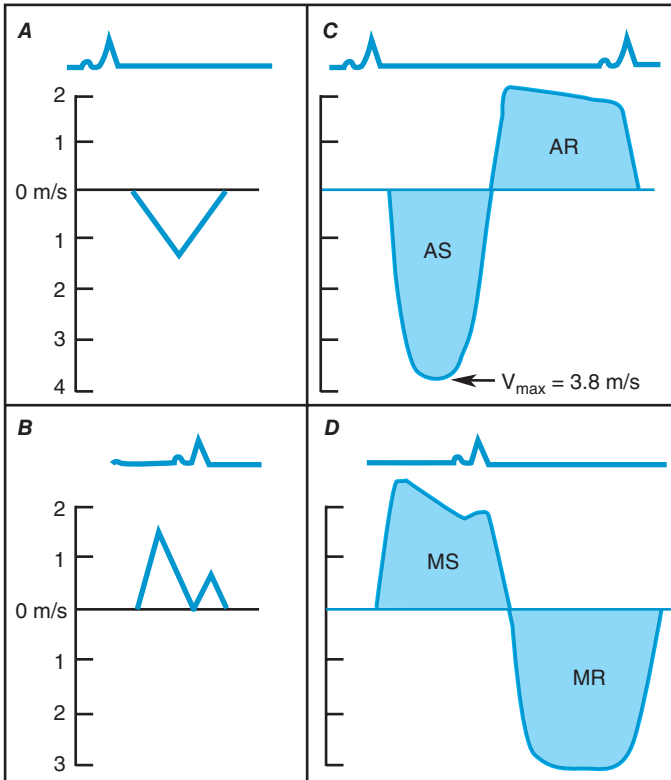


FIGURE 114-2 Schematic presentation of normal Doppler flow across the aortic (A) and mitral (B) valves. Abnormal continuous wave Doppler profiles: C. Aortic stenosis (AS) (peak transaortic gradient = $4 \times V_{\max}^2 = 4 \times [3.8]^2 = 58 \text{ mmHg}$) and regurgitation (AR). D. Mitral stenosis (MS) and regurgitation (MR).

RV collapse, dilatation of IVC, exaggerated respiratory alterations in transvalvular Doppler velocities. Actual thickness of pericardium (e.g., in suspected constrictive pericarditis) is more accurately measured by CT or MRI.

■ INTRACARDIAC MASSES

May visualize atrial or ventricular thrombus, intracardiac tumors, and valvular vegetations. Yield of identifying cardiac source of embolism is low in the absence of cardiac history or physical findings. TEE is more sensitive than standard transthoracic study for masses <1 cm in diameter.

■ AORTIC DISEASE

Aneurysm and dissection of the aorta may be evaluated and complications (aortic regurgitation, tamponade) assessed (**Chap. 127**) by standard transthoracic echo. TEE is more sensitive and specific for aortic dissection.

■ CONGENITAL HEART DISEASE (SEE **CHAP. 115**)

Echo, Doppler, and IV saline contrast echo are useful to identify congenital lesions and shunts, such as patent foramen ovale, atrial septal defects, ventricular septal defects, and patent ductus arteriosus.

■ STRESS ECHOCARDIOGRAPHY

Echo performed prior to, and after, treadmill or bicycle exercise identifies regions of prior MI and inducible myocardial ischemia (↓regional contraction with exercise). Dobutamine pharmacologic stress echo can be substituted for pts who cannot exercise.

NUCLEAR CARDIOLOGY

Uses nuclear isotopes to assess LV perfusion and contractile function, especially in pts with known or suspected CAD.

■ NUCLEAR MYOCARDIAL PERFUSION ASSESSMENT

SPECT imaging, most commonly using ^{99m}Tc -labeled compounds (sestamibi or tetrofosmin), or PET imaging (^{82}Rb or ^{13}N -ammonia), obtained at peak stress and at rest, depicts zones of prior infarction as fixed defects and regions of inducible myocardial ischemia as reversible defects. Nuclear imaging is more sensitive, but less specific, than stress echocardiography for detection of ischemia. Left ventricular contractile function can also be assessed during SPECT imaging.

For pts who cannot exercise, pharmacologic perfusion imaging with adenosine, regadenoson, dipyridamole, or dobutamine is used instead (**Chap. 123**). For pts with LBBB, perfusion imaging with adenosine or dipyridamole is preferred to avoid artifactual septal defects that are common with exercise imaging.

Pharmacologic PET scanning is especially useful in imaging obese pts and to assess myocardial viability (Thallium-201 SPECT imaging can assess viability when PET is not available). PET metabolic imaging is helpful in defining regions of myocardial inflammation and response to therapy in cardiac sarcoidosis.

CARDIAC MAGNETIC RESONANCE (CMR) IMAGING

Delineates cardiac structures with high resolution without ionizing radiation. Excellent technique to quantitate LV mass, to characterize the pericardium, myocardial infiltrative disease (e.g., amyloid), great vessels, anatomic relationships in congenital heart disease, abnormal cardiac masses, and to evaluate valvular heart disease as a complement to echocardiography. CMR with delayed gadolinium enhancement (avoid in pts with renal insufficiency) differentiates ischemic from nonischemic cardiomyopathy and is useful in assessing myocardial viability. Pharmacologic stress testing with CMR identifies significant CAD and detects subendocardial ischemia with higher sensitivity than SPECT imaging.

CARDIAC COMPUTED TOMOGRAPHY

Provides high-resolution images of cardiac structures (including the pericardium and cardiac masses) and detects coronary calcification in atherosclerosis with high sensitivity. CT angiography (CTA) delineates abnormalities of the great vessels, including aortic aneurysms and dissection, and pulmonary embolism. Multislice spiral CT provides high-resolution images of coronary anatomy. It is most useful in evaluation of suspected coronary anatomic anomalies and to exclude high-grade coronary stenoses in pts with chest pain and intermediate pretest probability of coronary artery disease. Its greatest accuracy is in detection of left main and proximal LAD and circumflex disease. CTA is also helpful in assessing the patency of bypass grafts.

Table 114-2 summarizes key diagnostic features of the noninvasive imaging modalities. **Figure 114-3** provides an algorithm for diagnostic imaging assessment of suspected CAD.

TABLE 114-2 Selection of Imaging Tests

	ECHOCARDIOGRAPHY	NUCLEAR IMAGING	COMPUTED TOMOGRAPHY	MAGNETIC RESONANCE IMAGING
LV size/function	Initial modality of choice Low cost, portable Provides ancillary structural and hemodynamic information	Available from gated SPECT stress imaging	Excellent resolution, but high cost	Excellent resolution, but high cost
Valve disease	Initial modality of choice Valve motion, stenosis, regurgitation Doppler hemodynamics		Assesses eligibility for TAVR	Visualize valve motion Delineate abnormal flow
Pericardial disease	Pericardial effusion Doppler in tamponade, constriction		Identifies pericardial thickening	Identifies pericardial thickening, inflammation, fibrosis
Aortic disease	TEE: rapid diagnosis of acute dissection		Image entire aorta Aortic aneurysms Aortic dissection	Image entire aorta Aortic aneurysms
Cardiac masses	TTE—large intracardiac thrombi/masses		Extracardiac masses	Extracardiac masses
	TEE—smaller intracardiac masses		Myocardial masses	Myocardial masses

Abbreviations: SPECT, single-photon emission CT; TAVR, transcatheter aortic valve replacement; TEE, transesophageal echocardiography; TTE, transthoracic echocardiogram.

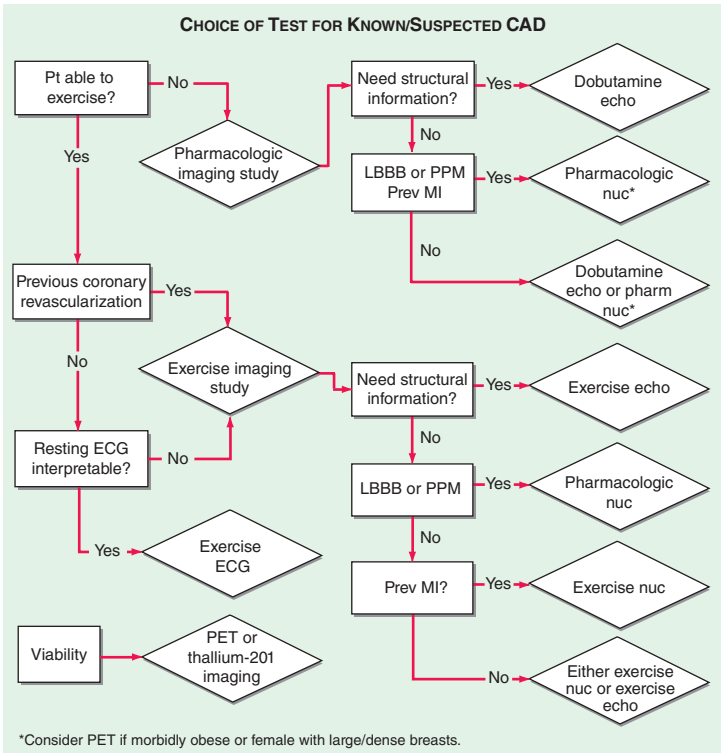


FIGURE 114-3 Flow diagram for selection of stress testing in a pt with chest pain. LBBB, left bundle branch block; Prev MI, previous myocardial infarction; Nuc, SPECT nuclear imaging study; Pharm nuc, pharmacologic nuclear imaging (adenosine, regadenoson, dipyridamole); PPM, permanent pacemaker.

115

Congenital Heart Disease in the Adult

ACYANOTIC CONGENITAL HEART LESIONS WITH LEFT-TO-RIGHT SHUNT

■ ATRIAL SEPTAL DEFECT (ASD)

Most common is *ostium secundum* ASD, located at mid interatrial septum. *Ostium primum* ASDs (e.g., typical of Down syndrome) appear at lower atrial septum and are associated with abnormal development of atrioventricular (AV) valves, especially a cleft appearance of the mitral valve. *Sinus venosus* type defects do not actually involve the atrial septum, but rather represent a defect localized between a right pulmonary vein and the junction of the superior vena cava or inferior vena cava with the right atrium (RA). Physiologically such defects mimic ASDs.

History

When discovered in adulthood, usually asymptomatic until third or fourth decades, when exercise intolerance, dyspnea, and palpitations may occur. Onset of symptoms may be associated with development of pulmonary hypertension (PHT) (see below).

Physical Examination

Wide, fixed splitting of S_2 , systolic murmur from flow across pulmonic valve, possible diastolic flow rumble across tricuspid valve, prominent jugular venous v wave.

ECG

Incomplete RBBB (rSR' in right precordial leads) common. Left-axis deviation frequently present with ostium primum defect. Ectopic atrial pacemaker or first degree AV block occur in sinus venosus defects.

CXR

Increased pulmonary vascular markings, prominence of RA, RV, and main pulmonary artery (LA enlargement *not* usually present).

Echocardiogram

RA, RV, and pulmonary artery enlargement; Doppler shows abnormal transatrial flow. Echo contrast (agitated saline injection into peripheral systemic vein) may visualize transatrial shunt.

TREATMENT**Atrial Septal Defect**

In the absence of contraindications an ASD with a significant pulmonary-to-systemic flow (Q_p/Q_s) ratio ($\geq 1.5:1.0$) with right heart enlargement should be considered for surgical or percutaneous transcatheter closure. Closure is usually contraindicated with significant PHT and is not undertaken for small defects with trivial left-to-right shunt flow.

■ VENTRICULAR SEPTAL DEFECT (VSD)

Most common congenital abnormality at birth but many close spontaneously during childhood. Symptoms relate to size of the defect and pulmonary vascular resistance.

History

CHF may develop in infancy. Adults may be asymptomatic or develop fatigue and reduced exercise tolerance. Pts are susceptible to endocarditis.

Physical Examination

Holosystolic murmur at lower left sternal border, which may be accompanied by a palpable thrill, loud P_2 ; diastolic flow murmur across mitral valve.

ECG

Normal with small defects. Large shunts result in LA and LV enlargement.

CXR

Enlargement of main pulmonary artery, LA, and LV, with increased pulmonary vascular markings.

Echocardiogram

LA and LV enlargement; defect may be directly visualized. Color Doppler demonstrates flow across the defect.

TREATMENT**Ventricular Septal Defect**

Percutaneous or surgical closure is indicated for pts with symptoms, or with volume overload, in the absence of irreversible pulmonary vascular disease; closure is also reasonable if $Q_p/Q_s > 1.5:1$ and pulmonary artery pressure $< 2/3$ systemic pressure and pulmonary vascular resistance $< 2/3$ systemic resistance.

■ PATENT DUCTUS ARTERIOSUS (PDA)

Abnormal communication between the descending aorta and pulmonary artery; associated with birth at high altitudes and maternal rubella.

History

Asymptomatic, or fatigue and dyspnea on exertion.

Physical Examination

Hyperactive LV impulse; loud continuous “machinery” murmur below the left clavicle. If PHT develops, diastolic component of the murmur may disappear.

ECG

LV hypertrophy is common; RV hypertrophy if PHT develops.

CXR

Increased pulmonary vascular markings: enlarged main pulmonary artery, LV, ascending aorta; occasionally, calcification of ductus.

Echocardiography

Hyperdynamic, enlarged LV; the PDA can often be visualized on two-dimensional echo and color Doppler demonstrates abnormal flow through it.

TREATMENT**Patent Ductus Arteriosus**

In absence of PHT, PDA should be surgically ligated or divided to prevent infective endocarditis, LV dysfunction, and PHT. Transcatheter device closure is frequently possible.

■ PROGRESSION TO PHT

Pts with large, uncorrected left-to-right shunts (e.g., ASD, VSD, or PDA) may develop progressive, irreversible PHT with reverse shunting of desaturated blood into the arterial circulation (right-to-left direction), resulting in *Eisenmenger syndrome*. Fatigue, lightheadedness, and chest pain due to RV ischemia are common, accompanied by cyanosis, clubbing of digits, loud P_2 , murmur of pulmonary valve regurgitation, and signs of RV failure. ECG and echocardiogram show RV hypertrophy. Therapeutic options are limited and include pulmonary artery vasodilators (see [Chap. 129](#)) and consideration of lung transplant with repair of the cardiac defect, or heart-lung transplantation. Pregnancy is contraindicated because of high mortality.

ACYANOTIC CONGENITAL HEART LESIONS WITHOUT A SHUNT**■ PULMONIC STENOSIS (PS)**

A transpulmonary valve gradient < 30 mmHg indicates mild PS, 30–50 mmHg is moderate PS, and > 50 mmHg is considered severe PS. Mild to moderate PS rarely

causes symptoms, and progression tends not to occur. Pts with higher gradients may manifest dyspnea, fatigue, light-headedness, chest pain (RV ischemia).

Physical Examination

Jugular venous distention with prominent *a* wave, RV parasternal impulse, wide splitting of S_2 with soft P_2 , ejection click followed by “diamond-shaped” systolic murmur at upper left sternal border, right-sided S_4 .

ECG

Normal in mild PS; RA and RV enlargement in advanced PS.

CXR

Often shows poststenotic dilatation of the pulmonary artery and RV enlargement.

Echocardiography

RV hypertrophy and systolic “doming” of the pulmonic valve. Doppler accurately measures transvalvular gradient.

TREATMENT

Pulmonic Stenosis

Symptomatic or severe stenosis requires balloon valvuloplasty or surgical correction.

■ CONGENITALLY BICUSPID AORTIC VALVE

One of the most common congenital heart malformations (up to 1.4% of the population); rarely results in childhood aortic stenosis (AS), but is a cause of AS and/or regurgitation later in life. May go undetected in early life or suspected by the presence of a systolic ejection click; often identified during echocardiography that was obtained for another reason. See [Chap. 116](#) for typical history, physical findings, and treatment of subsequent clinical aortic valve disease.

■ COARCTATION OF THE AORTA

Aortic constriction just distal to the origin of the left subclavian artery is a surgically correctable form of hypertension ([Chap. 119](#)). Usually asymptomatic, but may cause headache, fatigue, or claudication of lower extremities. Often accompanied by bicuspid aortic valve.

Physical Examination

Hypertension in upper extremities; delayed femoral pulses with decreased pressure in lower extremities. Pulsatile collateral arteries may be palpated in the intercostal spaces. Systolic murmur is best heard over the upper back at the left interscapular space. Continuous murmur over the scapula may also be present due to collateral blood flow.

ECG

LV hypertrophy.

CXR

Notching of the ribs due to collateral arteries; “figure 3” appearance of distal aortic arch.

Echocardiography

Can delineate site and length of coarctation, and Doppler determines the pressure gradient across it. MR or CT angiography also visualizes the site of coarctation and can identify associated collateral vessel formation.

TREATMENT**Coarctation of the Aorta**

Surgical correction (or percutaneous transcatheter stent dilation in selected pts), although hypertension may persist. Recurrent coarctation after surgical repair may be amenable to percutaneous balloon dilatation.

COMPLEX CONGENITAL HEART LESIONS

These lesions are often accompanied by cyanosis. Examples include:

■ TETRALOGY OF FALLOT

Most common form of cyanotic congenital heart disease. The four main components are (1) malaligned VSD, (2) obstruction to RV outflow, (3) aorta that overrides the VSD, and (4) RV hypertrophy (RVH). Degree of RV outflow obstruction largely determines clinical presentation; when severe, the large right-to-left shunt causes cyanosis and systemic hypoxemia. ECG shows RVH. CXR demonstrates "boot-shaped" heart with prominent RV. Echocardiography delineates VSD, overriding aorta, and RVH and quantitates degree of RV outflow obstruction. Current surgical treatment strategies include primary repair in infancy. Complications following repair include pulmonary regurgitation with RV enlargement and/or RV outflow tract obstruction, and LV dysfunction, especially in adults repaired later in life and in those with prior palliative shunt surgery.

■ COMPLETE TRANSPOSITION OF THE GREAT ARTERIES (TGA)

Accounts for 10% of pts with cyanotic congenital heart disease. Aorta and pulmonary artery arise abnormally from the right and left ventricles respectively, creating two separate parallel circulations; a communication must exist between the two sides (ASD, PDA, or VSD) to sustain life. Development of RV dysfunction and heart failure are common by the third decade. Echocardiography reveals the aberrant anatomy. Treatment of the common D-loop form of TGA involves an arterial switch procedure, with translocation of the coronary arteries.

■ EBSTEIN ANOMALY

Abnormal downward placement of tricuspid valve within the RV; tricuspid regurgitation, hypoplasia of RV, and a right-to-left shunt are common. Twenty percent of pts have Wolff-Parkinson White ECG pattern. Echocardiography shows apical displacement of tricuspid septal leaflet, abnormal RV size, and quantitates degree of tricuspid regurgitation. Treatment includes surgical tricuspid valve repair/replacement and closure of associated ASDs.

ENDOCARDITIS PROPHYLAXIS IN CONGENITAL HEART DISEASE

American Heart Association 2007 Guidelines recommend antibiotic prophylaxis only in specific pts with congenital heart disease, i.e., those who are to undergo a dental procedure associated with bacteremia who have:

1. Unrepaired cyanotic congenital heart disease (e.g., tetralogy of Fallot)
2. Repaired congenital heart disease with residual defects adjacent to site of a prosthetic patch or transcatheter device
3. A history of complete repair of congenital defects with prosthetic material or a transcatheter device within the previous 6 months

116 Valvular Heart Disease



MITRAL STENOSIS (MS)

■ ETIOLOGY

Most commonly rheumatic, though history of acute rheumatic fever is now uncommon; rare causes include congenital MS and severe calcification of the mitral annulus with extension onto the leaflets.

■ HISTORY

Symptoms most commonly begin in the fourth decade, but MS often causes severe disability at earlier ages in developing nations. Principal symptoms are dyspnea and cough precipitated by exertion, excitement, fever, anemia, tachycardia, pregnancy, sexual intercourse, and thyrotoxicosis.

■ PHYSICAL EXAMINATION

Right ventricular lift; palpable S_1 ; opening snap (OS) follows A_2 by 0.05–0.12 s; OS– A_2 interval inversely proportional to severity of obstruction. Diastolic rumbling murmur, best heard at apex in left lateral decubitus position, with presystolic accentuation when in sinus rhythm. Duration of murmur correlates with severity of obstruction.

■ COMPLICATIONS

Hemoptysis, pulmonary embolism, respiratory infections, systemic embolization; endocarditis is uncommon in pure MS.

■ ECG

Typically shows atrial fibrillation (AF) or left atrial (LA) enlargement when sinus rhythm is present. Right-axis deviation and RV hypertrophy in the presence of pulmonary hypertension.

■ CXR

LA and RV enlargement, pulmonary artery prominence, and Kerley B lines.

■ ECHOCARDIOGRAM

Shows reduced separation, thickening and calcification of mitral leaflets and subvalvular apparatus, LA enlargement. Doppler assessment provides estimation of transvalvular peak and mean gradients, mitral valve area, and degree of pulmonary hypertension (**Chap. 114**).

TREATMENT

Mitral Stenosis (See **Fig. 116-1**)

At-risk pts should receive prophylaxis for recurrent rheumatic fever (penicillin V 250–500 mg PO bid or benzathine penicillin G 1–2 M units IM monthly). For dyspnea, prescribe sodium restriction and oral diuretic therapy; beta blockers, rate-limiting calcium channel antagonists (i.e., verapamil or diltiazem), or digoxin are used to slow ventricular rate in AF. Warfarin (with target INR 2.0–3.0) for pts with AF or history of thromboembolism (direct acting oral anticoagulants [DOACs, e.g., apixaban, rivaroxaban, dabigatran] are not approved for pts with rheumatic MS). For AF of recent onset, consider conversion (chemical or electrical) to sinus rhythm, ideally after ≥ 3 weeks of anticoagulation. Mitral valvotomy in the presence of symptoms and mitral orifice ≤ 1.5 cm². In uncomplicated MS, percutaneous balloon valvuloplasty is the procedure of choice; if not feasible, then open surgical valvotomy (**Fig. 116-1**).

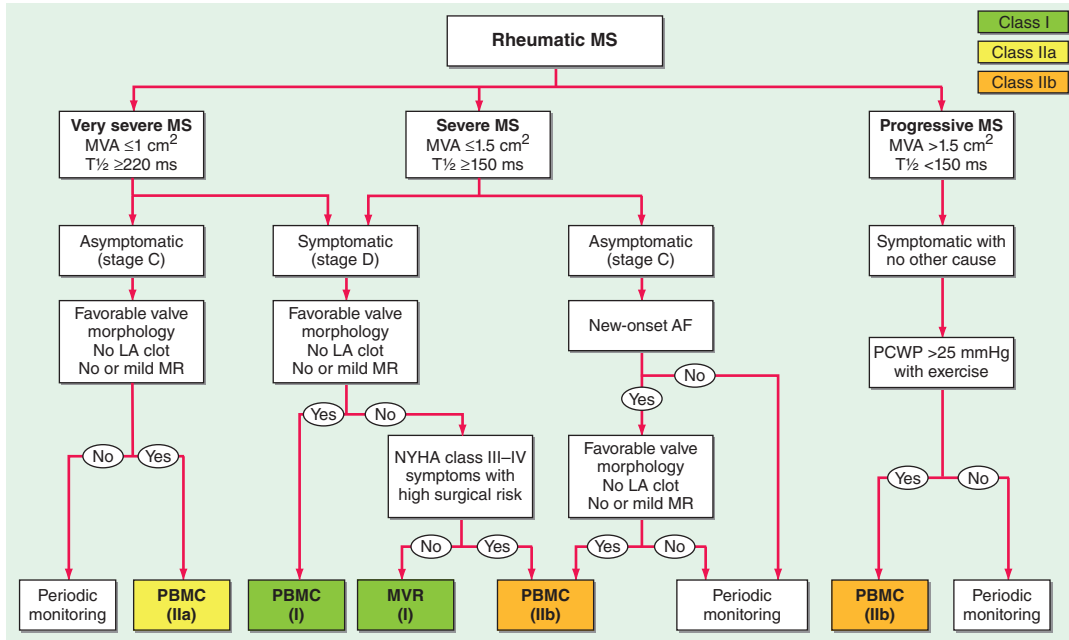


FIGURE 116-1 Management of rheumatic mitral stenosis. MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; MVR, mitral valve surgery (repair or replacement); NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PMBC, percutaneous mitral balloon commissurotomy; T_{1/2}, pressure half-time. (Adapted from Nishimura RA et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. *J Am Coll Cardiol* 63:e57, 2014.)

MITRAL REGURGITATION (MR)

■ ETIOLOGY

Acute MR: Infective endocarditis, papillary muscle rupture post-MI, ruptured chordae tendineae. *Chronic MR:* Myxomatous deformity (mitral valve prolapse [MVP]), mitral annular calcification, rheumatic, healed endocarditis, congenital, radiation damage, LV enlargement of any cause, hypertrophic cardiomyopathy (with systolic anterior motion of anterior mitral leaflet).

■ CLINICAL MANIFESTATIONS

Acute MR: Commonly presents with symptoms and signs of acute pulmonary edema. *Chronic MR:* Mild-moderate disease is typically asymptomatic. In chronic severe MR, fatigue, exertional dyspnea, orthopnea, palpitations are common, and physical examination shows sharp low-volume carotid upstroke, laterally displaced apical impulse, LV is hyperdynamic, S_1 diminished, wide splitting of S_2 ; S_3 common; loud holosystolic murmur at the apex and often a brief early-mid-diastolic murmur due to increased transvalvular flow. Murmur typically radiates to axilla, but may radiate to base instead when due to prolapsing or flail posterior leaflet.

■ ECHOCARDIOGRAPHY

Often identifies mechanism of MR (TEE provides greater anatomic detail, when needed). Measures LA size and LV dimensions and contractile function, which are important to follow serially over time. Doppler techniques quantify severity of MR and provide estimate of pulmonary artery systolic pressure.

TREATMENT

Mitral Regurgitation (See Fig. 116-2)

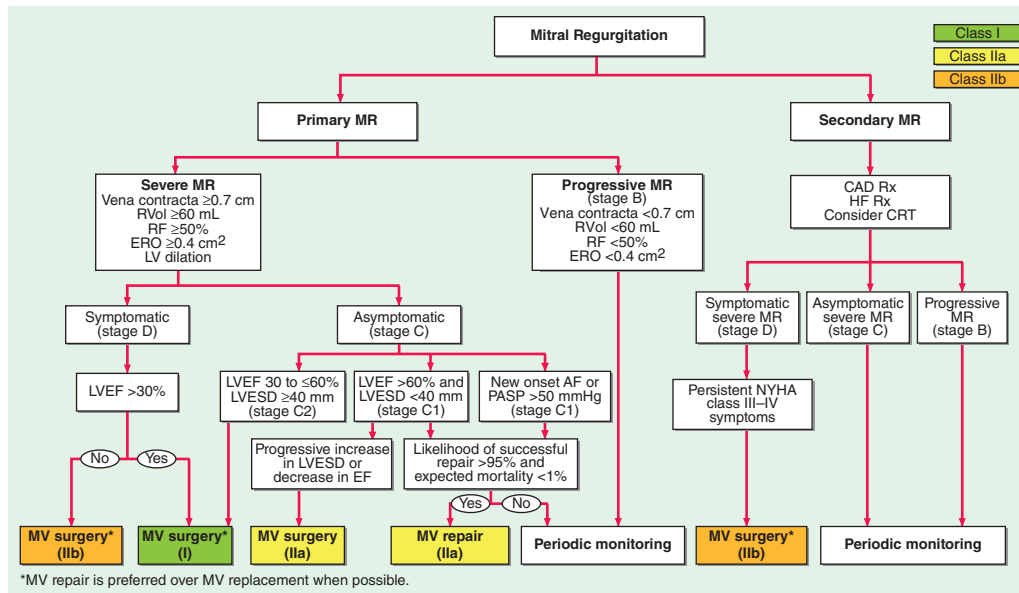
For severe/decompensated MR, treat as for heart failure (Chap. 126). IV vasodilators (e.g., nitroprusside) are beneficial for acute, severe MR. Anticoagulation (warfarin, or a DOAC, in the absence of rheumatic MS or a mechanical prosthetic heart valve) is indicated if AF is present, as guided by the CHA₂DS₂-VASc risk score. For chronic, severe, primary MR, surgical valve repair or replacement is appropriate if pt has symptoms or progressive LV dysfunction (e.g., LV ejection fraction [LVEF] <60% or end-systolic LV diameter \geq 40 mm). Operation should be carried out *before* development of chronic heart failure symptoms. Valve repair should also be considered for asymptomatic pts with severe chronic MR with recent onset AF, pulmonary hypertension (PA systolic pressure \geq 50 mmHg at rest, or \geq 60 mmHg with exercise), or a progressive decrease in LVEF, or increase in LV end-systolic diameter, on serial imaging. Pts with secondary MR due to ischemic disease may require coronary artery revascularization along with valve repair. For pts with secondary MR and significantly reduced LVEF (ischemic MR or MR due to LV enlargement/cardiomyopathy), the focus of therapy should be on aggressive guideline-directed nonsurgical therapy (Chap. 116 and Fig. 116-2), with invasive intervention reserved for refractory symptoms.

Transcatheter mitral valve repair, using a clip to tether the mid-portion of the leaflet edges together, is commercially available for symptomatic pts with severe, primary (e.g., myxomatous) MR at very high or prohibitive surgical risk.

MITRAL VALVE PROLAPSE

■ ETIOLOGY

Excessive/redundant mitral leaflet tissue typically of unknown cause; may also accompany certain connective tissue disorders, e.g., Marfan syndrome, Ehlers-Danlos syndrome.



*MV repair is preferred over MV replacement when possible.

FIGURE 116-2 Management of mitral regurgitation. CAD, coronary artery disease; CRT, cardiac resynchronization therapy; ERO, effective regurgitant orifice; HF, heart failure; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation, MV, mitral valve; MVR, mitral valve replacement; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; and Rx, therapy. Mitral valve repair preferred over MVR when possible. (Nishimura RA et al: 2017 Focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease. *Circulation* 2017;135:e1159–e1195. Reprinted with permission © 2017 American Heart Association.)

■ PATHOLOGY

Redundant mitral valve tissue often with myxedematous degeneration and increased glycosaminoglycans.

■ CLINICAL MANIFESTATIONS

More common in females, most pts are asymptomatic. Yet MVP is the most common cause of primary MR ultimately requiring surgical treatment in North America. Potential symptoms include vague chest discomforts and supraventricular and ventricular arrhythmias. Most important complication is progressive MR. Rarely, systemic emboli from platelet-fibrin deposits on valve lead to transient ischemic attacks. Sudden death is a very rare outcome of MVP.

■ PHYSICAL EXAMINATION

Mid or late systolic click(s) followed by high-pitched late systolic murmur at the apex (radiates to axilla with anterior leaflet prolapse, often to base with posterior leaflet prolapse). Click and murmur move earlier and are exaggerated by Valsalva maneuver; they are delayed and softened by squatting and isometric exercise ([Chap. 112](#)).

■ ECHOCARDIOGRAM

Shows posterior displacement of one or both mitral leaflets late in systole. Doppler techniques assess severity of accompanying MR. 3-D echo or magnetic resonance imaging are sometimes used to precisely determine LV volumes.

TREATMENT**Mitral Valve Prolapse**

Asymptomatic pts should be reassured. Beta blockers may lessen chest discomfort and palpitations. Prophylaxis for infective endocarditis is indicated only if prior history of endocarditis. Valve repair or replacement indicated for pts with severe MR who are symptomatic or show progressive LV systolic dysfunction, recent onset AF, or pulmonary hypertension.

AORTIC STENOSIS (AS)**■ ETIOLOGIES**

Most common: (1) degenerative calcification of a congenitally bicuspid valve, (2) chronic deterioration and calcification of a trileaflet valve, and (3) rheumatic disease (almost always associated with rheumatic *mitral* disease).

■ SYMPTOMS

Exertional dyspnea, angina, and syncope are cardinal symptoms; they occur late, after years of obstruction and aortic valve area ≤ 1.0 cm².

■ PHYSICAL EXAMINATION

Weak and delayed (parvus et tardus) arterial pulses with carotid thrill. A₂ soft or absent; S₄ common. Crescendo-decrescendo systolic murmur, often with systolic thrill. Murmur is typically loudest at second right intercostal space, with radiation to carotids and sometimes to the apex (*Gallavardin effect*).

■ ECG

Often shows LV hypertrophy, with lateral ST depression and T wave inversion.

■ ECHOCARDIOGRAM

Identifies LV hypertrophy, calcification and thickening of aortic valve cusps with reduced systolic opening, and any accompanying enlargement of aortic root and/or ascending aorta. Dilatation of LV and impaired contraction indicate

poor prognosis. Doppler quantitates systolic gradient and allows calculation of valve area. Dobutamine stress echocardiography is helpful to assess severity of AS when there is accompanying LV systolic dysfunction.

TREATMENT

Aortic Stenosis (See Fig. 116-3)

Avoid strenuous activity and hypovolemia/dehydration in severe AS. Beta-blockers and ACE inhibitors are generally safe to use for treatment of hypertension and ischemic heart disease in the presence of normal systolic function. Valve replacement is most clearly indicated for adults with severe obstruction (valve area $<1 \text{ cm}^2$) and (1) symptoms resulting from AS, (2) those with LVEF $<50\%$, or (3) if other cardiovascular surgery is planned. Transcatheter aortic valve replacement (TAVR) is an alternative approach with excellent results for pts at prohibitive, high, or intermediate surgical risk. TAVR is associated with early stroke hazard, and need for permanent pacemaker in $\sim 10\%$ of pts. Post-procedure paravalvular aortic regurgitation (AR) is a major predictor of subsequent mortality.

AORTIC REGURGITATION

■ ETIOLOGY

Valvular: Includes congenitally bicuspid valve, endocarditis, or rheumatic (especially if rheumatic mitral disease is present). *Dilated aortic root:* dilatation due to cystic medial necrosis, aortic dissection, ankylosing spondylitis, syphilis.

■ CLINICAL MANIFESTATIONS

When *chronic* severe AR is symptomatic, manifests as awareness of forceful heart-beat, exertional dyspnea, and other signs of LV failure (orthopnea, paroxysmal nocturnal dyspnea) and sometimes angina pectoris. A widened pulse pressure, rapidly rising "water hammer" pulse, capillary pulsations (Quincke's sign), and a heaving, laterally displaced LV impulse are common. On auscultation A_2 is soft or absent, an S_3 may be present, and there is a high-pitched, blowing, decrescendo early diastolic murmur along the left sternal border (but often along right sternal border when AR is due to aortic dilatation). In *acute* severe AR, the pulse pressure is typically not widened and the diastolic murmur is often short and soft.

■ LABORATORY ECG AND CXR

ECG: Signs of LV hypertrophy with "strain." *CXR:* apex is displayed downward and to the left; aneurysmal dilatation of the aorta may be present.

■ ECHOCARDIOGRAM

LV enlargement, possible aortic dilatation, high-frequency diastolic fluttering of mitral valve. Failure of coaptation of aortic valve leaflets may be present. Doppler studies detect and quantify AR. Cardiac magnetic resonance imaging helpful for quantification of AR, LV contractile function, and aortic enlargement if echo is inadequate.

TREATMENT

Aortic Regurgitation

Acute severe AR requires intravenous diuretics and vasodilators (e.g., sodium nitroprusside) and usually early surgical correction. For chronic AR, vasodilators (ACE inhibitor or long-acting nifedipine) are recommended if hypertension present. Avoid beta blockers, which prolong diastolic filling. Surgical valve

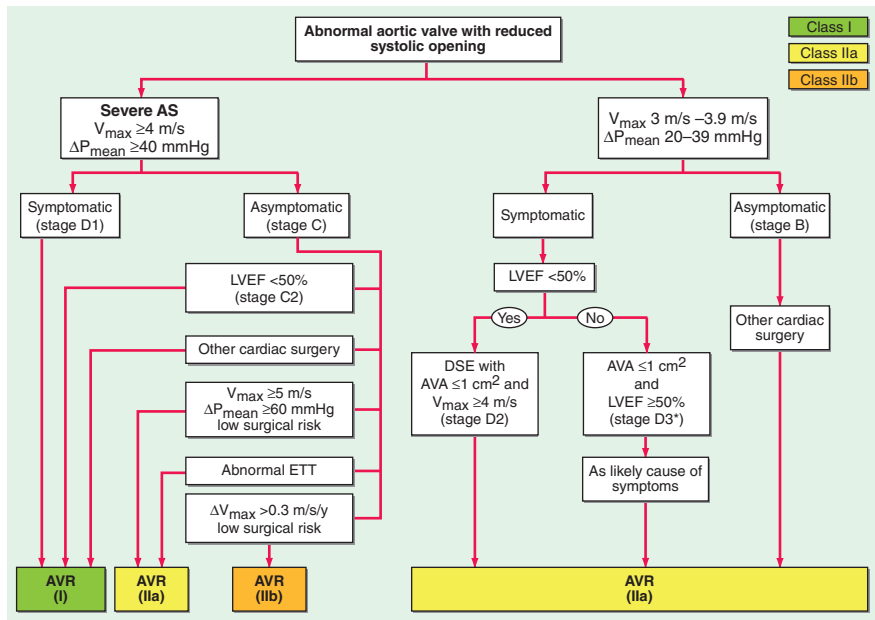


FIGURE 116-3 Algorithm for the management of aortic stenosis (AS). See Fig. 256-4, p. 1806, in HPIM-20 for explanation of specific stages A-D of disease progression. AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement by either surgical or transcatheter approach; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction; ΔP_{mean} , mean pressure gradient; and V_{max} , maximum velocity. (Adapted from Nishimura RA et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. *J Am Coll Cardiol* 63:e57, 2014.)

replacement should be considered in pts with chronic severe AR when symptoms develop or in asymptomatic pts with LV dysfunction (e.g., LVEF <50%, end-systolic diameter >50 mm, or LV diastolic dimension >65 mm) by imaging studies.

TRICUSPID STENOSIS (TS)

■ ETIOLOGY

Usually rheumatic; most common in females; almost invariably associated with MS.

■ CLINICAL MANIFESTATIONS

Hepatomegaly, ascites, peripheral edema, jaundice, jugular venous distention with slow *y* descent (**Chap. 112**). Diastolic rumbling murmur along left sternal border increased by inspiration with loud presystolic component. ECG shows tall P waves in lead II (right atrial enlargement) without RV hypertrophy. Chest X-ray shows right atrial and superior vena caval enlargement. Doppler echocardiography demonstrates thickened valve and impaired separation of leaflets and provides estimate of transvalvular gradient.

TREATMENT

Tricuspid Stenosis

In severe TS (mean gradient >4 mmHg, valve area <1.5–2.0 cm²), surgical relief is indicated, with valvular repair or replacement.

TRICUSPID REGURGITATION (TR)

■ ETIOLOGY

Usually functional and secondary to marked RV dilatation of any cause, often associated with pulmonary hypertension. Other causes include rheumatic disease, endocarditis, myxomatous valve disease, and carcinoid valvular disease.

■ CLINICAL MANIFESTATIONS

RV failure, with edema, hepatomegaly, and prominent *c-v* waves in jugular venous pulse with rapid *y* descent (**Chap. 112**). Systolic murmur along lower left sternal edge is increased by inspiration. A prominent RV pulsation at left sternal edge may be present. Doppler echocardiography confirms diagnosis and estimates severity of disease.

TREATMENT

Tricuspid Regurgitation

Intensive diuretic therapy when right-sided heart failure signs are present. In severe cases surgical treatment consists of tricuspid annuloplasty or valve replacement.

PULMONIC STENOSIS (PS)

■ ETIOLOGY

Almost always congenital; carcinoid syndrome is a rare cause of PS.

■ CLINICAL MANIFESTATIONS

Symptoms occur only with severe disease (peak transvalvular gradient >50 mmHg) and include exertional dyspnea, fatigue, and occasionally angina, owing to RV oxygen demand. Physical findings include a crescendo-decrescendo

systolic murmur at the second left interspace typically preceded by a systolic ejection click. A right-sided S_4 may be present. A prominent a wave is typical in the jugular venous pulse. The ECG in severe PS shows right ventricular hypertrophy and right atrial enlargement. The chest x-ray shows right atrial and right ventricular enlargement; post-stenotic enlargement of the pulmonary artery may be present. Doppler echocardiography demonstrates the stenotic valve and quantitates the transvalvular gradient.

TREATMENT

Pulmonic Stenosis

Diuretics for initial symptoms of right heart failure. Symptomatic pts with severe PS who have less than moderate pulmonic regurgitation are candidates for percutaneous balloon valvotomy; otherwise open surgery may be required.

117 Cardiomyopathies and Myocarditis



Cardiomyopathies are primary diseases of heart muscle. [Table 117-1](#) summarizes distinguishing presenting features of the three major types of cardiomyopathy (CMP). [Table 117-2](#) details the comprehensive initial evaluation of suspected cardiomyopathies.

DILATED CMP

Dilated left ventricle (LV) with poor systolic contractile function; right ventricle (RV) often involved.

■ ETIOLOGY

Over 30% of pts have a familial form; mutations in *TTN* (encodes large sarcomeric protein titin) are the most common. Additional causes include myocarditis (e.g., viral and other infections, sarcoidosis, giant cell, eosinophilic), toxins (e.g., ethanol, antineoplastic agents [e.g., doxorubicin, trastuzumab, imatinib], hydroxychloroquine, heavy metals), connective tissue disorders, hypothyroidism, hemochromatosis, muscular dystrophies, “peripartum,” transient stress “takotsubo” CMP. Impaired LV function owing to severe coronary disease/infarction or chronic aortic/mitral regurgitation may behave similarly.

■ SYMPTOMS

Heart failure ([Chap. 126](#)) often with secondary mitral and tricuspid regurgitation; tachyarrhythmias and peripheral emboli from LV mural thrombus occur.

■ PHYSICAL EXAMINATION

Jugular venous distention (JVD), pulmonary crackles, diffuse and dyskinetic LV apex, S_3 , hepatomegaly, peripheral edema; murmurs of mitral and tricuspid regurgitation are common.

■ LABORATORY ECG

Left bundle branch block or nonspecific ST-T-wave abnormalities are common.

■ CXR

Cardiomegaly, pulmonary vascular redistribution, pulmonary effusions common.

TABLE 117-1 Presentation with Symptomatic Cardiomyopathy

	DILATED	RESTRICTIVE	HYPERTROPHIC
Ejection fraction (normal >55%)	Usually <30% when symptoms severe	25–50%	>60%
Left ventricular diastolic dimension (normal <55 mm)	≥60 mm	<60 mm (may be decreased)	Often decreased
Left ventricular wall thickness	Normal or decreased	Normal or increased	Markedly increased
Atrial size	Increased	Increased; may be massive	Increased
Valvular regurgitation	Related to annular dilation	Related to endocardial involvement; frequent mitral and tricuspid regurgitation, rarely severe	Related to valve-septum interaction: mitral regurgitation
Common first symptoms	Exertional intolerance	Exertional intolerance, fluid retention early	Exertional intolerance; may have chest pain
Congestive symptoms ^a	Left before right, except right prominent in young adults	Right often dominates	Left-sided congestion may develop late
Arrhythmia	Ventricular tachyarrhythmia; conduction block in Chagas' disease, and some familial forms. Atrial fibrillation	Ventricular uncommon except in sarcoidosis, conduction block in sarcoidosis and amyloidosis. Atrial fibrillation	Ventricular tachyarrhythmias; atrial fibrillation

^aLeft-sided symptoms of pulmonary congestion: dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea. Right-sided symptoms of systemic venous congestion: hepatic and abdominal distention, discomfort on bending, peripheral edema.

■ ECHOCARDIOGRAM, CT, AND CARDIAC MRI

LV and RV enlargement with globally impaired contraction. Regional wall motion abnormalities suggest coronary artery disease rather than primary CMP.

■ B-TYPE NATRIURETIC PEPTIDE (BNP)

Level elevated in heart failure/CMP but not in pts with dyspnea due to lung disease.

TREATMENT

Dilated CMP

Possible use of immunosuppressive drugs if specific forms active myocarditis present on RV biopsy (e.g., for sarcoidosis or giant cell myocarditis). Standard therapy of heart failure ([Chap. 126](#)): Diuretic for volume overload, vasodilator therapy with ACE inhibitor (preferred), angiotensin receptor blocker or hydralazine-nitrate combination, and beta-blocker therapy (e.g., metoprolol succinate,

carvedilol) limit disease progression and improve longevity. Consider aldosterone antagonist therapy for pts with class II–IV heart failure, and chronic anticoagulation if there is accompanying atrial fibrillation (AF), prior embolism, or recent large anterior MI. Antiarrhythmic drugs (e.g., amiodarone or dofetilide) may be useful to maintain sinus rhythm in pts with AF. Consider implanted cardioverter defibrillator (ICD) for class II–III pts with LVEF <35%. For those with class III–IV heart failure, LVEF <35%, and prolonged QRS duration, consider cardiac resynchronization therapy (CRT) using biventricular pacing; greatest benefit in pts with LBBB and QRS \geq 150 msec (ICD and CRT functions can be provided by a single implanted device). In selected pts, consider cardiac transplantation.

RESTRICTIVE CMP

Characterized by abnormal diastolic relaxation, often with mildly reduced systolic function. Etiologies include infiltrative disease (e.g., amyloidosis, sarcoidosis), storage diseases (hemochromatosis, Fabry's disease), fibrotic disorders (radiation, scleroderma), endomyocardial disease (hypereosinophilic syndrome, endomyocardial fibrosis).

■ SYMPTOMS

Exercise intolerance, then symptoms of heart failure, often predominantly right-sided.

■ PHYSICAL EXAMINATION

Especially signs of right-sided heart failure: JVD (Kussmaul sign may be present), hepatomegaly, peripheral edema. S_4 is common.

■ LABORATORY ECG

Low limb lead voltage (e.g., in some forms of amyloidosis), sinus tachycardia, ST-T-wave abnormalities.

■ CXR

Mild LV enlargement.

■ ECHOCARDIOGRAM, CT, CARDIAC MRI, NUCLEAR IMAGING

Bilateral atrial enlargement, often to a marked degree; increased ventricular thickness ("speckled pattern") common in infiltrative disease, especially amyloidosis. Systolic function is usually normal or mildly reduced. Doppler analysis shows impaired diastolic function. Amyloid infiltration can be detected with MRI gadolinium enhancement. Technetium pyrophosphate nuclear imaging is sensitive for detection of transthyretin amyloidosis.

■ CARDIAC CATHETERIZATION

Increased LV and RV diastolic pressures with "dip and plateau" pattern; RV biopsy useful in detecting infiltrative disease.

Note: Must distinguish restrictive CMP from constrictive pericarditis, which is surgically correctable. Thickening of pericardium on CT or MR imaging is apparent in >80% of pts with constrictive pericarditis.

TREATMENT

Restrictive CMP

Salt restriction and diuretics ameliorate pulmonary and systemic congestion.

Note: Increased sensitivity to digitalis in amyloidosis. Anticoagulation often indicated, particularly in pts with eosinophilic endomyocarditis. For specific therapy of amyloidosis, hemochromatosis and sarcoidosis, see [Chaps. 108, 407 and 360](#), respectively, in HPIM-20.

TABLE 117-2 Initial Evaluation of Cardiomyopathy**Clinical Evaluation**

Thorough history and physical examination to identify cardiac and noncardiac disorders^a

Detailed family history of heart failure, cardiomyopathy, skeletal myopathy, conduction disorders and tachyarrhythmias, sudden death

History of alcohol, illicit drugs, chemotherapy, or radiation therapy^a

Assessment of ability to perform routine and desired activities^a

Assessment of volume status, orthostatic blood pressure, body mass index^a

Laboratory Evaluation

Electrocardiogram^a

Chest radiograph^a

Two-dimensional and Doppler echocardiogram^a

Magnetic resonance imaging to assess myocardial inflammation and fibrosis

Chemistry:

Serum sodium,^a potassium,^a calcium,^a magnesium^a

Fasting glucose (glycohemoglobin in diabetes mellitus)

Creatinine,^a blood urea nitrogen^a

Albumin,^a total protein,^a liver function tests^a

Lipid profile

Thyroid-stimulating hormone^a

Serum iron, transferrin saturation

Urinalysis

Creatine kinase isoforms

Cardiac troponin

Hematology:

Hemoglobin/hematocrit^a

White blood cell count with differential,^a including eosinophils

Erythrocyte sedimentation rate

Initial Evaluation When Specific Diagnoses Are Suspected

DNA sequencing for genetic disease; panel selection based on phenotype

Titers for infection in presence of clinical suspicion:

Acute viral (e.g., coxsackievirus, echovirus, influenza)

Human immunodeficiency virus

Chagas' disease, Lyme disease, toxoplasmosis

Coronary angiography in pts with angina who are candidates for intervention^a

Serologies for active rheumatologic disease

Endomyocardial biopsy including sample for electron microscopy when suspecting specific diagnosis with therapeutic implications

Screening for sleep-disordered breathing

^aLevel I Recommendations from ACC/AHA Practice Guidelines for Chronic Heart Failure in the adult.

HYPERTROPHIC CMP

Marked LV hypertrophy; often asymmetric, without underlying hypertension or valvular disease. Systolic function is usually normal; increased LV stiffness results in elevated diastolic filling pressures. Typically results from mutations in sarcomeric proteins (autosomal dominant transmission).

■ SYMPTOMS

Secondary to elevated diastolic pressure, dynamic LV outflow obstruction (if present), and arrhythmias; dyspnea on exertion, angina, and presyncope; sudden death may occur.

■ PHYSICAL EXAMINATION

Brisk carotid upstroke with pulsus bisferiens; S_4 , harsh systolic murmur along left sternal border, blowing murmur of mitral regurgitation at apex; murmur enhances with Valsalva and other maneuvers that decrease LV filling (Chap. 112).

■ LABORATORY ECG

LV hypertrophy with prominent “septal” Q waves in leads I, aVL, V_{5-6} . Episodic AF or ventricular tachycardia (VT) may be found on ambulatory monitoring.

■ ECHOCARDIOGRAM

LV hypertrophy, often with asymmetric involvement, especially of the septum or apex; LV contractile function typically excellent with small end-systolic volume. If LV outflow tract obstruction is present, systolic anterior motion (SAM) of mitral valve and midsystolic partial closure of aortic valve are present. Doppler shows early systolic accelerated blood flow through LV outflow tract.

TREATMENT**Hypertrophic CMP**

Strenuous exercise should be avoided. Beta blockers, verapamil, or disopyramide used individually to reduce symptoms. Digoxin, other inotropes, diuretics, and vasodilators should generally be avoided. Endocarditis antibiotic prophylaxis (Chap. 83) is necessary only in pts with prior history of endocarditis. Antiarrhythmic agents, especially amiodarone, may suppress atrial and ventricular arrhythmias. However, consider ICD for pts with high-risk profile, e.g., history of syncope or aborted cardiac arrest, nonsustained VT, marked LVH (>3 cm), exertional hypotension, or family history of sudden death. In selected pts, LV outflow gradient can be reduced by controlled septal infarction by ethanol injection into the septal artery. Surgical myectomy may be useful in pts refractory to medical therapy.

MYOCARDITIS

Inflammation of the myocardium that may progress to chronic dilated CMP, is most commonly related to acute viral infection (e.g., coxsackievirus, adenovirus, Epstein-Barr virus, parvovirus B19, human herpesvirus 6). Myocarditis may also develop in pts with HIV infection, hepatitis C, or Lyme disease. Chagas' disease (*Trypanosoma cruzi*) is a common cause of myocarditis in endemic areas, typically Central and South America. Noninfective causes of myocarditis include granulomatous disease (e.g., sarcoidosis, giant cell myocarditis), which should be considered if VT or conduction blocks dominate the presentation of heart failure in the absence of CAD. Rare etiologies include eosinophil myocarditis, hypersensitivity myocarditis, and systemic inflammatory diseases (e.g., polymyositis, dermatomyositis).

■ HISTORY

Fever, fatigue, palpitations; if LV dysfunction develops, symptoms of heart failure are present. Viral myocarditis may be preceded by URI.

■ PHYSICAL EXAMINATION

Fever, tachycardia, soft S_1 ; S_3 common.

LABORATORY

Cardiac troponins and creatine kinase-MB isoenzyme may be elevated in absence of MI. Convalescent antiviral antibody titers may rise.

ECG

Transient ST-T-wave abnormalities.

CXR

Cardiomegaly may be present.

ECHOCARDIOGRAM, CARDIAC MRI

Depressed LV function; pericardial effusion if accompanying pericarditis present. MRI demonstrates mid-wall gadolinium enhancement. Endomyocardial biopsy is rarely indicated (e.g., in suspected sarcoidosis or giant cell myocarditis).

TREATMENT**Myocarditis**

Treat as heart failure ([Chap. 126](#)); efficacy of immunosuppressive therapy (e.g., steroids) has not been demonstrated except in isolated conditions such as sarcoidosis and giant cell myocarditis. In fulminant cases, cardiac transplantation may be indicated.

118 Pericardial Disease

**ACUTE PERICARDITIS****ETIOLOGIES (SEE TABLE 118-1)****HISTORY**

Chest pain, which may be intense, mimicking acute MI, but characteristically sharp, pleuritic, positional (relieved by leaning forward). Pain is usually retrosternal or left precordial, radiating to neck, left shoulder, trapezius ridge, and/or arms; fever and palpitations are common. Typical pain may not be present in slowly developing pericarditis (e.g., tuberculous, post-irradiation, neoplastic, uremic).

PHYSICAL EXAMINATION

Rapid or irregular pulse, coarse pericardial friction rub (may come and go); is loudest with pt sitting forward.

LABORATORY ECG (SEE TABLE 118-2 AND FIG. 118-1)

Diffuse ST elevation (concave upward) usually present in all leads except aVR and V₁; PR-segment depression (and/or PR elevation in lead aVR) may be present; days later ST returns to baseline and T-wave inversion then develops. Distinguish from acute ST elevation MI (in which ST elevations are upwardly *convex* with reciprocal ST depression in opposite leads, PR depression does not occur, and T wave inversions appear while ST segments are still elevated). Differentiate from ECG of early repolarization (ER) (ratio of ST elevation/T wave height <0.25 in ER, but >0.25 in pericarditis). Atrial premature beats and atrial fibrillation are common.

TABLE 118-1 Etiologies of Pericarditis

"Idiopathic"

Infections (particularly viral)

Collagen vascular disease (e.g., rheumatoid arthritis, SLE)

Post-cardiac injury (i.e., following heart surgery or myocardial infarction)

Uremia

Neoplasms

Mediastinal radiation therapy

Drug reaction (e.g., procainamide, hydralazine)

■ CXR

Symmetrically increased size of cardiac silhouette only if large (>250 mL) pericardial effusion is present.

■ ECHOCARDIOGRAM

Most readily available test for detection of pericardial effusion, which commonly accompanies acute pericarditis.

TREATMENT**Acute Pericarditis**

Aspirin 650–975 mg qid or other NSAIDs (e.g., ibuprofen 600–800 mg tid or indomethacin 25–50 mg tid; at higher doses, consider gastric protection, e.g., omeprazole 20 mg daily); addition of colchicine 0.5 mg bid (0.5 mg once daily if weight <70 kg) enhances response and reduces frequency of recurrences. For *severe, refractory* pain, glucocorticoids (e.g., prednisone) can be prescribed. Intrac-table, prolonged pain or frequently recurrent episodes may require pericardiectomy. Anticoagulants are relatively contraindicated in acute pericarditis because of risk of pericardial hemorrhage.

CARDIAC TAMPONADE

Life-threatening condition resulting from accumulation of pericardial fluid under pressure; impaired filling of cardiac chambers and decreased cardiac output.

TABLE 118-2 ECG in Acute Pericarditis vs Acute ST-Elevation MI

ST-SEGMENT POSITION	ECG LEAD INVOLVEMENT	EVOLUTION OF ST AND T WAVES	PR-SEGMENT DEVIATION
Pericarditis			
Concave upward	All leads involved except aVR and V ₁	ST remains elevated for several days; after ST returns to baseline, T waves invert	Yes, in majority
Acute ST elevation MI			
Convex upward	ST elevation over infarcted region only; reciprocal ST depression in opposite leads	In absence of successful reperfusion therapies: T waves invert within hours, while ST still elevated; followed by Q-wave development	No

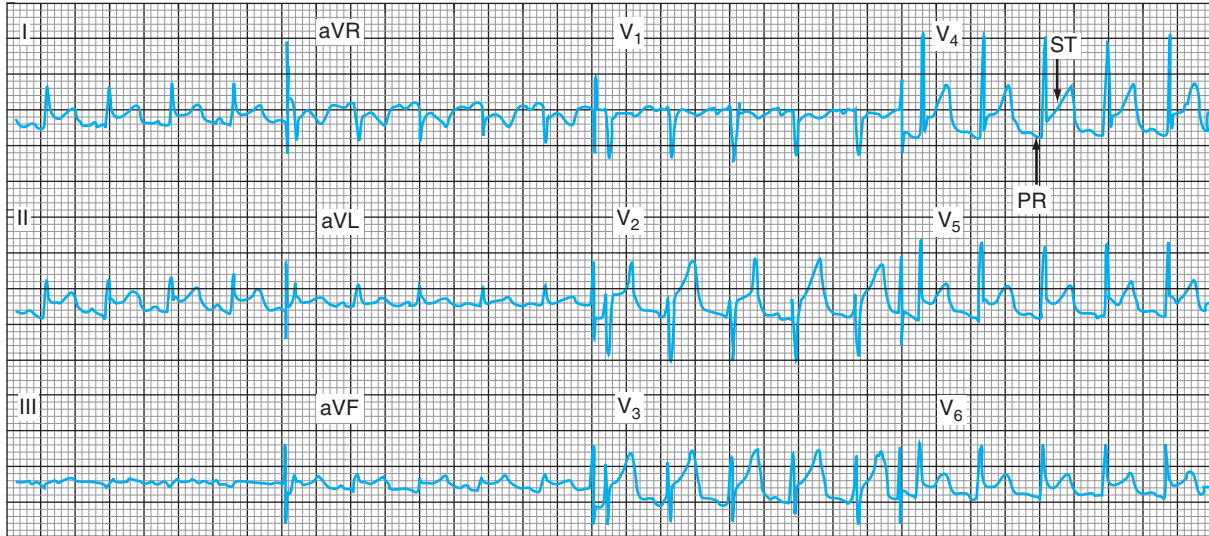


FIGURE 118-1 Electrocardiogram in acute pericarditis. Note diffuse ST-segment elevation and PR-segment depression.

■ ETIOLOGY

Previous viral/idiopathic pericarditis, metastatic tumor, uremia, cardiac trauma, myocardial perforation during intravascular procedures, tuberculosis.

■ HISTORY

Symptoms of hypotension; subacute symptoms include dyspnea, weakness, confusion.

■ PHYSICAL EXAMINATION

Tachycardia, hypotension with pulsus paradoxus (inspiratory fall in systolic blood pressure >10 mmHg), jugular venous distention with preserved x descent but loss of y descent; distant heart sounds. If tamponade develops subacutely, peripheral edema, hepatomegaly, and ascites may be present.

■ LABORATORY: ECG

Low limb lead voltage; large effusions may cause electrical alternans (alternating size of QRS complex due to swinging of heart).

■ CXR

Enlarged cardiac silhouette if large (>250 mL) effusion present.

■ ECHOCARDIOGRAM

Swinging motion of heart within large effusion; high pericardial pressure causes cyclical RA indentation and RV diastolic collapse. Doppler shows marked respiratory variation of transvalvular flow velocities.

■ CARDIAC CATHETERIZATION

Confirms diagnosis; shows elevated pericardial pressure with equalization of diastolic pressures in all cardiac chambers.

TREATMENT**Cardiac Tamponade**

Pericardiocentesis and IV volume expansion.

CONSTRUCTIVE PERICARDITIS

Condition in which a rigid pericardium impairs cardiac filling, causing elevation of systemic and pulmonary venous pressures and decreased cardiac output. Results from healing and scar formation in some pts with previous pericarditis. Viral, tuberculosis (mostly in developing nations), previous cardiac surgery, collagen vascular disorders, uremia, neoplastic, and radiation-associated pericarditis are potential causes.

■ HISTORY

Gradual onset of exertional dyspnea, fatigue, lower extremity edema, abdominal swelling; symptoms of LV failure are uncommon.

■ PHYSICAL EXAMINATION

Tachycardia, jugular venous distention (with prominent y descent) that increases further on inspiration (Kussmaul sign); hepatomegaly, ascites, peripheral edema are common; pulsus paradoxus in $\sim 1/3$ of pts. A sharp diastolic sound (pericardial knock) following S_2 is sometimes present.

■ LABORATORY ECG

Low limb lead voltage and atrial arrhythmias are common. Atrial fibrillation may appear.

■ CXR

Rim of pericardial calcification may be detected (most common in chronic tuberculous pericarditis).

TABLE 118-3 Noninvasive Features That Differentiate Constrictive Pericarditis from Restrictive Cardiomyopathy

	CONSTRUCTIVE PERICARDITIS	RESTRICTIVE CARDIOMYOPATHY
Physical examination		
Kussmaul sign	Present	May be present
Pericardial knock	May be present	Absent
Chest x-ray		
Pericardial calcification	May be present	Absent
Echocardiography		
Thickened pericardium	Present	Absent
Thickened myocardium	Absent	Often present
Exaggerated variation in transvalvular velocities	Present	Absent
CT or MRI		
Thickened pericardium	Present	Absent

ECHOCARDIOGRAM

Thickened pericardium, normal ventricular contraction; abrupt halt in ventricular filling after early diastole. Dilatation of IVC is typical. Dramatic effects of respiration: During inspiration the ventricular septum shifts to the left with prominent reduction of blood flow velocity across mitral valve; pattern reverses during expiration (opposite pattern across the tricuspid valve with respiration).

CT OR MRI

More precise than echocardiogram for demonstrating thickened pericardium (present in >80% of pts with constrictive pericarditis).

CARDIAC CATHETERIZATION

Equalization of diastolic pressures in all chambers; ventricular pressure tracings show “dip and plateau” appearance. Differentiate from restrictive cardiomyopathy (Table 118-3).

TREATMENT**Constrictive Pericarditis**

Surgical removal of the pericardium. Progressive improvement ensues over several months.

APPROACH TO THE PATIENT**Asymptomatic Pericardial Effusion of Unknown Cause**

If careful history and physical examination do not suggest etiology, the following may lead to diagnosis:

- Testing for tuberculosis (Chap. 97)
- Serum albumin and urine protein measurement (nephrotic syndrome)
- Serum creatinine and BUN (uremia)
- Thyroid function tests (myxedema)
- Antineutrophil antibodies (SLE and other collagen vascular diseases)
- Search for a primary tumor (especially lung and breast)

119 Hypertension



■ DEFINITION

Chronic elevation in blood pressure (bp), as defined by 2017 Hypertension Guidelines (Table 119-1). Hypertension is major contributor to cardiovascular diseases and complications; etiology is unknown in 80–95% of pts (“essential hypertension”). Always consider a secondary correctable form of hypertension, especially in pts aged ≤ 30 or those who become hypertensive after 55. Isolated systolic hypertension (systolic ≥ 140 , diastolic < 90) most common in elderly pts, due to reduced vascular compliance.

■ SECONDARY HYPERTENSION

Renal Artery Stenosis (Renovascular Hypertension)

Due to either atherosclerosis (older men) or fibromuscular dysplasia (young women). Presents with recent onset of hypertension, refractory to usual antihypertensive therapy. Abdominal bruit is present in 50% of cases; hypokalemia due to activation of the renin-angiotensin-aldosterone system may be present.

Renal Parenchymal Disease

Elevated serum creatinine and/or abnormal urinalysis, containing protein, cells, or casts.

Coarctation of Aorta

Presents in children or young adults (including 35% of pts with Turner syndrome); constriction is usually present in aorta at origin of left subclavian artery. Examination shows diminished, delayed femoral pulsations; systolic murmur loudest at left infrascapular region. CXR shows indentation of the aorta at the level of the coarctation and rib notching (due to development of collateral arterial flow). Doppler echocardiography identifies region of constriction and measures associated pressure gradient.

Pheochromocytoma

A catecholamine-secreting tumor, typically of the adrenal medulla or extraadrenal paraganglion tissue. Presents as paroxysmal or sustained hypertension in young to middle-aged pts. Sudden episodes of headache, palpitations, and profuse diaphoresis are common. Associated findings include chronic weight loss, orthostatic *hypotension*, and impaired glucose tolerance. Pheochromocytomas may be localized to the bladder wall and may present with micturition-associated symptoms of catecholamine excess. Diagnosis is suggested by elevated plasma metanephrine level or urinary catecholamine metabolites in a 24-h urine collection (see next); the tumor is then localized by CT or MRI.

TABLE 119-1 Definition of Hypertension

CATEGORY	SYSTOLIC PRESSURE (mmHg)		DIASTOLIC PRESSURE (mmHg)
Normal	< 120	and	< 80
Elevated	120–129	and	< 80
Stage 1 Hypertension	130–139	or	80–89
Stage 2 Hypertension	≥ 140	or	≥ 90

Source: Whelton PK, Carey RM, Aronow WS, et al: 2017 Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. *J Am Coll Cardiol* 71:e127–e248, 2018.

Hyperaldosteronism

Usually due to aldosterone-secreting adenoma or bilateral adrenal hyperplasia; a cause of refractory hypertension that should be suspected when hypokalemia is present in a hypertensive pt off diuretics ([Chap. 174](#)).

Other Causes

Oral contraceptive usage, obstructive sleep apnea ([Chap. 140](#)), Cushing's and adrenogenital syndromes ([Chap. 174](#)), thyroid disease ([Chap. 173](#)), hypercalcemia (e.g., hyperparathyroidism), and acromegaly ([Chap. 171](#)). In pts with systolic hypertension and wide pulse pressure, consider thyrotoxicosis, aortic regurgitation ([Chap. 116](#)), and systemic AV fistula.

APPROACH TO THE PATIENT

Hypertension

History: Most pts are asymptomatic. Severe hypertension may lead to headache, dizziness, or blurred vision.

Clues to specific forms of secondary hypertension: Use of medications (e.g., birth control pills, glucocorticoids, decongestants, erythropoietin, NSAIDs, cyclosporine); paroxysms of headache, sweating, or tachycardia (pheochromocytoma); history of renal disease or abdominal trauma (renal hypertension); daytime somnolence and snoring (sleep apnea).

Physical examination: Measure bp with appropriate-sized cuff (large cuff for large arm). Measure bp in both arms as well as a leg (to evaluate for aortic coarctation). Signs of hypertension include retinal arteriolar changes (narrowing/nicking); left ventricular lift, loud A₂, S₄. Clues to secondary forms of hypertension include cushingoid appearance, thyromegaly, abdominal bruit (renal artery stenosis), delayed femoral pulses (coarctation of aorta).

Laboratory Workup *Screening tests for secondary hypertension:* Should be carried out on all pts with documented hypertension: (1) serum creatinine, BUN, and urinalysis (renal parenchymal disease); (2) serum K⁺ measured off diuretics (hypokalemia prompts workup for hyperaldosteronism or renal artery stenosis); (3) CXR (rib notching or indentation of distal aortic arch in coarctation of the aorta); (4) ECG (LV hypertrophy suggests chronicity of hypertension); (5) other useful screening blood tests including CBC, glucose, lipid levels, calcium, uric acid; (6) thyroid-stimulating hormone if thyroid disease suspected.

Further workup: Indicated for specific diagnoses if screening tests are abnormal or bp is refractory to antihypertensive therapy: (1) *renal artery stenosis:* captopril radionuclide scan, renal duplex ultrasound, magnetic resonance angiography, renal arteriography; (2) *Cushing's syndrome:* dexamethasone suppression test ([Chap. 174](#)); (3) *pheochromocytoma:* 24-h urine collection for catecholamines, metanephrines, and vanillylmandelic acid and/or measurement of plasma metanephrine; (4) *primary hyperaldosteronism:* depressed plasma renin activity and hypersecretion of aldosterone, both of which fail to change with volume expansion; (5) *renal parenchymal disease* ([Chap. 142](#)).

TREATMENT

Hypertension

Beneficial lifestyle modifications include weight reduction (goal BMI <25 kg/m²); sodium restriction; diet rich in fruits, vegetables, and low-fat dairy products; regular exercise; and moderation of alcohol consumption.

DRUG THERAPY OF ESSENTIAL HYPERTENSION (SEE TABLE 119-2)

2017 Hypertension Guidelines recommend initiating antihypertensive drug therapy for primary prevention when systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg (note that if 10-year atherosclerotic event risk is $\geq 10\%$, or if pt has had prior cardiovascular event, initiate drug treatment for systolic BP ≥ 130 or diastolic BP ≥ 80). Goal is to control hypertension with minimal side effects. A combination of medications with complementary actions is often required. First-line agents include diuretics, ACE inhibitors, angiotensin receptor antagonists, calcium channel antagonists, and sometimes beta blockers. On-treatment blood pressure goal is $<130/80$.

Diuretics

Thiazides preferred over loop diuretics because of longer duration of action; however, the latter are more potent when serum creatinine >2.5 mg/dL. Major side effects include hypokalemia, hyperglycemia, and hyperuricemia, which can be minimized by using low dosage (e.g., hydrochlorothiazide 6.25–50 mg qd). Diuretics are particularly effective in elderly and African-American pts.

ACE Inhibitors and Angiotensin II Receptor Blockers (ARBs)

ACE inhibitors and ARBs are well tolerated with low frequency of side effects. May be used as monotherapy or in combination with a diuretic, calcium antagonist, or beta blocker. Side effects are uncommon and include angioedema ($<1\%$ of pts; more common with ACE inhibitors than ARBs), hyperkalemia, and azotemia (particularly in pts with elevated baseline serum creatinine). A nonproductive cough may develop in the course of therapy in up to 15% of pts on an ACE inhibitor, prompting substitution with an ARB (cough is not common side effect) or alternate antihypertensives. Note that renal function may deteriorate rapidly as a result of inhibition of the renin-angiotensin system in pts with bilateral renal artery stenosis.

Potassium supplements and potassium-sparing diuretics should be used cautiously with ACE inhibitors or ARBs to prevent hyperkalemia.

Calcium Antagonists

Direct arteriolar vasodilators; all have negative inotropic effects (particularly verapamil) and should be used cautiously if LV dysfunction is present. Verapamil and, to a lesser extent, diltiazem can result in bradycardia and AV block, so combination with beta blockers is generally avoided. Use sustained-release formulations, as short-acting dihydropyridine calcium channel blockers may increase incidence of coronary events. Common side effects include peripheral edema and constipation.

If bp proves refractory to drug therapy, evaluate for secondary forms of hypertension, especially renal artery stenosis and pheochromocytoma.

Beta Blockers

May be useful in young pts with “hyperkinetic” circulation. Begin with low dosage (e.g., metoprolol succinate 25–50 mg daily). Relative contraindications: bronchospasm, CHF, AV block, bradycardia, and “brittle” insulin-dependent diabetes.

Table 119-3 lists compelling indications for specific initial drug treatment.

SPECIAL CIRCUMSTANCES**Pregnancy**

Most commonly used antihypertensives include methyldopa (250–1000 mg PO bid-tid), labetalol (100–200 mg bid), and hydralazine (10–150 mg PO bid-tid). Calcium channel blockers (e.g., nifedipine, long-acting, 30–90 mg daily) also appear to be safe in pregnancy. Beta blockers should be used cautiously; fetal hypoglycemia and low birth weights have been reported. ACE inhibitors and ARBs are *contraindicated* in pregnancy.

TABLE 119-2 Oral Drugs Commonly Used in Treatment of Hypertension

DRUG CLASS	EXAMPLES	USUAL TOTAL DAILY DOSE (DOSING FREQUENCY/DAY)	POTENTIAL ADVERSE EFFECTS
Diuretics			
Thiazides	Hydrochlorothiazide	6.25–50 mg (1–2)	Hypokalemia, hyperuricemia, gout, hyperglycemia, ↑ cholesterol, ↑ triglycerides
Thiazide-like	Chlorthalidone	25–50 mg (1)	same as above
Loop diuretics	Furosemide	40–80 mg (2–3)	Hypokalemia, hyperuricemia
	Ethacrynic acid	50–100 mg (2–3)	
Aldosterone antagonists	Spironolactone	25–100 mg (1–2)	Hyperkalemia, gynecomastia
	Eplerenone	50–100 mg (1–2)	Hyperkalemia
K ⁺ -retaining	Amiloride	5–10 mg (1–2)	
	Triamterene	50–100 mg (1–2)	
Beta blockers			
β ₁ -selective	Atenolol	25–100 mg (1–2)	Bronchospasm, bradycardia, heart block, fatigue, sexual dysfunction
	Metoprolol	25–100 mg (1–2)	same as above
Nonselective	Propranolol	40–160 mg (2)	same as above
	Propranolol LA	60–180 mg (1)	same as above
Combined alpha/beta	Labetolol	200–800 mg (2)	Bronchospasm, bradycardia, heart block
	Carvedilol	12.5–50 mg (2)	

(Continued)

TABLE 119-2 Oral Drugs Commonly Used in Treatment of Hypertension (Continued)

DRUG CLASS	EXAMPLES	USUAL TOTAL DAILY DOSE (DOSING FREQUENCY/DAY)	POTENTIAL ADVERSE EFFECTS
ACE inhibitors	Captopril	25–200 mg (2)	Cough, hyperkalemia, azotemia, angioedema
	Lisinopril	10–40 mg (1)	
	Ramipril	2.5–20 mg (1–2)	
Angiotensin II receptor blockers	Losartan	25–100 mg (1–2)	Hyperkalemia, azotemia
	Valsartan	80–320 mg (1)	
	Candesartan	2–32 mg (1–2)	
Calcium channel antagonists			
Dihydropyridines	Nifedipine long-acting	30–60 mg (1)	Edema, constipation
Nondihydropyridines	Verapamil long-acting	120–360 mg (1–2)	Edema, constipation, bradycardia, heart block
	Diltiazem long-acting	180–420 mg (1)	

TABLE 119-3 Guidelines for Selecting Initial Drug Treatment of Hypertension

CLASS OF DRUG	COMPELLING INDICATIONS	POSSIBLE INDICATIONS	COMPELLING CONTRAINDICATIONS	POSSIBLE CONTRAINDICATIONS
Diuretics	Heart failure Elderly pts Systolic hypertension		Gout	
Beta blockers	Angina After MI Tachyarrhythmias	Heart failure Pregnancy	Uncontrolled asthma and COPD Heart block ^a	Athletes and physically active pts Peripheral vascular disease
ACE inhibitors	Heart failure LV dysfunction Following an MI Diabetic nephropathy	Chronic renal parenchymal disease	Pregnancy Hyperkalemia Bilateral renal artery stenosis	
Angiotensin receptor blockers	ACE inhibitor cough Heart failure Diabetic nephropathy	Chronic renal parenchymal disease	Pregnancy Bilateral renal artery stenosis Hyperkalemia	
Calcium channel blockers	Angina Elderly pts Systolic hypertension	Peripheral vascular disease	Heart block ^b	Heart failure with reduced ejection fraction ^c

^aSecond- or third-degree atrioventricular block.

^bSecond- or third-degree atrioventricular block with verapamil or diltiazem.

^cVerapamil or diltiazem.

Abbreviations: ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease.

TABLE 119-4 Usual Intravenous Doses of Antihypertensive Agents Used in Hypertensive Emergencies^a

ANTIHYPERTENSIVE AGENT	IV DOSE
Nitroprusside	Initial 0.3 (mcg/kg)/min; usual 2–4 (mcg/kg)/min; maximum 10 (mcg/kg)/min for 10 min
Nicardipine	Initial 5 mg/h; titrate by 2.5 mg/h at 5–15 min intervals; max 15 mg/h
Labetalol	2 mg/min up to 300 mg or 20 mg over 2 min, then 40–80 mg at 10-min intervals up to 300 mg total
Enalaprilat	Usual 0.625–1.25 mg over 5 min every 6–8 h; maximum 5 mg/dose
Esmolol	Initial 80–500 mcg/kg over 1 min, then 50–300 (mcg/kg)/min
Phentolamine	5–15 mg bolus
Nitroglycerin	Initial 5 mcg/min, then titrate by 5 mcg/min at 3–5 min intervals; if no response is seen at 20 mcg/min, incremental increases of 10–20 mcg/min may be used
Hydralazine	10–50 mg at 30-min intervals

^aConstant blood pressure monitoring is required. Start with the lowest dose. Subsequent doses and intervals of administration should be adjusted according to the blood pressure response and duration of action of the specific agent.

Renal Disease

Standard thiazide diuretics may not be effective. Consider metolazone, furosemide, or bumetanide, alone or in combination.

Diabetes

Consider ACE inhibitors and angiotensin receptor blockers as first-line therapy to control bp and slow renal function deterioration.

Malignant Hypertension

Defined as an abrupt increase in bp in pt with chronic hypertension or sudden onset of severe hypertension; a medical emergency. Immediate therapy is mandatory if there is evidence of cardiac decompensation (CHF, angina), encephalopathy (headache, seizures, visual disturbances), or deteriorating renal function. Inquire about use of cocaine, amphetamines, or monoamine oxidase inhibitors. Drugs to treat hypertensive crisis are listed in [Table 119-4](#). In absence of hypertensive encephalopathy, goal is to lower mean arterial pressure gradually over several hours to prevent precipitous reduction in cerebral, coronary, and renal blood flow. Replace with PO antihypertensive as pt becomes asymptomatic and bp improves.

120 Metabolic Syndrome



The *metabolic syndrome* (*insulin resistance syndrome*, *syndrome X*) is an important risk factor for cardiovascular disease and type 2 diabetes; it consists of a constellation of metabolic abnormalities that includes central obesity, insulin resistance, hypertension, dyslipidemia, high triglycerides, and low HDL. The prevalence of

metabolic syndrome varies among ethnic groups; it increases with age, degree of obesity, and propensity to type 2 diabetes.

■ ETIOLOGY

Overweight/obesity (especially central adiposity), sedentary lifestyle, increasing age, and lipodystrophy are all risk factors for the metabolic syndrome. The exact cause is not known and may be multifactorial. Insulin resistance is central to the development of the metabolic syndrome. Increased intracellular fatty acid metabolites contribute to insulin resistance by impairing insulin-signaling pathways and accumulating as triglycerides in skeletal and cardiac muscle, while stimulating hepatic glucose and triglyceride production. Excess adipose tissue leads to increased production of proinflammatory cytokines.

■ CLINICAL FEATURES

There are no specific symptoms of the metabolic syndrome. The major features include central obesity, hypertriglyceridemia, low HDL cholesterol, hyperglycemia, and hypertension (Table 120-1). Associated conditions include

TABLE 120-1 NCEP:ATPIII^a 2001 and Harmonizing Definition Criteria for the Metabolic Syndrome

NCEP:ATPIII 2001	HARMONIZING DEFINITION ^b														
<p>Three or more of the following:</p> <ul style="list-style-type: none"> • Central obesity: waist circumference >102 cm (M), >88 cm (F) • Hypertriglyceridemia: triglyceride level ≥ 150 mg/dL or specific medication • Low HDL^c cholesterol: <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication • Hypertension: blood pressure ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic or specific medication • Fasting plasma glucose level ≥ 100 mg/dL or specific medication or previously diagnosed type 2 diabetes 	<p>Three of the following:</p> <p>Waist circumference (cm)</p> <table border="1" data-bbox="539 820 957 1094"> <thead> <tr> <th data-bbox="539 820 625 851">Men</th> <th data-bbox="625 820 739 851">Women</th> <th data-bbox="739 820 957 851">Ethnicity</th> </tr> </thead> <tbody> <tr> <td data-bbox="539 851 625 956">≥ 94</td> <td data-bbox="625 851 739 956">≥ 80</td> <td data-bbox="739 851 957 956">Europid, sub-Saharan African, Eastern and Middle Eastern</td> </tr> <tr> <td data-bbox="539 956 625 1062">≥ 90</td> <td data-bbox="625 956 739 1062">≥ 80</td> <td data-bbox="739 956 957 1062">South Asian, Chinese, and ethnic South and Central American</td> </tr> <tr> <td data-bbox="539 1062 625 1094">≥ 85</td> <td data-bbox="625 1062 739 1094">≥ 90</td> <td data-bbox="739 1062 957 1094">Japanese</td> </tr> </tbody> </table> <ul style="list-style-type: none"> • Fasting triglyceride level >150 mg/dL or specific medication • HDL cholesterol level <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication • Blood pressure >130 mm systolic or >85 mm diastolic or previous diagnosis or specific medication • Fasting plasma glucose level ≥ 100 mg/dL (alternative indication: drug treatment of elevated glucose levels) 			Men	Women	Ethnicity	≥ 94	≥ 80	Europid, sub-Saharan African, Eastern and Middle Eastern	≥ 90	≥ 80	South Asian, Chinese, and ethnic South and Central American	≥ 85	≥ 90	Japanese
Men	Women	Ethnicity													
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≥ 85	≥ 90	Japanese													

^aNational Cholesterol Education Program and Adult Treatment Panel III.

^bIn this analysis, the following thresholds for waist circumference were used: white men, ≥ 94 cm; African-American men, ≥ 94 cm; Mexican-American men, ≥ 90 cm; white women, ≥ 80 cm; African-American women, ≥ 80 cm; Mexican-American women, ≥ 80 cm. For participants whose designation was "other race—including multiracial," thresholds that were once based on Europid cutoffs (≥ 94 cm for men and ≥ 80 cm for women) and on South Asian cutoffs (≥ 90 cm for men and ≥ 80 cm for women) were used. For participants who were considered "other Hispanic," the International Diabetes Federation thresholds for ethnic South and Central Americans were used.

^cHigh-density lipoprotein.

cardiovascular disease, type 2 diabetes, nonalcoholic fatty liver disease, hyperuricemia/gout, polycystic ovary syndrome, and obstructive sleep apnea.

■ DIAGNOSIS

The diagnosis of the metabolic syndrome relies on satisfying the criteria listed in Table 120-1. Screening for associated conditions should be undertaken.

TREATMENT

Metabolic Syndrome

Obesity is the driving force behind the metabolic syndrome. Thus, weight reduction is the primary approach to this disorder. In general, recommendations for weight loss include a combination of caloric restriction, increased physical activity, and behavior modification. Weight loss drugs or bariatric surgery are adjuncts that may be considered for obesity management ([Chap. 175](#)). Hypertension ([Chap. 119](#)), impaired fasting glucose or diabetes ([Chap. 170](#)), and lipid abnormalities ([Chap. 181](#)) should be managed according to current guidelines. The antihypertensive regimen should include an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker when possible.

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ST-Segment Elevation Myocardial Infarction



Early recognition and immediate treatment of acute ST-segment elevation myocardial infarction (STEMI) are essential; diagnosis is based on characteristic history, ECG, and serum cardiac biomarkers.

■ SYMPTOMS

Chest pain similar to angina ([Chap. 33](#)) but more intense and persistent; not fully relieved by rest or nitroglycerin, often accompanied by nausea, sweating, apprehension. However, 20–25% of MIs are clinically silent.

■ PHYSICAL EXAMINATION

Pallor, diaphoresis, tachycardia, S_4 , dyskinetic cardiac impulse may be present. If heart failure exists, pulmonary crackles and S_3 may be present. Jugular venous distention is common in right ventricular infarction.

■ ECG

ST elevation in at least two contiguous leads (≥ 2 mm in men, or ≥ 1.5 mm in women, in leads V2–V3, or ≥ 1 mm in other leads), followed (if acute reperfusion is not achieved) by T-wave inversion then Q-wave development over several hours.

■ CARDIAC BIOMARKERS

Cardiac-specific troponins T and I are highly specific for myocardial injury and are the preferred biochemical markers for diagnosis of acute MI. Serum levels remain elevated for 7–10 days. Creatine kinase (CK), another biomarker (which is not necessary to measure if cardiac troponin is assessed) rises within 4–8 h, peaks at 24 h, and returns to normal by 48–72 h. CK-MB isoenzyme is more specific for MI than total CK (which may be elevated in skeletal muscle injury). The decision

to proceed with reperfusion therapies in acute STEMI should be made urgently from the pt's history and ECG, and not await the results of biomarker assays.

■ NONINVASIVE IMAGING TECHNIQUES

May be useful when diagnosis of MI is not clear. *Echocardiography* detects infarct-associated regional wall motion abnormalities (but cannot distinguish acute MI from a previous myocardial scar). Echo is also useful in detecting RV infarction, LV aneurysm, and LV thrombus. *MRI with delayed gadolinium enhancement* accurately indicates regions of infarction, but is technically difficult to perform in acutely ill pts.

TREATMENT

STEMI

INITIAL THERAPY

Initial goals are to (1) quickly identify if pt is candidate for reperfusion therapy, (2) relieve pain, and (3) prevent/treat arrhythmias and mechanical complications.

- Aspirin should be administered immediately (162–325 mg chewed at presentation, then 75–162 mg PO qd), unless pt is aspirin-intolerant.
- Perform targeted history, examination, and ECG to identify STEMI (>1 mm ST elevation in two contiguous limb leads, ≥2 mm ST elevation in two contiguous precordial leads, or new LBBB) and appropriateness of reperfusion therapy (percutaneous coronary intervention [PCI] or IV fibrinolytic agent), which reduces infarct size, LV dysfunction, and mortality.
- Primary PCI is more effective than fibrinolysis and is preferred at experienced centers capable of performing the procedure rapidly (Fig. 121-1), especially when diagnosis is in doubt, cardiogenic shock is present, bleeding risk is increased, or symptoms have been present for >3 h.
- Proceed with IV fibrinolysis if PCI is not available, or if logistics would delay the time between first medical contact and PCI >120 min (Fig. 121-1). Door-to-needle time for fibrinolysis should be <30 min for maximum benefit. Ensure absence of contraindications (Fig. 121-2) before administering fibrinolytic agent. Those treated within 1–3 h benefit most; can still be useful up to 12 h if chest pain is persistent or ST remains elevated in leads that have not developed new Q waves. Complications include bleeding, reperfusion arrhythmias, and, in case of streptokinase (SK), allergic reactions. Enoxaparin or heparin (60 U/kg [maximum 4000 U], then 12 [U/kg]/h [maximum 1000 U/h]) should be initiated with fibrinolytic agents (Fig. 121-2); maintain activated partial thromboplastin time (aPTT) at 1.5–2.0 × control (~50–70 s).
- If chest pain or ST elevation persists >90 min after fibrinolysis, consider referral for rescue PCI. Coronary angiography after fibrinolysis should also be considered for pts with recurrent angina or high-risk features (Fig. 121-2) including extensive ST elevation, signs of heart failure (rales, S₃, jugular venous distension, left ventricular ejection fraction [LVEF] ≤35%), or systolic bp <100 mmHg.

The initial management of NSTEMI (non-Q MI) is different (Chap. 122). In particular, fibrinolytic therapy should not be administered.

ADDITIONAL STANDARD TREATMENT

(Whether or not reperfusion therapy is undertaken):

- Hospitalize in CCU, or for lower risk pts, in an intermediate care unit with continuous ECG monitoring.

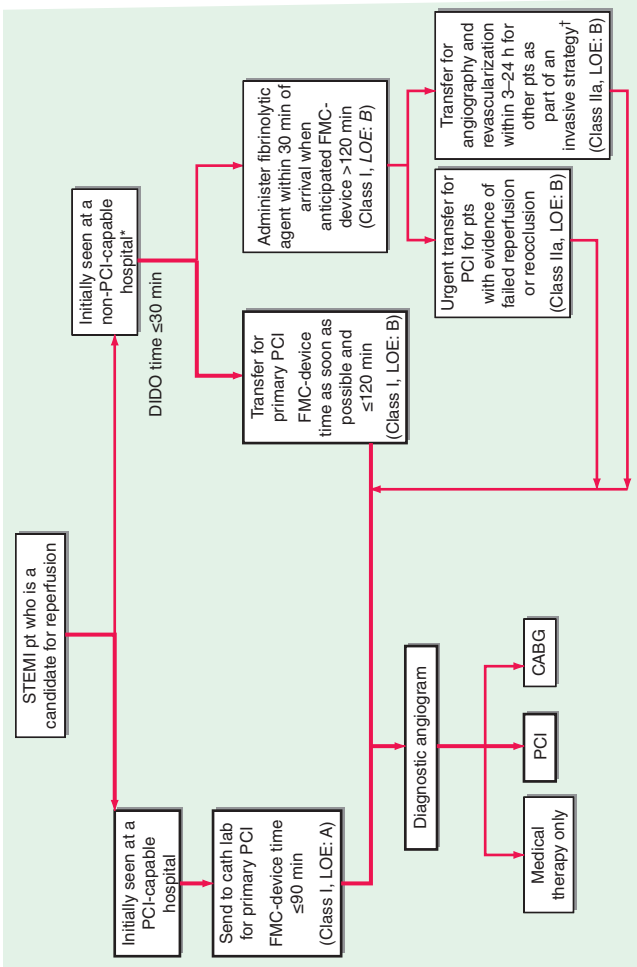


FIGURE 121-1 Reperfusion strategies in STEMI. DIDO, door-in-door-out; FMC, first medical contact; LOC, level of evidence. (From O’Gara P et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *Circulation* 127:e362, 2013.)

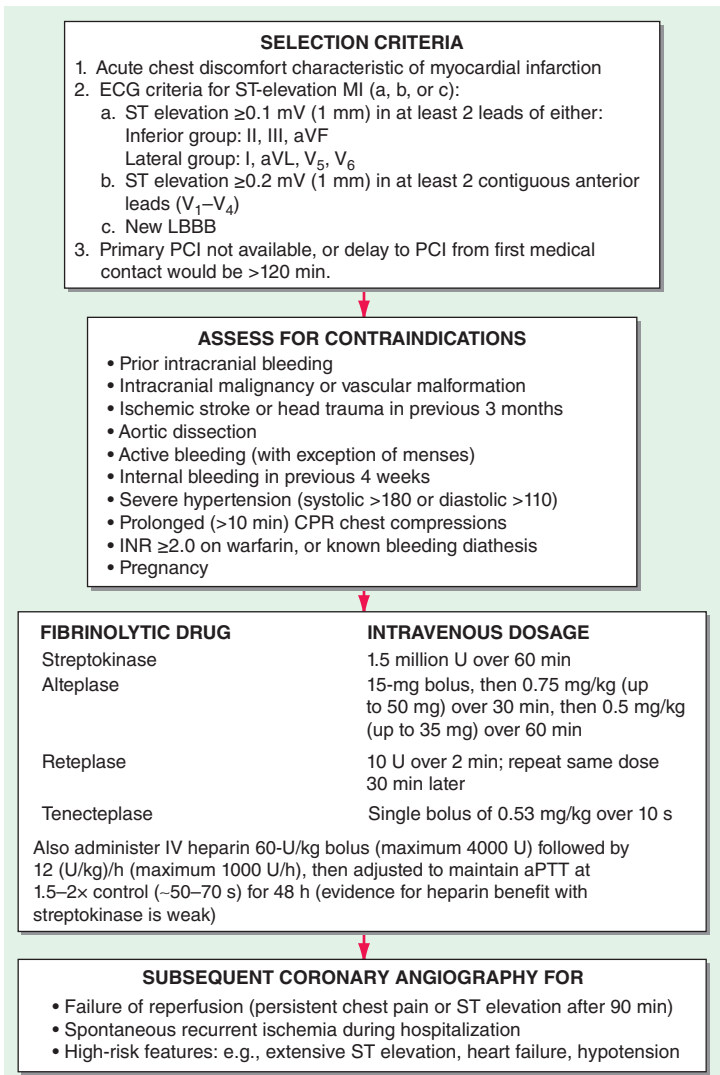


FIGURE 121-2 Algorithm for fibrinolytic therapy of acute STEMI.

- *IV line* for emergency arrhythmia treatment.
- *Pain control:* (1) Morphine sulfate 2–4 mg IV q5–10 min until pain is relieved or side effects develop (nausea, vomiting, respiratory depression [treat with naloxone 0.4–1.2 mg IV], hypotension [if bradycardic, treat with atropine 0.5 mg IV; otherwise use careful volume infusion]); (2) nitroglycerin 0.3 mg SL if systolic bp >100 mmHg; for refractory pain: IV nitroglycerin (begin at 10 μ g/min, titrate upward to maximum of 200 μ g/min, monitoring bp closely); do not administer nitrates within 24 h of sildenafil or vardenafil, or within 48 h

of tadalafil (phosphodiesterase type 5 inhibitors used for erectile dysfunction); (3) β -adrenergic antagonists (see below).

- *Oxygen*: 2–4 L/min by nasal cannula (if needed, to maintain O_2 saturation >90%).
- *Mild sedation* (e.g., diazepam 5 mg, oxazepam 15–30 mg, or lorazepam 0.5–2 mg PO three to four times daily).
- *Soft diet* and stool softeners (e.g., docusate sodium 100–200 mg/d).
- *β -Adrenergic blockers* (**Chap. 119**) reduce myocardial O_2 consumption, limit infarct size, and reduce mortality. Especially useful in pts with hypertension, tachycardia, or persistent ischemic pain; contraindications include active CHF, systolic bp <95 mmHg, heart rate <50 beats/min, AV block, or history of bronchospasm. Consider IV (e.g., metoprolol 5 mg q2–5min to total dose of 15 mg) if pt is hypertensive. Otherwise, begin PO regimen (e.g., metoprolol tartrate 25–50 mg four times daily).
- *Anticoagulants*: Most pts with STEMI should receive an anticoagulant (typically unfractionated heparin [UFH] or bivalirudin for those undergoing PCI [discontinued at end of procedure or shortly thereafter]; enoxaparin [for up to 8 days, or until discharge, whichever is earlier] or UFH [for ≥ 2 days] for those receiving fibrinolysis or no reperfusion therapy). Continued full-dose IV heparin (PTT 1.5–2 \times control) or LMWH (e.g., enoxaparin 1 mg/kg SC q12h) followed by warfarin is recommended for pts with high risk of thromboembolism (severe LV dysfunction, presence of ventricular thrombus, large dyskintetic region in acute anterior MI, or pulmonary embolism). If used, warfarin is continued for 3–6 months.
- *Antiplatelet agents*: Continue aspirin 162–325 mg daily and an oral P2Y₁₂ platelet receptor antagonist after STEMI (e.g., ticagrelor, clopidogrel, or prasugrel [the latter only if PCI is undertaken]).
- *ACE inhibitors* reduce mortality in pts following acute MI and should be prescribed within 24 h of hospitalization for pts with STEMI—e.g., captopril (6.25 mg PO test dose advanced to 50 mg PO tid). ACE inhibitors should be continued indefinitely after discharge in pts with heart failure or those with asymptomatic LV dysfunction (ejection fraction $\leq 40\%$); if pt is ACE inhibitor intolerant, use ARB (e.g., valsartan or candesartan).
- *Aldosterone antagonists* (spironolactone or eplerenone 25–50 mg daily) further reduce mortality in pts with LVEF $\leq 40\%$ and either symptomatic heart failure or diabetes; do not use in pts with advanced renal insufficiency (e.g., creatinine ≥ 2.5 mg/dL) or hyperkalemia.
- *Serum magnesium* level should be measured and repleted if necessary to reduce risk of arrhythmias.

■ COMPLICATIONS

(For arrhythmias, see also **Chaps. 124** and **125**.)

Ventricular Arrhythmias

Isolated ventricular premature beats (VPBs) occur frequently. Precipitating factors should be corrected (hypoxemia, acidosis, hypokalemia, hypomagnesemia, CHF, arrhythmogenic drugs). Routine beta blocker administration (see above) diminishes ventricular ectopy. Other in-hospital antiarrhythmic therapy should be reserved for pts with sustained ventricular arrhythmias.

Ventricular Tachycardia

If hemodynamically unstable, perform immediate electrical countershock (unsynchronized discharge of 200–300 J or 50% less if using biphasic device).

If hemodynamically tolerated, use IV amiodarone (bolus of 150 mg over 10 min, then infusion of 1.0 mg/min for 6 h, then 0.5 mg/min).

Ventricular Fibrillation (VF)

VF requires immediate defibrillation (200–400 J). If unsuccessful, initiate cardiopulmonary resuscitation (CPR) and standard resuscitative measures (Chap. 11). Ventricular arrhythmias that appear several days or weeks following MI often reflect pump failure and may warrant invasive electrophysiologic study and implantation of a cardioverter defibrillator (ICD).

Accelerated Idioventricular Rhythm

Wide QRS complex, regular rhythm, rate 60–100 beats/min, is common and usually benign; if it causes hypotension, treat with atropine 0.6 mg IV.

Supraventricular Arrhythmias

Sinus tachycardia may result from heart failure, hypoxemia, pain, fever, pericarditis, hypovolemia, administered drugs. If no cause is identified, suppressive beta blocker therapy may be beneficial to reduce myocardial oxygen demand. Other *supraventricular arrhythmias* (paroxysmal supraventricular tachycardia, atrial flutter, and fibrillation) are often secondary to heart failure. If hemodynamically unstable, proceed with electrical cardioversion. In absence of acute heart failure, suppressive alternatives include beta blockers, verapamil, or diltiazem (Chap. 125).

Bradycardias and AV Block

(See Chap. 124.) In *inferior MI*, usually represent heightened vagal tone or discrete AV nodal ischemia. If hemodynamically compromised (CHF, hypotension, emergence of ventricular arrhythmias), treat with atropine 0.5 mg IV q5min (up to 2 mg). If no response, use temporary external or transvenous pacemaker. Isoproterenol should be avoided. In *anterior MI*, AV conduction defects usually reflect extensive tissue necrosis. Consider temporary external or transvenous pacemaker for (1) complete heart block, (2) Mobitz type II block (Chap. 124), (3) new bifascicular block (LBBB, RBBB + left anterior hemiblock, RBBB + left posterior hemiblock), (4) any bradycardia associated with hypotension or CHF.

Heart Failure

CHF may result from systolic “pump” dysfunction, increased LV diastolic “stiffness,” and/or acute mechanical complications.

SYMPTOMS Dyspnea, orthopnea, tachycardia.

EXAMINATION Jugular venous distention, S₃ and S₄ gallop, pulmonary rales; systolic murmur if acute mitral regurgitation or ventricular septal defect (VSD) has developed.

TREATMENT

Heart Failure (See Chap. 126)

Initial therapy includes diuretics (begin with furosemide 10–20 mg IV), inhaled O₂, and vasodilators, particularly nitrates (PO, topical, or IV [Chap. 126] unless pt is hypotensive [systolic bp <100 mmHg]); digitalis is usually of little benefit in acute MI. Diuretic, vasodilator, and inotropic therapy (Table 121-1) may be guided by invasive hemodynamic monitoring (Swan-Ganz pulmonary artery catheter, arterial line), particularly in pts with accompanying hypotension (Table 121-2; Fig. 121-3). In acute MI, an acceptable pulmonary capillary wedge (PCW) pressure is 15–20 mmHg; in the absence of hypotension, PCW >20 mmHg is treated with diuretic plus vasodilator therapy (IV nitroglycerin [begin at 10 µg/min] or

TABLE 121-1 IV VASODILATORS AND INOTROPIC DRUGS USED IN ACUTE MI

DRUG	USUAL DOSAGE RANGE	COMMENT
Nitroglycerin	5–100 µg/min	May improve coronary blood flow to ischemic myocardium
Nitroprusside	0.5–10 (µg/kg)/min	More potent vasodilator, but improves coronary blood flow less than nitroglycerin With therapy >24 h or in renal failure, watch for thiocyanate toxicity (blurred vision, tinnitus, delirium)
Dobutamine	2–20 (µg/kg)/min	Results in ↑ cardiac output, ↓ PCW, but does not raise bp
Dopamine	2–20 (µg/kg)/min	More appropriate than dobutamine if hypotensive Hemodynamic effect depends on dose: (µg/kg)/min <5: ↑ renal blood flow 2.5–10: positive inotrope >10: vasoconstriction
Norepinephrine	0.5–30 µg/min	Less likely than dopamine to cause arrhythmias in cardiogenic shock

nitroprusside [begin at 0.5 µg/kg per min]) and titrated to optimize bp, PCW, and systemic vascular resistance (SVR).

$$\text{SVR} = \frac{(\text{mean arterial pressure} - \text{mean RA pressure}) \times 80}{\text{cardiac output}}$$

Normal SVR = 900 – 1350 dyne • s/cm⁵. If PCW >20 mmHg and pt is hypotensive (Table 121-2 and Fig. 121-3), evaluate for VSD or acute mitral regurgitation, consider dobutamine (begin at 1–2 [µg/kg]/min), titrate upward to maximum of 10 (µg/kg)/min; beware of drug-induced tachycardia or ventricular ectopy.

After stabilization on parenteral vasodilator therapy, oral therapy follows with an ACE inhibitor or an ARB (Chap. 126). Consider addition of long-term aldosterone antagonist (spironolactone 25–50 mg daily or eplerenone 25–50 mg daily) to ACE inhibitor if LVEF ≤40% or symptomatic heart failure or diabetes are present—do not use if renal insufficiency or hyperkalemia are present.

Cardiogenic Shock

(See Chap. 12.) Severe LV failure with hypotension (bp <90 mmHg), elevated PCW (>20 mmHg), cardiac index <2.2 L/min/m², accompanied by oliguria, peripheral vasoconstriction, dulled sensorium, and metabolic acidosis.

TREATMENT

Cardiogenic Shock (Fig. 121-3)

Swan-Ganz catheter and intraarterial bp monitoring are not always essential but may be helpful; aim for mean PCW of 18–20 mmHg with adjustment of volume (diuretics or infusion) as needed. Vasopressors (e.g., norepinephrine or dopamine [Table 121-1]) and/or intraaortic balloon counterpulsation may be necessary to

TABLE 121-2 HEMODYNAMIC COMPLICATIONS IN ACUTE MI

CONDITION	CARDIAC INDEX, (L/min)/m ²	PCW, mmHg	SYSTOLIC BP, mmHg	TREATMENT
Uncomplicated Hypovolemia	>2.5 <2.5	≤18 <15	>100 <100	— Successive boluses of normal saline In setting of inferior wall MI, consider RV infarction (esp. if RA pressure >10)
Volume overload	>2.5	>20	>100	Diuretic (e.g., furosemide 10–20 mg IV) Nitroglycerin, topical paste or IV (Table 121-1)
LV failure	<2.5	>20	>100	Diuretic (e.g., furosemide 10–20 mg IV) IV nitroglycerin (or if hypertensive, use IV nitroprusside)
Severe LV failure	<2.5	>20	<100	If bp ≥90: IV dobutamine ± IV nitroglycerin or sodium nitroprusside If bp <90: IV dopamine If accompanied by pulmonary edema: attempt diuresis with IV furosemide; may be limited by hypotension If new systolic murmur present, consider acute VSD or mitral regurgitation
Cardiogenic shock	<2.2	>20	<90 with oliguria and confusion	IV norepinephrine or dopamine Mechanical circulatory support Reperfusion by PCI or CABG may be life-saving

Abbreviations: CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; PCW, pulmonary capillary wedge pressure; RA, right atrium; VSD, ventricular septal defect.

maintain systolic bp >90 mmHg and reduce PCW. Administer high concentration of O₂ by mask; if pulmonary edema coexists, consider bilateral positive airway pressure (BiPAP) or intubation and mechanical ventilation. Acute mechanical complications (see below) should be sought and promptly treated.

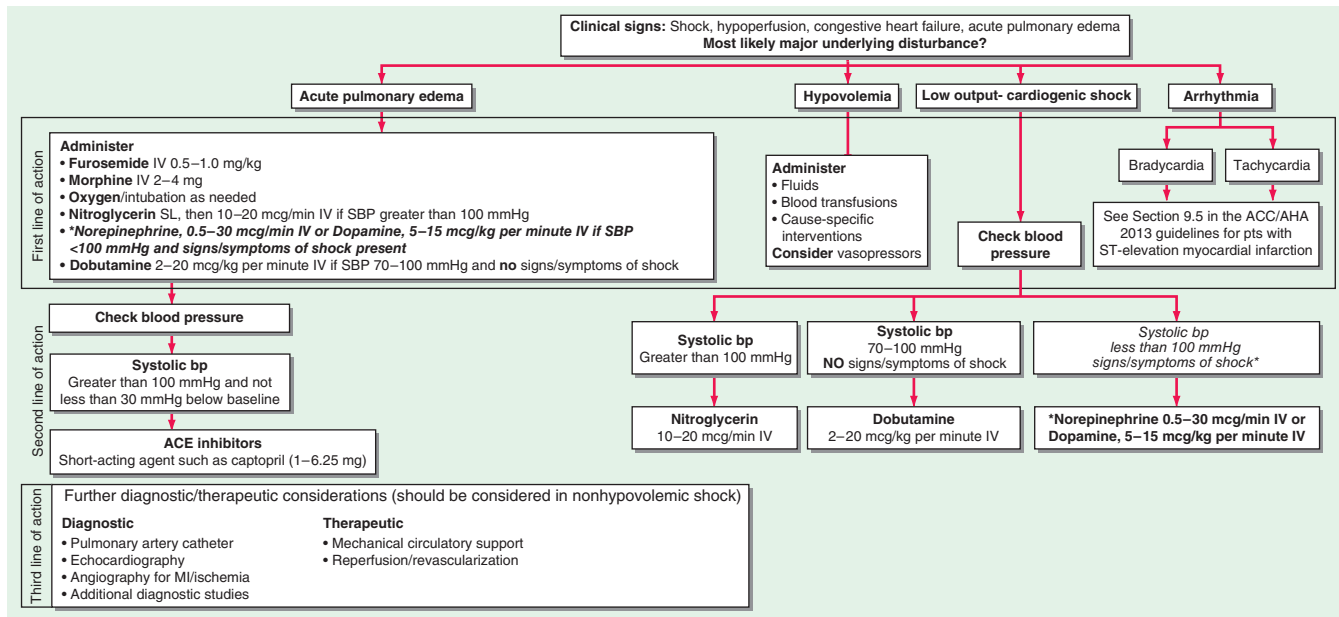


FIGURE 121-3 Emergency management of cardiogenic shock and pulmonary edema. (Modified from Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 7: The era of reperfusion: Section 1: Acute coronary syndromes [acute myocardial infarction]. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. *Circulation* 102:1172, 2000.)

If cardiogenic shock develops within 36 h of acute STEMI, reperfusion by PCI or coronary artery bypass grafting (CABG) may markedly improve LV function.

Hypotension

May also result from *right ventricular MI*, which should be suspected in inferior or posterior MI, if jugular venous distention and elevation of right-heart pressures predominate (rales are typically absent and PCW may be normal); right-sided ECG leads typically show ST elevation, and echocardiography may confirm diagnosis. *Treatment* consists of volume infusion. Noncardiac causes of hypotension should be considered: hypovolemia, acute arrhythmia, or sepsis.

Acute Mechanical Complications

Ventricular septal rupture and acute mitral regurgitation due to papillary muscle ischemia/infarct develop during the first week following MI and are characterized by sudden onset of CHF and new systolic murmur. Echocardiography and Doppler interrogation can confirm presence of these complications. PCW tracings may show large *v* waves in either condition, but an oxygen “step-up” as the catheter is advanced from right atrium to right ventricle suggests septal rupture.

Acute medical therapy of these conditions includes vasodilator therapy (IV nitroprusside: begin at 10 $\mu\text{g}/\text{min}$ and titrate to maintain systolic bp ~ 100 mmHg); intraaortic balloon pump may be required to maintain cardiac output. Mechanical correction is the definitive therapy. Acute ventricular free-wall rupture presents with sudden loss of bp, pulse, and consciousness, while ECG shows an intact rhythm (pulseless electrical activity); emergent surgical repair is crucial, and mortality is high.

Pericarditis

Characterized by *pleuritic, positional* pain, and pericardial rub (**Chap. 118**); atrial arrhythmias are common; must be distinguished from recurrent angina. Often responds to aspirin, 650 mg PO qid. Anticoagulants should be avoided when pericarditis is suspected to avoid development of pericardial bleeding/tamponade.

Ventricular Aneurysm

Localized “bulge” of LV chamber due to infarcted myocardium. *True aneurysms* consist of scar tissue and do not rupture. However, complications include CHF, ventricular arrhythmias, and thrombus formation. Typically an aneurysm is confirmed by echocardiography or by left ventriculography. The presence of thrombus within the aneurysm, or a large aneurysmal segment due to anterior MI, warrants consideration of oral anticoagulation with warfarin for 3–6 months.

Pseudoaneurysm is a form of cardiac rupture contained by a local area of pericardium and organized thrombus; direct communication with the LV cavity is present; surgical repair usually necessary to prevent rupture.

Recurrent Angina

Usually associated with transient ST-T wave changes; signals high incidence of reinfarction; when it occurs in early post-MI period, coronary arteriography and revascularization should follow.

■ SECONDARY PREVENTION

For pts who have not already undergone coronary angiography and PCI, submaximal exercise testing should be performed prior to or soon after discharge. A positive test in certain subgroups (angina at a low workload, a large region of provokable ischemia, or provokable ischemia with a reduced LVEF) suggests need for cardiac catheterization to evaluate myocardium at risk of recurrent infarction. *Beta blockers* (e.g., metoprolol, 25–200 mg daily) should be prescribed

routinely for at least 2 years following acute MI, unless contraindications present (asthma, active heart failure, bradycardia). Continue oral antiplatelet agents (e.g., aspirin 81–325 mg daily and a P2Y₁₂ platelet receptor antagonist) to reduce incidence of reinfarction. If LVEF $\leq 40\%$, an ACE inhibitor or ARB (if ACE inhibitor is not tolerated) should be used indefinitely. Consider addition of aldosterone antagonist (see “Heart Failure,” above).

Modification of cardiac risk factors must be encouraged: discontinue smoking; control hypertension, diabetes, and serum lipids (typically atorvastatin 80 mg daily in immediate post-MI period—see [Chap. 181](#)); and pursue graduated exercise.

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Unstable Angina and Non-ST-Elevation Myocardial Infarction



Unstable angina (UA) and non-ST-elevation MI (NSTEMI) are acute coronary syndromes with similar mechanisms, clinical presentations, and treatment strategies.

■ CLINICAL PRESENTATION

UA includes (1) new onset of severe angina, (2) angina at rest or with minimal activity, and (3) recent increase in frequency and intensity of chronic angina. NSTEMI is diagnosed when symptoms of UA are accompanied by evidence of myocardial necrosis (e.g., elevated cardiac biomarkers). Pts with NSTEMI may present with symptoms identical to STEMI—the two are differentiated by ECG findings.

■ PHYSICAL EXAMINATION

May be normal or include diaphoresis, pale cool skin, tachycardia, S₄, basilar rales; if large region of ischemia, may demonstrate S₃, hypotension.

■ ELECTROCARDIOGRAM

May include ST depression and/or T-wave inversion; unlike STEMI, there is no Q-wave development.

■ CARDIAC BIOMARKERS

Cardiac-specific troponins (specific and sensitive markers of myocardial necrosis) and CK-MB (less sensitive marker) are elevated in NSTEMI. Small troponin elevations may also occur in pts with heart failure, myocarditis, pulmonary embolism, and other conditions in [Table 122-1](#).

TREATMENT

Unstable Angina and Non-ST-Elevation Myocardial Infarction

First step is appropriate triage based on likelihood of coronary artery disease (CAD) and acute coronary syndrome ([Fig. 122-1](#)) as well as identification of higher-risk pts. Pts with low likelihood of active ischemia are initially monitored by serial ECGs and serum cardiac biomarkers, and for recurrent chest discomfort; if these are negative, stress testing (or CT angiography if probability of CAD is low) can be used for further therapeutic planning.

Therapy of UA/NSTEMI is directed (1) against the inciting intracoronary thrombus, and (2) toward restoration of balance between myocardial oxygen

TABLE 122-1 Causes of Elevated Cardiac Troponin Reflecting Direct Myocardial Damage Other Than Spontaneous Myocardial Infarction (Type 1)

CARDIAC	NON-CARDIAC OR SYSTEMIC
Tachyarrhythmias	Pulmonary embolism/pulmonary hypertension
Congestive heart failure	Trauma (e.g., electrical shock, burns, blunt chest wall)
Hypertensive emergencies	Hypo or hyperthyroidism
Infection/inflammation (e.g., myocarditis, pericarditis)	Toxicity (e.g., anthracyclines, snake venom)
Stress cardiomyopathy (Tako-Tsubo cardiomyopathy)	Renal failure
Structural heart disease (e.g., aortic stenosis)	Sepsis, shock
Aortic dissection	Stroke or other acute neurologic event
Coronary spasm	Extreme endurance efforts (e.g., ultra-marathon)
Cardiac procedures (endomyocardial biopsy, ablation, CABG, PCI)	Rhabdomyolysis
Infiltrative diseases (e.g., amyloidosis, hemochromatosis, malignancy)	

Source: Data from Newby LK et al: *J Am Coll Cardiol* 60:2427, 2012; Roffi M: *Eur Heart J* 37:267, 2016.

supply and demand. Pts with the highest-risk scores benefit the most from aggressive interventions.

ANTITHROMBOTIC THERAPIES

- Aspirin (325 mg initially, then 75–100 mg/d).
- Platelet P2Y₁₂ receptor antagonist (unless excessive risk of bleeding or immediate coronary artery bypass grafting [CABG] likely): Clopidogrel (300–600 mg PO load, then 75 mg/d), ticagrelor (180 mg PO, then 90 mg PO bid [chronic aspirin dose should not exceed 100 mg daily]), prasugrel (60 mg PO, then 10 mg daily—use prasugrel only if PCI is planned), or intravenous cangrelor (30 µg/kg bolus, then 4 µg/kg/min via a dedicated IV line).
- Anticoagulant: Unfractionated heparin (UFH) [70–100 U/kg (maximum 5000 U) then 12 (U/kg)/h (maximum 1000 U/h)] to achieve aPTT 1.5–2.5 × control, *or* low-molecular-weight heparin (e.g., enoxaparin 1 mg/kg SC q12h), which is superior to UFH for reduction of future cardiac events. Alternatives include (1) the factor Xa inhibitor fondaparinux (2.5 mg SC daily), which is associated with lower bleeding risk, or (2) the direct thrombin inhibitor bivalirudin (0.75-mg/kg bolus, then 1.75 [mg/kg]/h), which causes less bleeding in pts undergoing catheterization compared with UFH plus a GP IIb/IIIa inhibitor.
- For high-risk unstable pts who undergo PCI, consider an IV GP IIb/IIIa antagonist (e.g., tirofiban, 25 [µg/kg]/min load, then 0.15 [µg/kg]/min; or eptifibatid, 180-µg/kg bolus, then 2.0 [µg/kg]/min).

ANTI-ISCHEMIC THERAPIES

- Nitroglycerin 0.3–0.6 mg sublingually or by buccal spray. If chest discomfort persists after three doses given 5 min apart, consider IV nitroglycerin (5–10 µg/min, then increase by 10 µg/min every 3–5 min until symptoms relieved or systolic bp <100 mmHg). Do not use nitrates in pts with recent use

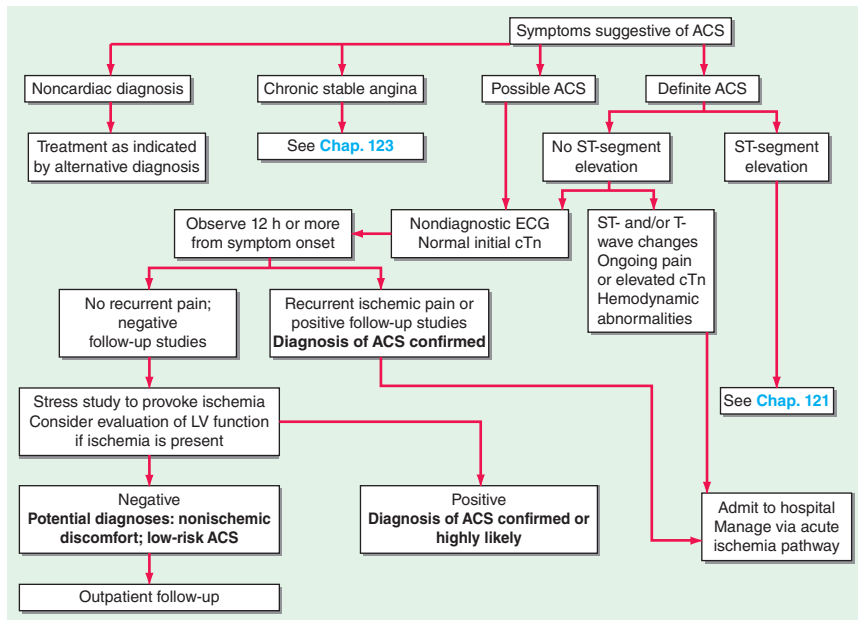


FIGURE 122-1 Algorithm for evaluation and treatment of pts with a suspected acute coronary syndrome. ACS, acute coronary syndrome; cTn, cardiac troponin. (Adapted from Anderson JL et al: 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 61:e179, 2013.)

of phosphodiesterase-5 inhibitors for erectile dysfunction (e.g., not within 24 h of sildenafil or vardenafil, or within 48 h of tadalafil).

- Beta blockers (e.g., metoprolol 25–50 mg PO q6h) targeted to a heart rate of 50–60 beats/min. In pts with contraindications to beta blockers (e.g., bronchospasm), consider long-acting verapamil or diltiazem (**Table 119-2**) if LV contractile function is not impaired.

ADDITIONAL RECOMMENDATIONS

- Admit to unit with continuous ECG monitoring, initially with bed rest.
- Consider morphine sulfate 2–5 mg IV q5–30min for refractory chest discomfort.
- Add HMG-CoA reductase inhibitor (initially at high dose, e.g., atorvastatin 80 mg daily) and consider ACE inhibitor (**Chap. 121**).

INVASIVE VS CONSERVATIVE STRATEGY

In highest-risk pts an early invasive strategy (coronary arteriography within ~48 h followed by percutaneous intervention or CABG) improves outcomes (**Table 122-2**). In lower-risk pts, angiography can be deferred but should be

TABLE 122-2 Factors Associated with Appropriate Selection of Early Invasive Strategy or Ischemia-Guided Strategy in Pts with NSTEMI-ACS

Immediate invasive (within 2 h)	Refractory angina Signs or symptoms of heart failure or new or worsening mitral regurgitation Hemodynamic instability Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy Sustained ventricular tachycardia or ventricular fibrillation
Early invasive (within 24 h)	None of the above, but GRACE ^a risk score >140 Temporal change in troponin New or presumably new ST segment depression
Delayed invasive (within 25–72 h)	None of the above but diabetes mellitus Renal insufficiency (eGFR <60 mL/min per 1.73 m ²) Reduced left ventricular systolic function (ejection fraction <0.40) Early postinfarction angina Percutaneous coronary intervention within 6 months prior Prior coronary artery bypass graft surgery GRACE ^a risk score 109–140 or TIMI ^b risk score ≥2
Ischemia-guided strategy	Low-risk score (e.g., TIMI ^b [0 or 1], GRACE ^a [<109]) Low-risk, troponin-negative female pts Pt or clinician preference in the absence of high-risk features

^aSee CB Granger (Arch Intern Med 163:2345, 2003).

^bSee EM Antman (JAMA 284:835, 2000).

Abbreviations: eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; TIMI, Thrombolysis in Myocardial Infarction.

Source: Modified from Amsterdam EA et al: J Am Coll Cardiol 64:e139, 2014.

pursued if myocardial ischemia recurs spontaneously (angina or ST deviations at rest or with minimal activity) or is provoked by stress testing.

LONG-TERM MANAGEMENT

- Stress importance of smoking cessation, achieving optimal weight, diet low in saturated and trans fats, regular exercise, and blood pressure, lipid and diabetic control; these principles can be reinforced by encouraging pt to enter cardiac rehabilitation program.
- Continue aspirin (75–100 mg/d), a P2Y₁₂ receptor antagonist (clopidogrel, prasugrel or ticagrelor for at least 1 year), beta blocker, high-dose statin (e.g., atorvastatin 80 mg daily; add ezetimibe 10 g daily if needed to achieve LDL <70 mg/dL), and ACE inhibitor or angiotensin receptor blocker (especially if hypertensive, or diabetic, or LV ejection fraction is reduced).

123 Chronic Stable Angina



ANGINA

Angina pectoris, the most common clinical manifestation of coronary artery disease (CAD), results from an imbalance between myocardial O₂ supply and demand, most often due to atherosclerotic coronary artery obstruction. Other major conditions that upset this balance and result in angina include aortic valve disease ([Chap. 116](#)), hypertrophic cardiomyopathy ([Chap. 117](#)) and coronary artery spasm (see below).

■ SYMPTOMS

Angina is typically associated with exertion or emotional upset; relieved quickly by rest or nitroglycerin ([Chap. 33](#)). Major risk factors are cigarette smoking, hypertension, hypercholesterolemia (↑LDL; ↓HDL), diabetes, obesity, and family history of CAD before age 55.

■ PHYSICAL EXAMINATION

Often normal; arterial bruits or retinal vascular abnormalities suggest generalized atherosclerosis; S₄ is common. During acute anginal episode, other signs may appear: e.g., an S₄, diaphoresis, rales, and a transient murmur of mitral regurgitation due to papillary muscle ischemia.

■ LABORATORY ECG

May be normal between anginal episodes or show old infarction ([Chap. 113](#)). During angina, ST- and T-wave abnormalities typically appear (ST-segment depression reflects subendocardial ischemia; ST-segment elevation may reflect acute infarction or transient coronary artery spasm). Ventricular arrhythmias frequently accompany acute ischemia.

■ STRESS TESTING

Enhances diagnosis of CAD; exercise is performed on treadmill or bicycle until target heart rate is achieved or pt becomes symptomatic (chest pain, light-headedness, hypotension, marked dyspnea, ventricular tachycardia) or develops diagnostic ST-segment changes. Useful information includes duration of exercise achieved; peak heart rate and bp; depth, morphology, and persistence of ST-segment depression; and whether and at which level of exercise pain, hypotension, or ventricular arrhythmias develop. Exercise testing with radionuclide, echocardiographic, or magnetic resonance imaging increases sensitivity and specificity and is particularly useful if baseline ECG abnormalities prevent interpretation of test. **Note:** Exercise testing should not be performed in pts with acute MI, unstable angina, or severe aortic stenosis. If the pt is unable to exercise, pharmacologic stress with IV dipyridamole, adenosine, regadenoson, or dobutamine can be performed in conjunction with radionuclide or echocardiographic imaging (Table 123-1). Pts with LBBB on baseline ECG should be referred for adenosine or dipyridamole radionuclide imaging, which is most specific for diagnosis of CAD in this setting.

The prognostic utility of coronary calcium detection (by electron-beam or multidetector CT) in the diagnosis and management of CAD continues to be defined.

Some pts do not experience chest pain during ischemic episodes with exertion ("silent ischemia") but are identified by transient ST-T-wave abnormalities during stress (see below).

■ CORONARY ARTERIOGRAPHY

Major indications are (1) angina refractory to medical therapy, (2) markedly positive exercise test (≥ 2 -mm ST-segment depression, onset of ischemia at low workload, or ventricular tachycardia or hypotension with exercise) suggestive of left main or three-vessel disease, (3) recurrent angina or positive exercise test after MI, (4) to assess for coronary artery spasm, and (5) to evaluate pts with perplexing chest pain in whom noninvasive tests are not diagnostic.

TABLE 123-1 Stress Testing Recommendations

SUBGROUP	RECOMMENDED STUDY
Pt able to exercise	
If baseline ST-T on ECG is normal	Standard exercise test (treadmill, bicycle, or arm ergometry)
If baseline ST-T impairs test interpretation (e.g., LVH with strain, digoxin)	Standard exercise test (above) combined with <i>either</i> Perfusion scintigraphy (e.g., ^{99m}Tc -sestamibi) or Echocardiography
Pt <i>not</i> able to exercise (regardless of baseline ST-T abnormality)	Pharmacologic stress test (IV adenosine, regadenoson, dipyridamole, dobutamine) combined with imaging: Perfusion scintigraphy (e.g., ^{99m}Tc -sestamibi or PET [rubidium-82 or N-13 ammonia]) or Echocardiography or Cardiac MRI
LBBB on baseline ECG	Pharmacologic stress test with imaging

The role of *noninvasive* coronary imaging techniques (CT and MR angiography) continues to be defined.

TREATMENT

Chronic Stable Angina (Fig. 123-1)

GENERAL

- Identify and treat risk factors: mandatory cessation of smoking; treatment of diabetes, hypertension, and lipid disorders (**Chap. 181**); advocate a diet low in saturated fat and trans fats.
- Correct exacerbating factors contributing to angina: morbid obesity, CHF, anemia, hyperthyroidism.
- Reassurance and pt education.

DRUG THERAPY

Sublingual nitroglycerin (TNG 0.3–0.6 mg); may be repeated at 5-min intervals; warn pts of possible headache or light-headedness; teach prophylactic use of TNG prior to activity that regularly evokes angina. If chest pain persists for >10 min despite 2–3 TNG, pt should report promptly to nearest medical facility for evaluation of possible acute coronary syndrome.

Long-Term Angina Suppression

The following classes of drugs are used, frequently in combination.

Long-Acting Nitrates

May be administered by many routes (**Table 123-2**); start at the lowest dose and frequency to limit tolerance and side effects of headache, light-headedness, tachycardia.

Beta Blockers (See **Table 119-2**)

All have antianginal properties; β_1 -selective agents are less likely to exacerbate airway or peripheral vascular disease. Dosage should be titrated to resting heart rate of 50–60 beats/min. *Contraindications* to beta blockers include CHF, AV block, bronchospasm, “brittle” diabetes. Side effects include fatigue, bronchospasm, depressed LV function, impotence, depression, and masking of hypoglycemia in diabetics.

Calcium Antagonists (See **Table 119-2**)

Useful for stable and unstable angina, as well coronary vasospasm. Combination with other antianginal agents is beneficial, but verapamil should be administered cautiously to pts on beta blockers (additive effects on slowing heart rate). Use sustained-release, not short-acting, calcium antagonists; the latter are associated with increased coronary mortality.

Ranolazine

For pts who continue to experience stable angina despite the above standard medications, consider addition of ranolazine (500–1000 mg PO bid), which reduces anginal frequency and improves exercise capacity without affecting blood pressure or heart rate. Ranolazine is contraindicated in hepatic impairment, in pts with prolongation of the QT_c interval, or in combination with drugs

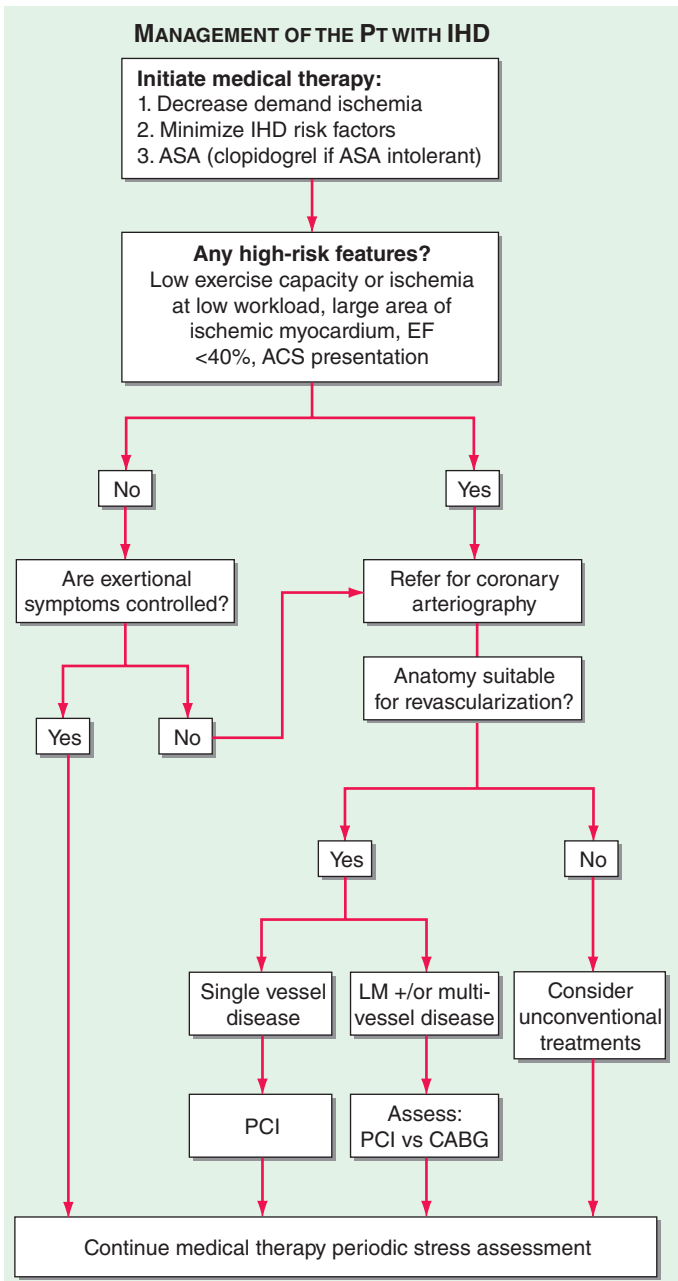


FIGURE 123-1 Algorithm for management of ischemic heart disease. ACS, acute coronary syndrome; ASA, aspirin; EF, ejection fraction; IHD, ischemic heart disease; LM, left main.

TABLE 123-2 Examples of Commonly Used Nitrates

	USUAL DOSE	RECOMMENDED DOSING FREQUENCY
Short-acting agents		
Sublingual TNG	0.3–0.6 mg	As needed
Aerosol TNG	0.4 mg (1 inhalation)	As needed
Sublingual ISDN	2.5–10 mg	As needed
Long-acting agents		
ISDN		
Oral	10–40 mg	2–3 times daily
Sustained-action	80–120 mg	1–2 times daily
TNG ointment (2%)	0.5–2	2–3 times daily
TNG transdermal patch	0.2–0.8 mg/h	Apply in morning, remove at bedtime
ISMO		
Oral	20–40 mg	2 times daily (once in the A.M., then 7 h later)
Sustained-action	30–240 mg	Once daily

Abbreviations: ISDN, isosorbide dinitrate; ISMO, isosorbide mononitrate; TNG, nitroglycerin.

that inhibit its metabolism (e.g., ketoconazole, macrolide antibiotics, HIV protease inhibitors, diltiazem, and verapamil).

Aspirin

81–162 mg/d reduces the incidence of MI in chronic stable angina, following MI, and in asymptomatic men. It is recommended in pts with CAD in the absence of contraindications (GI bleeding or allergy). Consider clopidogrel (75 mg/d) for aspirin-intolerant individuals.

The addition of an **ACE inhibitor** is recommended in pts with CAD and LV ejection fraction <40%, hypertension, diabetes, or chronic kidney disease.

MECHANICAL REVASCULARIZATION

Used in conjunction with, not as replacement for, risk factor modification and medical therapies.

Percutaneous Coronary Intervention (PCI)

Technique of balloon dilatation, usually with intracoronary stent implantation. Performed on anatomically suitable stenoses of native vessels and bypass grafts; more effective than medical therapy for relief of angina. Has not been shown to reduce risk of MI or death in chronic stable angina; should not be performed on asymptomatic or only mildly symptomatic individuals. With PCI initial relief of angina occurs in 95% of pts; however, restenosis develops in 30–45% following balloon dilatation alone, in ~20% after bare metal stenting, but in <10% after drug-eluting stent (DES) implantation. Late stent thrombosis may occur rarely in pts with DES; it is diminished by prolonged antiplatelet therapy (aspirin indefinitely and a platelet P2Y₁₂ receptor antagonist for a minimum of 12 months).

Coronary Artery Bypass Graft (CABG)

Appropriately used for angina refractory to medical therapy or when the latter is not tolerated (and when lesions are not amenable to PCI) or if severe CAD is present (e.g., left main, three-vessel disease with impaired LV function). In type 2

TABLE 123-3 Comparison of Revascularization Procedures in Multivessel Disease

PROCEDURE	ADVANTAGES	DISADVANTAGES
Percutaneous coronary revascularization	Less invasive Shorter hospital stay Lower initial cost Lower stroke rate	Possible incomplete revascularization May require repeat procedures Limited to specific anatomic subsets
Coronary artery bypass grafting	Lower rate of recurrent angina Ability to achieve complete revascularization	Cost Risk of a repeat procedure due to late graft closure Morbidity and mortality of major surgery

diabetics with multivessel CAD, CABG plus optimal medical therapy is superior to medical therapy alone in prevention of major coronary events.

The relative advantages of PCI and CABG are summarized in [Table 123-3](#).

PRINZMETAL'S VARIANT ANGINA (CORONARY VASOSPASM)

Intermittent focal spasm of coronary artery; often associated with atherosclerotic lesion near site of spasm. Chest discomfort is similar to angina but more severe and occurs typically at rest, with transient ST-segment elevation. Acute infarction or malignant arrhythmias may develop during spasm-induced ischemia. Evaluation includes observation of ECG for transient ST elevation during discomfort; diagnosis confirmed at coronary angiography using provocative (e.g., IV acetylcholine) testing. Primary treatment consists of long-acting nitrates and calcium antagonists. Prognosis is better in pts with anatomically normal coronary arteries than in those with fixed coronary stenoses.

124 Bradyarrhythmias



Bradyarrhythmias arise from (1) failure of impulse initiation (sinoatrial [SA] node dysfunction) or (2) impaired electrical conduction (e.g., AV conduction blocks).

SINOATRIAL NODE DYSFUNCTION

Etiologies are either *intrinsic* (degenerative, ischemic, inflammatory, infiltrative [e.g., amyloid], or rare mutations in sodium channel or pacemaker current genes) or *extrinsic* (e.g., drugs [beta blockers, Ca⁺⁺ channel blockers, digoxin], autonomic dysfunction, hypothyroidism).

Symptoms are due to *bradycardia* (fatigue, weakness, lightheadedness, syncope) and/or episodes of associated *tachycardia* (e.g., rapid palpitations, angina) in pts with sick sinus syndrome (SSS).

■ DIAGNOSIS

Examine ECG for evidence of sinus bradycardia (sinus rhythm at <60 beats/min) or failure of rate to increase with exercise (chronotropic incompetence), sinus pauses, or exit block. In pts with SSS, periods of tachycardia (i.e., atrial fibrillation/flutter) also occur. Prolonged ECG monitoring (24–48 h Holter, 30-day loop recorder, or long-term implanted monitor) aids in identifying these abnormalities. Invasive electrophysiologic testing is rarely necessary to establish diagnosis.

TREATMENT**Sinoatrial Node Dysfunction**

Remove or treat extrinsic causes such as contributing drugs or hypothyroidism. Otherwise, symptoms of bradycardia respond to permanent pacemaker placement ([Table 124-1](#)). In SSS, treat associated atrial fibrillation or flutter as indicated in [Chap. 125](#).

AV BLOCK

Impaired conduction from atria to ventricles may be structural and permanent, or reversible (e.g., autonomic, metabolic, drug-related)—see [Table 124-2](#).

■ FIRST DEGREE (SEE FIG. 124-1A)

Prolonged, constant PR interval (>0.20 s). May be normal or secondary to increased vagal tone or drugs (e.g., beta blocker, diltiazem, verapamil, digoxin); treatment not usually required.

TABLE 124-1 Summary of Guidelines for Pacemaker Implantation in SA Node Dysfunction

Class I

1. SA node dysfunction with symptomatic bradycardia or sinus pause
2. Symptomatic SA node dysfunction as a result of essential long-term drug therapy with no acceptable alternatives
3. Symptomatic chronotropic incompetence
4. Atrial fibrillation with bradycardia and pauses >5 s

Class IIa

1. SA node dysfunction with heart rates <40 beats/min without a clear and consistent relationship between bradycardia and symptoms
2. SA node dysfunction with heart rates <40 beats/min on an essential long-term drug therapy with no acceptable alternatives, without a clear and consistent relationship between bradycardia and symptoms
3. Syncope of unknown origin when major abnormalities of SA node dysfunction are discovered or provoked by electrophysiologic testing

Class IIb

1. Mildly symptomatic pts with waking chronic heart rates <40 beats/min

Class III

1. SA node dysfunction in asymptomatic pts, even those with heart rates <40 beats/min
2. SA node dysfunction in which symptoms suggestive of bradycardia are not associated with a slow heart rate
3. SA node dysfunction with symptomatic bradycardia due to nonessential drug therapy

Source: Data from Epstein AE et al: *J Am Coll Cardiol* 51:e1, 2008; Tracy CM et al: *J Am Coll Cardiol* 61:e6, 2013.

TABLE 124-2 Etiologies of Atrioventricular Block

Autonomic	
Carotid sinus hypersensitivity	Vasovagal
Metabolic/Endocrine	
Hyperkalemia	Hypothyroidism
Hypermagnesemia	Adrenal insufficiency
Drug-Related	
Beta blockers	Adenosine
Calcium channel blockers	Antiarrhythmics (class I and III)
Digitalis	Lithium
Infectious	
Endocarditis	Tuberculosis
Lyme disease	Diphtheria
Chagas' disease	Toxoplasmosis
Syphilis	
Heritable/Congenital	
Congenital heart disease	Kearns-Sayre syndrome
Maternal SLE	Myotonic dystrophy and other muscular dystrophies
Inflammatory	
SLE	MCTD
Rheumatoid arthritis	Scleroderma
Infiltrative	
Amyloidosis	Hemochromatosis
Sarcoidosis	
Neoplastic/Traumatic	
Lymphoma	Radiation
Mesothelioma	Catheter ablation
Melanoma	
Degenerative	
Lev's disease	Lenègre's disease
Coronary Artery Disease	
Acute MI	

Abbreviations: MCTD, mixed connective tissue disease; MI, myocardial infarction.

■ SECOND DEGREE

Mobitz I (Wenckebach; Fig. 124-1B)

Narrow QRS, progressive increase in PR interval until a ventricular beat is dropped, then sequence repeats. Seen with drug intoxication (digitalis, beta blockers), increased vagal tone, inferior MI. Usually transient, no therapy required; if symptomatic, use atropine (0.6 mg IV, repeated \times 3–4) or temporary pacemaker.

Mobitz II (Fig. 124-1C)

Fixed PR interval (i.e., no progressive lengthening) with occasional dropped beats, e.g., in 2:1, 3:1, or 4:1 pattern; the QRS complex is usually wide. Seen with MI or degenerative conduction system disease; more serious than Mobitz I—may progress suddenly to complete AV block; permanent pacemaker is indicated.

■ THIRD DEGREE (COMPLETE AV BLOCK) (SEE FIG. 124-1D)

Complete failure of conduction from atria to ventricles; atria and ventricles depolarize independently. May occur with MI, digitalis toxicity, or degenerative conduction system disease. Permanent pacemaker is usually indicated, except when reversible (e.g., drug-related or appears only transiently in MI without associated bundle branch block).

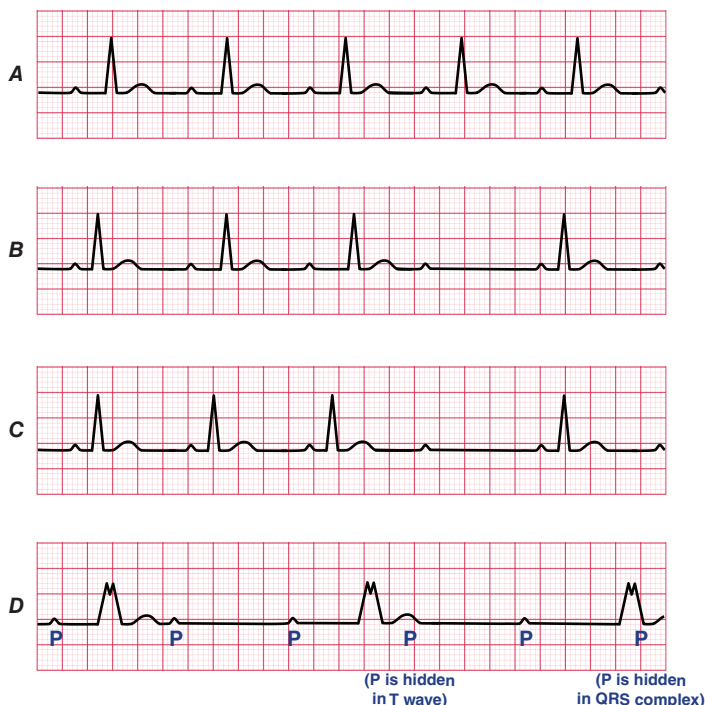


FIGURE 124-1 **A.** First degree AV block (PR interval is prolonged). **B.** Second degree AV block—Mobitz type I (progressive PR prolongation preceding a dropped QRS). **C.** Second degree AV block—Mobitz type II (A dropped QRS is not preceded by progressive PR prolongation). **D.** Third degree AV block (P waves and QRS complexes are independent of one another).

125 Tachyarrhythmias

Tachyarrhythmias may appear in the presence or absence of structural heart disease; they are more serious in the former. Conditions that provoke arrhythmias include (1) myocardial ischemia, (2) heart failure, (3) hypoxemia, (4) hypercapnia, (5) hypotension, (6) electrolyte disturbances (e.g., hypokalemia and/or hypomagnesemia), (7) drug toxicity (digoxin, drugs that prolong the QT interval), (8) caffeine consumption, (9) ethanol consumption.

■ DIAGNOSIS

Examine ECG for evidence of ischemic changes ([Chap. 113](#)), prolonged or shortened QT interval, characteristics of Wolff-Parkinson-White (WPW) syndrome (see below), or ST elevation in leads V_1 - V_3 typical of Brugada syndrome. See [Table 125-1](#) for diagnosis of tachyarrhythmias; always identify atrial activity and relationship between P waves and QRS complexes. To aid the diagnosis:

TABLE 125-1 Clinical and Electrocardiographic Features of Common Arrhythmias

RHYTHM	ATRIAL RATE	FEATURES	CAROTID SINUS MASSAGE	PRECIPITATING CONDITIONS	INITIAL TREATMENT
Narrow QRS complex					
Atrial premature beats	—	P wave abnormal; QRS width normal	—	Can be normal or due to anxiety, CHF, hypoxia, caffeine, abnormal electrolytes ($\downarrow K^+$ $\downarrow Mg^{2+}$)	Remove precipitating cause; if symptomatic: beta blocker
Sinus tachycardia	100–160	Normal P wave contour	Rate gradually slows	Fever, anxiety, pain, anemia, dehydration, CHF, hyperthyroidism, COPD	Remove precipitating cause; if symptomatic: beta blocker
AV nodal tachycardia (reentrant)	120–250	Absent or retrograde P wave	Abruptly converts to sinus rhythm (or no effect)	Can occur in healthy individuals	Vagal maneuvers; if unsuccessful: adenosine, verapamil, beta blocker, cardioversion (100–200 J). To prevent recurrence: beta blocker, verapamil, diltiazem, digoxin, class IC agent, or catheter ablation
Focal atrial tachycardia	130–200	P contour different from sinus P wave; AV block may occur; automatic form shows “warm-up” in rate in first several beats	AV block may \uparrow	Digitalis toxicity; pulmonary disease; scars from prior cardiac surgery or ablation	If digitalis toxic: hold digoxin, correct $[K^+]$ In absence of digoxin toxicity: slow rate with beta blocker, verapamil, or diltiazem; can attempt conversion with IV adenosine; if unsuccessful, consider cardioversion; for long-term suppression, consider class I or III antiarrhythmic or catheter ablation

(Continued)

TABLE 125-1 Clinical and Electrocardiographic Features of Common Arrhythmias (Continued)

RHYTHM	ATRIAL RATE	FEATURES	CAROTID SINUS MASSAGE	PRECIPITATING CONDITIONS	INITIAL TREATMENT
Atrial flutter Atrial fibrillation	260–300 >350	“Sawtooth” flutter waves; 2:1, 4:1 block No discrete P; irregularly spaced QRS	↑ AV block with ↓ventricular rate ↓ ventricular rate	Mitral valve disease, hypertension, pulmonary embolism, pericarditis, post-cardiac surgery, hyperthyroidism; obstructive lung disease, EtOH; atypical atrial flutter usually arises from atrial scars	<ol style="list-style-type: none"> 1. Slow the ventricular rate: beta blocker, verapamil, diltiazem, or digoxin 2. Consider conversion to NSR (after anticoagulation if chronic) electrically (50–100 J for atrial flutter, ≥200 J for atrial fibrillation) or chemically with IV ibutilide or oral class IC, III, or IA^a agent <p>Atrial flutter may respond to rapid atrial pacing, and radio frequency ablation highly effective to prevent recurrences; consider ablation for recurrences of atrial fibrillation, especially if class IC or class III agents fail to control</p>
Multifocal atrial tachycardia	100–150	At least three distinct P wave shapes with varying PR intervals	No effect	Severe respiratory insufficiency	Treat underlying lung disease; verapamil or diltiazem may be used to slow ventricular rate; class IC agents or amiodarone may ↓ episodes
Wide QRS complex					
Ventricular premature beats		Fully compensatory pause between normal beats	No effect	CAD, MI, CHF, hypoxia, hypokalemia, digitalis toxicity, prolonged QT interval (congenital or drug-related)	May not require therapy; if needed for symptomatic suppression, use beta blocker

Ventricular tachycardia		QRS rate 100–250; slightly irregular rate	No effect	<p><i>Monomorphic:</i> myocardial scar (e.g., prior MI, sarcoid), ARVC, idiopathic outflow tract tachycardias</p> <p><i>Polymorphic:</i> Myocardial ischemia, hypertrophic cardiomyopathy, electrolyte disturbances, drug toxicities, genetic arrhythmia syndromes (see “torsade de pointes” below)</p>	<p>If unstable: electrical conversion/defibrillation (≥ 200 J monophasic, or ≥ 100 J biphasic)</p> <p>Otherwise: acute (IV): amiodarone, procainamide, lidocaine; chronic management: usually ICD</p> <p>Pts without structural heart disease (e.g., focal outflow tract ventricular tachycardia) may respond to beta blockers or verapamil</p>
Accelerated idioventricular rhythm (AIVR)		Gradual onset and offset; QRS rate 40–120		Acute MI, myocarditis	Usually none; for symptoms, use atropine or atrial pacing
Ventricular fibrillation		Erratic electrical activity	No effect		Immediate defibrillation
Torsade de pointes		Ventricular tachycardia with sinusoidal oscillations of QRS height	No effect	Prolonged QT interval (congenital or drug-related)	<p>IV magnesium (1- to 2-g bolus); overdrive pacing; isoproterenol for bradycardia-dependent torsades (unless CAD present); lidocaine</p> <p>Drugs that prolong QT interval are contraindicated</p>

(Continued)

TABLE 125-1 Clinical and Electrocardiographic Features of Common Arrhythmias (Continued)

RHYTHM	ATRIAL RATE	FEATURES	CAROTID SINUS MASSAGE	PRECIPITATING CONDITIONS	INITIAL TREATMENT
Supraventricular tachycardias with aberrant ventricular conduction		P wave typical of the supraventricular rhythm; wide QRS complex due to conduction through partially refractory pathways		Etiologies of the respective supraventricular rhythms listed above; atrial fibrillation with rapid, wide QRS may occur in preexcitation (WPW)	Same as treatment of respective supraventricular rhythm; if ventricular rate rapid (>200), treat as WPW (see text)

^aAntiarrhythmic drug groups listed in Table 125-2.

Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EtOH, ethyl alcohol; ICD, implantable cardioverter defibrillator; NSR, normal sinus rhythm; WPW, Wolff-Parkinson-White.

VT versus Supraventricular Tachycardia with Aberrancy

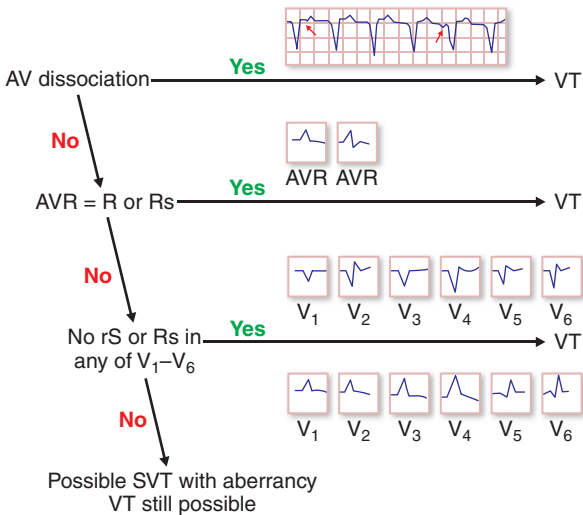


FIGURE 125-1 Algorithm for differentiation of ventricular tachycardia (VT) from supraventricular tachycardia (SVT).

- Obtain long rhythm strip of lead II, aVF, or V₁. P waves can be made more evident by intentionally doubling the ECG voltage.
- Place accessory ECG leads (e.g., right-sided chest leads) to help identify P waves. Record ECG during carotid sinus massage (Table 125-1). **Note:** Do not massage both carotids simultaneously.
- For intermittent symptoms, consider 24-h Holter monitor (if symptoms occur daily), a pt-activated or continuously recording event monitor over 2–4 weeks, or, if symptoms are very infrequent but severely symptomatic, an implanted loop monitor. A standard exercise test may be used to provoke arrhythmias for diagnostic purposes.

Tachyarrhythmias with wide QRS complex beats may represent ventricular tachycardia or supraventricular tachycardia with aberrant conduction. Factors favoring ventricular tachycardia include (1) AV dissociation, (2) monomorphic R or Rs in lead AVR, (3) concordance of QRS with monophasic R or S waves in V₁-V₆ (Fig. 125-1).

TREATMENT

Tachyarrhythmias (Tables 125-1 and 125-2)

Precipitating causes (listed earlier) should be corrected. If pt is hemodynamically compromised (angina, hypotension, CHF), proceed to immediate cardioversion.

Do not cardiovert sinus tachycardia; exercise caution if digitalis toxicity is suspected. Initiate drugs as indicated in the tables; follow ECG intervals (esp. QRS and QT). Reduce dosage for pts with hepatic or renal dysfunction as indicated in Table 125-2. Drug efficacy is confirmed by ECG (or Holter) monitoring, stress testing, and, in special circumstances, invasive electrophysiologic study.

TABLE 125-2 Commonly Used Antiarrhythmic Drugs

DRUG	LOADING DOSE	MAINTENANCE DOSE	SIDE EFFECTS	EXCRETION
Class IA				
Quinidine		PO: 300–600 mg q6h	Diarrhea, tinnitus, QT prolongation, hypotension, anemia, thrombocytopenia	Hepatic and renal
Procainamide	IV: 15 mg/kg over 60 min	IV: 1–4 mg/min PO: 500–1000 mg q4h	Nausea, lupus-like syndrome, agranulocytosis, QT prolongation	Renal and hepatic
Sustained-release		PO: 1000–2500 mg q12h		
Disopyramide		PO: 100–300 mg q6–8h	Myocardial depression, AV block, QT prolongation anticholinergic effects	Renal and hepatic
Sustained-release		PO: 200–400 mg q12h		
Class IB				
Lidocaine	IV: 1–3 mg/kg at 20–50 mg/min	IV: 1–4 mg/min	Confusion, seizures, respiratory arrest	Hepatic
Mexiletine		PO: 150–300 mg q8–12h	Nausea, tremor, gait disturbance	Hepatic
Class IC				
Flecainide		PO: 50–200 mg q12h	Nausea, exacerbation of ventricular arrhythmia, prolongation of PR and QRS intervals	Hepatic and renal
Propafenone		PO: 150–300 mg q8h		Hepatic
Class II				
Metoprolol	IV: 5 mg over 3–5 min × 3 doses	PO: 25–100 mg q6h	Bradycardia, AV block, CHF, bronchospasm	Hepatic
Esmolol	IV: 500 µg/kg over 1 min	IV: 50 (µg/kg)/min		

Class III				
Amiodarone	PO: 800–1600 mg qd × 1–2 weeks, then 400–600 mg/d × 3 weeks	PO: 100–400 mg qd	Thyroid abnormalities, pulmonary fibrosis, transaminitis, bluish skin	Hepatic
	IV: 150 mg over 10 min	IV: 1 mg/min × 6 h, then 0.5 mg/min		
Ibutilide	IV (>60 kg): 1 mg over 10 min, can repeat after 10 min	—	Torsade de pointes, hypotension, nausea	Hepatic
Dofetilide		PO: 125–500 µg bid	Torsade de pointes, headache, dizziness	Renal
Sotalol		PO: 80–160 mg q12h	Fatigue, bradycardia, exacerbation of ventricular arrhythmia	Renal
Dronedarone		PO: 400 mg q12h	Bradycardia, AV block, prolonged QT, exacerbation of heart failure, GI discomfort	Hepatic
Class IV				
Verapamil	IV: 5–10 mg over 3–5 min	IV: 2.5–10 mg/h PO: 80–120 mg q6–8 h	AV block, CHF, hypotension, constipation	Hepatic
Diltiazem	IV: 0.25 mg/kg over 3–5 min (maximum 20 mg)	IV: 5–15 mg/h PO: 30–60 mg q6h		Hepatic
Other				
Digoxin	IV: 0.25 mg q2h until 1 mg total	IV, PO: 0.125–0.25 mg qd	Nausea, AV block, ventricular and supraventricular arrhythmias	Renal
Adenosine	IV: 6-mg rapid bolus; if no effect then 12-mg bolus	—	Transient hypotension or atrial standstill	—

Antiarrhythmic agents all have potential toxic side effects, including provocation of ventricular arrhythmias, esp. in pts with LV dysfunction or history of sustained ventricular arrhythmias. Drug-induced QT prolongation and associated torsade de pointes ventricular tachycardia (Table 125-1) is most common with class IA and III agents; the drug should be discontinued if the QTc interval (QT divided by square root of RR interval) increases by >25%. Antiarrhythmic drugs should be avoided in pts with asymptomatic ventricular arrhythmias after MI, since mortality risk increases.

CHRONIC ATRIAL FIBRILLATION (AF)

Evaluate potential underlying cause (e.g., thyrotoxicosis, mitral stenosis, excessive ethanol consumption, pulmonary embolism). Pts with rheumatic mitral stenosis, hypertrophic cardiomyopathy, or CHA₂DS₂-VASc score ≥ 2 (1 point each for CHF, hypertension, diabetes, vascular disease, age 65–75, female gender; 2 points each for age ≥ 75 , history of stroke or TIA) should receive anticoagulation; may also consider for CHA₂DS₂-VASc score of 1. Use warfarin (INR 2.0–3.0) or in absence of mitral stenosis or mechanical heart valve, consider direct-acting oral anticoagulants (DOACs) that do not require prothrombin time monitoring—e.g., dabigatran (150 mg bid; 75 mg bid for creatinine clearance [CrCl] 15–30 mL/min), rivaroxaban (20 mg daily; 15 mg daily for CrCl 15–50 mL/min), apixaban (5 mg bid; 2.5 mg bid for 2 of the following: age >80 , weight <60 kg, creatinine ≥ 1.5 mg/dL), or edoxaban (60 mg daily for CrCl 60–90 mL/min; 30 mg daily for CrCl 15–60 mL/min). Bleeding effects of warfarin can be reversed with prothrombin complex concentrate, fresh frozen plasma, and/or vitamin K. Reversal agents for some DOACs are also now available, if needed for severe bleeding or prior to urgent invasive procedures (idarucizumab for dabigatran, andexanet alfa for rivaroxaban and apixaban).

Control ventricular rate (60–80 beats/min at rest, <100 beats/min with mild exercise) with beta blocker, calcium channel blocker (verapamil, diltiazem), or digoxin.

Consider cardioversion (100–200 J) after ≥ 3 weeks therapeutic anticoagulation, or acutely if no evidence of left atrial thrombus by transesophageal echo, especially if symptomatic despite rate control. Initiation of class IC, III, or IA agents prior to electrical cardioversion facilitates maintenance of sinus rhythm after successful procedure. Class IC (Table 125-2) drugs are preferred in pts without structural heart disease, and class III drugs are recommended in presence of left ventricular dysfunction or coronary artery disease. Anticoagulation should be continued for a minimum of 3 weeks after successful cardioversion.

Consider catheter-based ablation (pulmonary vein isolation) for recurrent symptomatic AF if sufficiently responsive to pharmacologic measures (more effective in pts with paroxysmal AF: ~60% success at maintaining sinus rhythm after first ablation, 70–80% after additional ablation). Rare late complications of ablation include pulmonary vein stenosis (presents with dyspnea or hemoptysis) and atrio-esophageal fistula (consider if fever, neurologic symptoms, or chest pain arise).

PREEXCITATION SYNDROME (WPW)

Conduction occurs through an accessory pathway between atria and ventricles. Baseline ECG typically shows a short PR interval and slurred upstroke of the QRS (“delta” wave). Associated tachyarrhythmias are of two types:

- Narrow QRS “orthodromic” tachycardia (antegrade conduction through AV node). Treat cautiously with IV adenosine or beta blocker, verapamil, or diltiazem (Table 125-2).

- Wide QRS complex “antidromic” tachycardia (antegrade conduction through accessory pathway); wide complex tachycardia may also be associated with AF with a very rapid (>250/min) ventricular rate, which can degenerate into VF. If hemodynamically compromised, immediate cardioversion is indicated; otherwise, treat with IV procainamide or ibutilide (Table 125-2), *not* beta blocker, verapamil, diltiazem, digoxin, or amiodarone.
- Refer to electrophysiologist to consider catheter ablation of accessory pathway for long-term prevention of tachycardia.

126

Heart Failure and Cor Pulmonale



HEART FAILURE (HF)

■ DEFINITION

Abnormality of cardiac structure and/or function resulting in clinical symptoms (e.g., dyspnea, fatigue) and signs (e.g., edema, pulmonary crackles), hospitalizations, poor quality of life, and shortened survival. It is important to identify the underlying nature of the cardiac disease and the factors that precipitate acute HF.

■ UNDERLYING CARDIAC DISEASE

Includes (1) states that depress systolic ventricular function with reduced ejection fraction (HFrEF; e.g., coronary artery disease [CAD], dilated cardiomyopathies, valvular disease, congenital heart disease); and (2) states of HF with preserved ejection fraction (HFpEF; e.g., restrictive cardiomyopathies, hypertrophic cardiomyopathy, fibrosis, endomyocardial disorders), also termed *diastolic failure*.

■ ACUTE PRECIPITATING FACTORS

Include (1) excessive Na⁺ intake, (2) noncompliance with HF medications, (3) acute MI (may be silent), (4) exacerbation of hypertension, (5) acute arrhythmias, (6) infection and/or fever, (7) pulmonary embolism, (8) anemia, (9) thyrotoxicosis, (10) pregnancy, (11) acute myocarditis or infective endocarditis, and (12) certain drugs (e.g., nonsteroidal anti-inflammatory agents).

■ SYMPTOMS

Due to inadequate perfusion of peripheral tissues (fatigue) and elevated intracardiac filling pressures (dyspnea, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema).

■ PHYSICAL EXAMINATION

Jugular venous distention, S₃ (in HFrEF/volume overload), pulmonary congestion (crackles, dullness over pleural effusion), peripheral edema, hepatomegaly, and ascites. Sinus tachycardia is common. In pts with HFpEF, S₄ is often present.

■ LABORATORY

CXR may reveal cardiomegaly, pulmonary vascular redistribution, interstitial edema, pleural effusions. Left ventricular systolic and diastolic dysfunction are most readily evaluated by *echocardiography* with Doppler, and EF calculated or estimated. In addition, echo can identify underlying valvular, pericardial, or congenital heart disease, and regional wall motion abnormalities typical of CAD. *Cardiac MR* may be valuable in assessing ventricular structure, mass, volumes, and can help determine cause of HF (e.g., CAD, amyloid, hemochromatosis).

Measurement of *B-type natriuretic peptide* (BNP) or *N-terminal pro-BNP* differentiates cardiac from pulmonary causes of dyspnea (elevated in the former).

■ CONDITIONS THAT MIMIC CHF

Pulmonary Disease: Chronic bronchitis, emphysema, and asthma (**Chaps. 131 and 133**); assess for sputum production and abnormalities on CXR and pulmonary function tests. **Other Causes of Peripheral Edema:** Obesity, varicose veins, and venous insufficiency do not cause jugular venous distention. Edema due to renal dysfunction is often accompanied by elevated serum creatinine and abnormal urinalysis (**Chap. 38**).

TREATMENT

Heart Failure

Aimed at symptomatic relief, prevention of adverse cardiac remodeling, and prolonging survival. Overview of treatment of chronic HF is shown in **Table 126-1**; notably, ACE inhibitors and beta blockers are cornerstones of therapy in pts with HFrEF. Once symptoms develop:

- **Control excess fluid retention:** (1) **Dietary sodium restriction** (eliminate salty foods, e.g., potato chips, canned soups, bacon, salt added at table); more stringent requirements (<2 g NaCl/d) in advanced CHF. If dilutional hyponatremia present, restrict fluid intake (<1000 mL/d). (2) **Diuretics:** *Loop diuretics* (e.g., furosemide or torsemide [**Table 126-2**]) are most potent and, unlike thiazides, remain effective when GFR <25 mL/min. Combine loop diuretic with thiazide or metolazone for augmented effect.
- **ACE inhibitors** (**Table 126-2**): Standard initial HF therapy that reduces mortality in pts with symptomatic HF, delays the onset of HF in pts with asymptomatic LV dysfunction, and lowers mortality when begun soon after acute MI. ACE inhibitors may result in hypotension in pts who are volume depleted, so start at lowest dosage (e.g., captopril 6.25 mg PO tid). Angiotensin receptor blockers (ARBs) (**Table 126-2**) may be substituted if pt is intolerant of ACE inhibitor (e.g., because of cough or angioedema). For pts with persistent class II–III symptoms, consider converting ACE inhibitor or ARB to an angiotensin receptor-neprilysin inhibitor (**Table 126-2**; hold ACE inhibitor for 36 hours prior to initiation).
- **Beta blockers** (**Table 126-2**), specifically metoprolol succinate, carvedilol, and bisoprolol, administered in gradually augmented dosage improve symptoms and prolong survival in pts with HF and reduced EF <40%. Begin at low dosage and increase gradually (e.g., carvedilol 3.125 mg bid, double q2weeks as tolerated to maximum of 25 mg bid [for weight <85 kg] or 50 mg bid [weight >85 kg]).
- **Aldosterone antagonist therapy** (*spironolactone* or *eplerenone* [**Table 126-2**]), added to standard therapy in pts with advanced HF reduces mortality. Such therapy should be considered in pts with class II–IV HF symptoms and left ventricular ejection fraction (LVEF) ≤35%. Should be used cautiously when combined with ACE inhibitor or ARB to avoid hyperkalemia.
- **Digoxin** may be useful in HF due to (1) marked systolic dysfunction and (2) HF with atrial fibrillation (AF) and rapid ventricular rates. Unlike ACE inhibitors and beta blockers, digoxin does not prolong survival in HF pts but reduces hospitalizations. Digoxin is contraindicated in hypertrophic cardiomyopathy and in pts with AV conduction blocks.
 - Digoxin dosing (0.125–0.25 mg qd) depends on age, weight, and renal function and can be guided by measurement of serum digoxin level (maintain level <1.0 ng/mL).

TABLE 126-1 Therapy for Chronic Heart Failure

1. General measures
 - a. Restrict salt intake
 - b. Avoid NSAIDs
 - c. Immunize against influenza and pneumococcal pneumonia
2. Diuretics
 - a. Use in volume-overloaded pts
 - b. Weigh daily to adjust dose
 - c. For diuretic resistance, administer IV or use two diuretics in combination (e.g., furosemide plus metolazone)
3. ACE inhibitor or angiotensin receptor blocker
 - a. For all pts with LV systolic heart failure or asymptomatic LV dysfunction
 - b. Contraindications: Serum K^+ >5.5 , advanced renal disease (e.g., creatinine >3 mg/dL), bilateral renal artery stenosis, pregnancy
4. Beta blocker
 - a. For pts with symptomatic or asymptomatic heart failure and LVEF $<40\%$, combined with ACE inhibitor and diuretics
 - b. Contraindications: Bronchospasm, symptomatic bradycardia or advanced heart block, unstable heart failure
5. Aldosterone antagonist
 - a. Consider for class II–IV heart failure and LVEF $<35\%$
 - b. Avoid if K^+ >5.0 or creatinine >2.5 mg/dL
6. Digitalis
 - a. For persistently symptomatic pts with systolic heart failure (especially if atrial fibrillation present) added to ACE inhibitor, diuretics, beta blocker
7. Other measures
 - a. Consider combination of hydralazine and oral nitrate if not tolerant of ACE inhibitor/ARB, and as additive therapy in African-Americans
 - b. Consider ivabradine for LVEF $\leq 35\%$, if in sinus rhythm, rate >70 , already on maximum tolerated beta blocker, or if contraindication to beta blocker
 - c. Consider ventricular resynchronization (biventricular pacemaker) for pts with class III–IV heart failure, LVEF $<35\%$, and prolonged QRS (especially LBBB with QRS ≥ 150 msec)
 - d. Consider implantable cardioverter-defibrillator in pts with class II–III heart failure and ejection fraction $<35\%$
 - e. Assess and treat sleep apnea

Abbreviation: LBBB, left bundle branch block.

- *Digitalis toxicity* may be precipitated by hypokalemia, hypoxemia, hypercalcemia, hypomagnesemia, hypothyroidism, or myocardial ischemia. Early signs of toxicity include anorexia, nausea, and lethargy. *Cardiac toxicity* includes ventricular and supraventricular dysrhythmias and all degrees of AV block. At first sign of digitalis toxicity, discontinue the drug; maintain serum K^+ concentration between 4.0 and 5.0 mmol/L. Bradyarrhythmias and AV block may respond to atropine (0.6 mg IV); otherwise, a temporary pacemaker may be required. Antidigoxin antibodies are available for massive overdose.

TABLE 126-2 Drugs for the Treatment of Chronic Heart Failure with Reduced EF

	INITIATING DOSE	MAXIMAL DOSE
Diuretics		
Furosemide	20–40 mg qd or bid	240 mg/d
Torsemide	10–20 mg qd or bid	100 mg/d
Bumetanide	0.5–1.0 mg qd or bid	5 mg/d
Hydrochlorothiazide	25 mg qd	100 mg/d
Metolazone	2.5–5.0 mg qd or bid	20 mg/d
Angiotensin-converting enzyme inhibitors		
Captopril	6.25 mg tid	50 mg tid
Enalapril	2.5 mg bid	10–20 mg bid
Lisinopril	2.5–5.0 mg qd	20–40 mg qd
Ramipril	1.25–2.5 mg bid	2.5–5 mg bid
Trandolapril	0.5 mg qd	4 mg qd
Angiotensin receptor blockers		
Valsartan	40 mg bid	160 mg bid
Candesartan	4 mg qd	32 mg qd
Losartan	25–50 mg qd	150 mg qd
Angiotensin receptor-neprilysin inhibitor		
Valsartan/sacubitril	24/26–49/51 mg bid	97/103 mg bid
β-receptor blockers		
Carvedilol	3.125 mg bid	25–50 mg bid
Bisoprolol	1.25 mg qd	10 mg qd
Metoprolol succinate	12.5–25 mg qd	200 mg qd
Aldosterone antagonists		
Spirolactone	12.5–25 mg qd	25–50 mg qd
Eplerenone	25 mg qd	50 mg qd
Additional therapies		
Combination of hydralazine/isosorbide dinitrate	10–25 mg/10 mg tid	75 mg/40 mg tid
Fixed dose of hydralazine/isosorbide dinitrate	37.5 mg/20 mg tid	75 mg/40 mg tid
Digoxin	0.125 mg qd	Guided by renal function and serum level
Ivabradine	2.5–5.0 mg bid	7.5 mg bid

- The combination of the oral vasodilators *hydralazine* (10–75 mg tid) and *isosorbide dinitrate* (10–40 mg tid) may be of benefit for chronic administration in pts intolerant of ACE inhibitors and ARBs and is also beneficial as part of standard therapy, along with ACE inhibitor and beta blocker, in African Americans with class II–IV HF.
- Ivabradine, an inhibitor of the sinoatrial nodal I_f current, has been shown to reduce hospitalizations and cardiovascular endpoints in HF. It is a second-line agent (starting at 2.5–5.0 mg orally twice daily) for pts with LVEF $\leq 35\%$, in sinus rhythm with heart rate >70 bpm, already on maximally tolerated beta-blocker dose or have a contraindication to beta-blocker use.

TABLE 126-3 Drugs for Treatment of Acute Heart Failure

	INITIATING DOSE	MAXIMAL DOSE
Vasodilators		
Nitroglycerin	20 µg/min	up to 200 µg/min
Nitroprusside	10 µg/min	up to 5 µg/kg/min
Nesiritide	Bolus 2 µg/kg	0.01 µg/kg per min
Inotropes		
Dobutamine	1–2 µg/kg per min	2–20 µg/kg per min
Milrinone	Bolus 50 µg/kg slowly over 10 min	0.1–0.75 µg/kg per min

- For hospitalized pts with acute decompensated HF, use IV loop diuretics for volume overload, either by bolus or continuous infusion; obtain daily weights, aiming for loss of 1–1.5 kg/d. IV vasodilator therapy (Table 126-3) is often necessary. *Nitroprusside* is a potent mixed vasodilator for pts with markedly elevated systemic vascular resistance. It is metabolized to thiocyanate, which is excreted via the kidneys. To avoid thiocyanate toxicity (seizures, altered mental status, nausea), follow thiocyanate levels in pts with renal dysfunction or if administered for >2 days. IV *nesiritide* (Table 126-3), a purified preparation of BNP, is a vasodilator that reduces pulmonary capillary wedge pressure in pts with acutely decompensated CHF, but has neutral effects on mortality or sense of dyspnea. It should be considered only in pts with refractory HF.
- IV inotropic agents (see Table 126-3) are administered to hospitalized pts for refractory symptoms or acute exacerbation of CHF to augment cardiac output, improve perfusion, and help relieve congestion. They are contraindicated in hypertrophic cardiomyopathy. *Dobutamine* augments cardiac output without significant peripheral vasoconstriction or tachycardia. *Milrinone* is a nonsympathetic positive inotrope and vasodilator that acts by inhibiting phosphodiesterase type 3.
- The initial approach to treatment of acute decompensated HF can rely on the pt's hemodynamic profile (Fig. 126-1) based on clinical examination and, if necessary, invasive hemodynamic monitoring:
 - *Profile A "Warm and dry"*: Symptoms due to conditions other than HF (e.g., acute ischemia). Treat underlying condition.
 - *Profile B "Warm and wet"*: Treat with diuretic and vasodilators.
 - *Profile C "Cold and wet"*: Treat with IV vasodilators and inotropic agents.
 - *Profile L "Cold and dry"*: If low filling pressure (PCW <12 mmHg) confirmed, proceed with trial of volume repletion.
- Consider implantable cardioverter defibrillator (ICD) prophylactically for chronic class II–III HF and LVEF <35%. Pts with LVEF <35%, refractory CHF (NYHA class III–IV), and prolonged QRS (especially left bundle branch with QRS ≥150 msec) are candidates for biventricular pacing (cardiac resynchronization therapy), often combined with an ICD. Pts with severe disease and very limited, short-term expected survival, and who meet stringent criteria, may be candidates for cardiac transplantation or prolonged-assisted mechanical circulation (see HPIM-20, Chap. 255, p. 1797).
- Pts with HFpEF are treated with salt restriction and diuretics, and attention to underlying causes (e.g., treatment of hypertension). Beta blockers and ACE inhibitors may be of benefit in blunting neurohormonal activation, but have not been shown to lower mortality in this population.

		Elevated LV filling pressures?	
		No	Yes
↓ CO? ↑ SVR?	No	Profile A “Warm and dry”	Profile B “Warm and wet”
	Yes	Profile L “Cold and dry”	Profile C “Cold and wet”

FIGURE 126-1 Hemodynamic profiles in pts with acute heart failure. CO, cardiac output; SVR, systemic vascular resistance. (Data from Grady KL et al: *Team management of patients with heart failure. Circulation* 102:2443, 2000.)

COR PULMONALE

RV enlargement and/or altered function resulting from primary lung disease; leads to RV hypertrophy and eventually to RV failure. Etiologies include:

- *Pulmonary parenchymal or airway disease* leading to hypoxemic vasoconstriction: e.g., chronic obstructive pulmonary disease (COPD), interstitial lung diseases, bronchiectasis, cystic fibrosis (**Chaps. 133** and **136**).
- *Diseases of the pulmonary vasculature*: e.g., recurrent pulmonary emboli, pulmonary arterial hypertension (PAH) (**Chap. 129**), vasculitis, sickle cell anemia.
- *Inadequate mechanical ventilation (chronic hypoventilation)*. Kyphoscoliosis, neuromuscular disorders, marked obesity, sleep apnea (**Chap. 140**).

■ SYMPTOMS

Depend on underlying disorder but include dyspnea, cough, fatigue, and sputum production (in parenchymal diseases).

■ PHYSICAL EXAMINATION

Tachypnea, RV impulse along left sternal border, loud P_2 , right-sided S_4 ; cyanosis, clubbing are late findings. If RV failure develops, elevated jugular venous pressure, hepatomegaly with ascites, pedal edema; murmur of tricuspid regurgitation is common.

■ LABORATORY ECG

Right axis deviation, RV hypertrophy, and RA enlargement (**Chap. 113**); tachyarrhythmias are common.

■ RADIOLOGIC STUDIES

CXR shows RV and pulmonary artery enlargement; if PAH present, tapering of the pulmonary artery branches. *Chest CT* identifies emphysema, interstitial lung disease, and acute pulmonary embolism; *V/Q nuclear scan* is more reliable for diagnosis of chronic thromboemboli. *Pulmonary function tests* and *ABGs* characterize intrinsic pulmonary disease.

■ ECHOCARDIOGRAM

RV hypertrophy; LV function typically normal. RV function can be quantitated by measuring tricuspid annular excursion during systole and Doppler velocity of the RV free wall. RV systolic pressure is estimated from Doppler measurement of tricuspid regurgitant velocity. If imaging is difficult because of air in distended lungs, RV volume and wall thickness can be evaluated by MR imaging.

■ RIGHT-HEART CATHETERIZATION

Confirms presence of pulmonary hypertension and can exclude left-HF as contributor.

TREATMENT

COR Pulmonale

Aimed at underlying pulmonary disease and may include bronchodilators, antibiotics, oxygen administration, and noninvasive mechanical ventilation. For pts with PAH, pulmonary vasodilator therapy may be beneficial to reduce RV afterload (Chap. 129). See Chap. 135 for treatment of pulmonary embolism.

If RV failure is present, treat as HF, instituting low-sodium diet and diuretics; digoxin is of uncertain benefit and must be administered cautiously (toxicity increased due to hypoxemia, hypercapnia, acidosis). Loop diuretics must also be used with care to prevent significant metabolic alkalosis that blunts respiratory drive.

127 Diseases of the Aorta



AORTIC ANEURYSM

Abnormal dilatation of the thoracic or abdominal aorta; in ascending aorta most commonly secondary to medial degeneration (e.g., familial, Marfan's syndrome, Loays-Dietz syndrome, Ehlers-Danlos syndrome type IV, bicuspid aortic valve); aneurysms of descending thoracic and abdominal aorta are primarily atherosclerotic. Rare causes of aneurysms are infections (syphilis, tuberculosis, mycotic), vasculitis (e.g., Takayasu's arteritis, giant cell arteritis), and spondyloarthropathies (e.g., rheumatoid arthritis).

■ HISTORY

May be clinically silent, but thoracic aortic aneurysms can result in deep, diffuse chest pain, dysphagia, hoarseness, hemoptysis, dry cough; abdominal aneurysms may result in abdominal or lower back pain or sense of abdominal pulsation.

■ PHYSICAL EXAMINATION

Abdominal aneurysms are often palpable, most commonly in periumbilical area. Pts with ascending thoracic aneurysms may show features of Marfan's syndrome (Chap. 406, HPIM-20).

■ LABORATORY

Suspect thoracic aneurysm by abnormal CXR (enlarged aortic silhouette) and confirm by *echocardiography*, *contrast CT*, or *MRI*. Confirm abdominal aneurysm by *abdominal plain film* (rim of calcification), *ultrasound*, *CT*, *MRI*, or *contrast aortography*. If clinically suspected, obtain serologic test for syphilis, especially if ascending thoracic aneurysm shows thin shell of calcification. Screening abdominal ultrasound to assess for abdominal aortic aneurysm (AAA) is recommended for men aged 65–75 who have ever smoked, for individuals with a history of a thoracic aortic aneurysm, and for first-degree relatives of pts with AAA.

TREATMENT

Aortic Aneurysm

Pharmacologic control of hypertension (**Chap. 119**) is essential, usually including a beta blocker for thoracic aortic aneurysms (losartan may have similar benefit in reducing rate of growth in pts with Marfan's syndrome). Surgical resection for symptoms, for large aneurysms (ascending thoracic aortic aneurysms ≥ 5.5 cm, descending thoracic aortic aneurysms >6.0 cm, or AAA ≥ 5.5 cm), for persistent pain despite bp control, or for evidence of rapid expansion (>0.5 cm/year). In pts with Marfan's syndrome thoracic aortic aneurysms >4 – 5 cm usually warrant repair. Less invasive endovascular repair is an option for some pts with descending thoracic or AAAs.

AORTIC DISSECTION (FIG. 127-1)

Potentially life-threatening condition in which disruption or aortic intima allows dissection of blood into vessel wall; may involve ascending aorta (type II), descending aorta (type III), or both (type I). More commonly used classification:

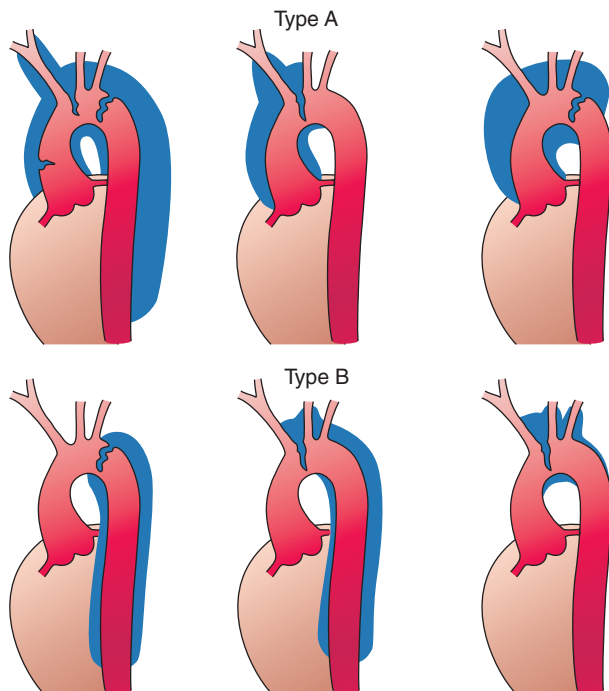


FIGURE 127-1 Classification of aortic dissections. Stanford classification: *Top panels* illustrate type A dissections that involve the ascending aorta independent of site of tear and distal extension; type B dissections (*bottom panels*) involve transverse and/or descending aorta without involvement of the ascending aorta. DeBakey classification: Type I dissection involves ascending to descending aorta (*top left*); type II dissection is limited to ascending or transverse aorta, without descending aorta (*top center + top right*); type III dissection involves descending aorta only (*bottom left*). (From DC Miller, in RM Doroghazi, EE Slater [eds]. *Aortic Dissection*. New York, McGraw-Hill, 1983, with permission.)

Type A—dissection involves ascending aorta; type B—limited to transverse and/or descending aorta. Involvement of the ascending aorta is most lethal form. Variant acute aortic syndromes include intramural hematoma without an intimal flap, and penetrating atherosclerotic ulcer.

■ ETIOLOGY

Conditions that predispose to medial degeneration or aortic wall stress, including hypertension, Marfan's, Loeys-Dietz and Ehlers-Danlos syndromes. Risk is increased in pts with coarctation of aorta, bicuspid aortic valve, inflammatory aortitis (Takayasu's arteritis, giant cell arteritis), and rarely in third trimester of pregnancy in otherwise normal women.

■ SYMPTOMS

Sudden onset of severe anterior or posterior chest pain, with "ripping" quality; maximal pain may travel if dissection propagates. Additional symptoms relate to obstruction of aortic branches (stroke, MI), dyspnea (acute aortic regurgitation), or symptoms of low cardiac output due to cardiac tamponade (dissection into pericardial sac).

■ PHYSICAL EXAMINATION

Sinus tachycardia common; if cardiac tamponade develops, hypotension, pulsus paradoxus, and pericardial rub appear. Asymmetry of carotid or brachial pulses, aortic regurgitation, and neurologic abnormalities associated with interruption of carotid artery flow are possible findings.

■ LABORATORY

CXR: Widening of mediastinum; dissection can be confirmed by CT, *transesophageal echocardiography*, or MRI. Aortography is rarely required, as sensitivity of these noninvasive techniques is >90%.

TREATMENT

Aortic Dissection

Reduce cardiac contractility and treat hypertension to maintain systolic bp between 100 and 120 mmHg using IV agents (Table 127-1), e.g., sodium nitroprusside accompanied by a beta blocker (e.g., IV metoprolol, labetalol, or esmolol, for target heart rate ~60 beats/min), followed by oral therapy. If beta blocker contraindicated, consider IV verapamil or diltiazem (see Table 127-1). Avoid direct vasodilators (e.g., hydralazine) because they may increase shear stress. Ascending aortic dissection (type A) requires surgical repair emergently or, if pt can be stabilized with medications, semielectively. Descending aortic dissections are stabilized medically (maintain systolic bp between 110 and 120 mmHg) with oral antihypertensive agents (esp. beta blockers); surgical (or endovascular) repair is not usually indicated unless continued pain or extension of dissection is observed (by serial MRI or CT performed every 6–12 months).

TABLE 127-1 Treatment of Aortic Dissection

PREFERRED REGIMEN	DOSE
Sodium nitroprusside	20–400 µg/min IV
<i>plus a beta blocker:</i>	
Propranolol or	0.5 mg IV; then 1 mg q5min, to total of 0.15 mg/kg
Esmolol or	500 µg/kg IV over 1 min; then 50–200 (µg/kg)/min
Labetalol	20 mg IV over 2 min, then 40–80 mg q10 min to max of 300 mg

OTHER ABNORMALITIES OF THE AORTA

■ ATHEROSCLEROTIC OCCLUSIVE DISEASE OF ABDOMINAL AORTA

Particularly common in presence of diabetes mellitus or cigarette smoking. Symptoms include intermittent claudication of the buttocks and thighs and impotence (Leriche syndrome); femoral and other distal pulses are absent. Diagnosis is established by noninvasive leg pressure measurements and Doppler velocity analysis, and confirmed by MRI, CT, or aortography. Catheter-based endovascular treatment or aortic-femoral bypass surgery is required for symptomatic treatment or in cases of critical limb ischemia.

■ TAKAYASU'S ("PULSELESS") DISEASE

Arteritis of aorta and major branches predominantly in young women. Anorexia, weight loss, fever, and night sweats occur. Localized symptoms relate to occlusion of aortic branches (cerebral ischemia, claudication, and loss of pulses in arms). ESR and C-reactive protein are increased; diagnosis confirmed by CT, MRI, or aortography. Glucocorticoid and immunosuppressive therapy may be beneficial.

128 Peripheral Vascular Disease



Occlusive or inflammatory disease that develops within the peripheral arteries, veins, or lymphatics. Pathologic contributors include atherosclerosis, thromboembolism, vasculitis, and fibromuscular dysplasia.

ARTERIOSCLEROSIS OF PERIPHERAL ARTERIES

■ HISTORY

Most common symptom is *intermittent claudication*, a muscular aching or cramping with exercise, quickly relieved by rest. Pain in buttocks and thighs suggests aortoiliac disease; calf muscle pain implies femoral or popliteal artery disease. More advanced arteriosclerotic obstruction results in pain at rest; painful ulcers of the feet (sometimes painless in diabetics) may result.

■ PHYSICAL EXAMINATION

Decreased peripheral pulses (ankle:brachial index usually <0.90 ; <0.5 indicates severe ischemia), blanching of affected limb with elevation, dependent rubor (redness). Ischemic ulcers or gangrene of toes may be present.

■ LABORATORY

Segmental pressure measurements and Doppler ultrasound of peripheral pulses before and immediately after exercise localizes stenoses; magnetic resonance angiography, computed tomographic angiography (CTA), or conventional arteriography is performed if mechanical revascularization (surgical or percutaneous) is planned.

TREATMENT

Arteriosclerosis

Most pts can be managed medically with daily exercise program, careful foot care (especially in diabetics), treatment of hypercholesterolemia, and local

debridement of ulcerations. Abstinence from cigarettes is mandatory. Antiplatelet and statin therapies are indicated to reduce future cardiovascular events. Some, but not all, pts note symptomatic improvement with drug therapy (cilostazol or pentoxifylline). Pts with severe claudication, rest pain, or gangrene are candidates for revascularization (arterial reconstructive surgery or percutaneous transluminal angioplasty/stent placement).

OTHER CONDITIONS THAT IMPAIR PERIPHERAL ARTERIAL FLOW

■ ARTERIAL EMBOLISM

Most common sources are thrombus or vegetation in the heart or aorta, or paradoxically from a venous thrombus through a right-to-left intracardiac shunt.

■ HISTORY

Sudden pain or numbness in an extremity in the absence of previous history of claudication.

■ PHYSICAL EXAMINATION

Absent pulse, pallor, and decreased temperature of limb distal to the occlusion. Diagnosis confirmed by CT, MR, or conventional angiography.

TREATMENT

Arterial Embolism

IV heparin is administered to prevent propagation of clot. For acute severe ischemia, immediate endovascular or surgical embolectomy is indicated. Thrombolytic therapy (e.g., tissue plasminogen activator, reteplase, or tenecteplase) may be effective for recent (<2 weeks) thrombus within atherosclerotic vessel or arterial bypass graft.

■ ATHEROEMBOLISM

A subset of acute arterial occlusion due to embolization of fibrin, platelets, and cholesterol debris from more proximal atheromas or aneurysm; typically occurs after intraarterial instrumentation. Depending on location, may lead to stroke, renal insufficiency, or pain and tenderness in embolized tissue. Atheroembolism to lower extremities results in blue toe syndrome, which can progress to necrosis and gangrene. Treatment is supportive; for recurrent episodes, surgical intervention in the proximal atherosclerotic vessel or aneurysm may be required.

■ THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE)

Typically occurs in men age <40 who are heavy smokers and involves both upper and lower extremities; non-atheromatous inflammatory reaction develops in veins and small arteries, leading to superficial thrombophlebitis and arterial obstruction with ulceration or gangrene of digits. Imaging with CT, MR, or conventional angiography shows smooth tapering lesions in distal vessels, often without proximal atherosclerotic disease. Abstinence from tobacco is essential.

■ VASOSPASTIC DISORDERS

Manifest by Raynaud's phenomenon in which cold exposure results in triphasic color response: blanching of the fingers, followed by cyanosis, then rubor. Most often a benign disorder. However, suspect an underlying disease ([Table 128-1](#)) if tissue necrosis occurs, if disease is unilateral, or if it develops after age 50.

TABLE 128-1 Classification of Raynaud's Phenomenon**Primary or idiopathic Raynaud's phenomenon: Raynaud's disease**

Secondary Raynaud's phenomenon

Collagen vascular diseases: scleroderma, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, polymyositis, Sjögren's syndrome

Arterial occlusive diseases: atherosclerosis of the extremities, thromboangitis obliterans, acute arterial occlusion, thoracic outlet syndrome

Pulmonary hypertension

Neurologic disorders: intervertebral disk disease, syringomyelia, spinal cord tumors, stroke, poliomyelitis, carpal tunnel syndrome

Blood dyscrasias: cold agglutinins, cryoglobulinemia, cryofibrinogenemia, myeloproliferative disorders, lymphoplasmacytic lymphoma

Trauma: vibration injury, hammer hand syndrome, electric shock, cold injury, typing, piano playing

Drugs: ergot derivatives, methysergide, β -adrenergic receptor blockers, bleomycin, vinblastine, cisplatin, gemcitabine

TREATMENT**Vasospastic Disorders**

Keep extremities warm. Tobacco use is contraindicated. Dihydropyridine calcium channel blockers (e.g., nifedipine XL 30–90 mg PO qd) or α_1 -adrenergic antagonists (e.g., prazosin 1–5 mg tid) may be effective. Phosphodiesterase type 5 inhibitors (e.g., sildenafil, tadalafil, vardenafil) may improve symptoms in secondary Raynaud's phenomenon.

VENOUS DISEASE**■ SUPERFICIAL THROMBOPHLEBITIS**

A benign disorder characterized by erythema, tenderness, and edema along involved vein. Conservative therapy includes local heat, elevation, and anti-inflammatory drugs such as aspirin. More serious conditions such as cellulitis or lymphangitis may present similarly, but these are associated with fever, chills, lymphadenopathy, and red superficial streaks along inflamed lymphatic channels.

■ DEEP-VEIN THROMBOSIS (DVT)

More serious condition that may lead to pulmonary embolism as described in [Chap. 135](#).

■ CHRONIC VENOUS INSUFFICIENCY

Results from prior DVT or venous valvular incompetence and manifests as chronic dull ache in leg that worsens with prolonged standing, edema, and superficial varicosities. May lead to erythema, hyperpigmentation, and recurrent cellulitis; ulcers may appear at medial and lateral malleoli. Treatment includes graduated compression stockings and leg elevation. Associated varicose veins can be treated with endovenous thermal ablation, sclerotherapy or surgery.

LYMPHEDEMA

Chronic, painless edema, usually of the lower extremities; may be primary (inherited) or secondary to lymphatic damage or obstruction (e.g., recurrent lymphangitis, tumor, after surgical excision or irradiation of regional lymph nodes, filariasis).

PHYSICAL EXAMINATION

Marked pitting edema in early stages; limb becomes indurated with *non*pitting edema chronically. Differentiate from chronic *venous* insufficiency, which displays hyperpigmentation, stasis dermatitis, and superficial venous varicosities.

LABORATORY

Abdominal and pelvic ultrasound or CT or MRI to identify obstructing lesions. Lymphangiography or lymphoscintigraphy (rarely done) can confirm diagnosis. If *unilateral* edema, differentiate from DVT by noninvasive venous studies (earlier).

TREATMENT**Lymphedema**

(1) Meticulous foot hygiene to prevent infection, (2) leg elevation, (3) compression stockings, and/or pneumatic compression boots. Diuretics should be *avoided* to prevent intravascular volume depletion.

129**Pulmonary Hypertension****DEFINITION**

Elevation of pulmonary artery (PA) pressure (i.e., mean PA pressure >22 mmHg) due to pulmonary vascular or parenchymal disease, increased left heart filling pressures, or a combination. [Table 129-1](#) lists etiologies of pulmonary hypertension (PH) by categories.

SYMPTOMS

Exertional dyspnea, fatigue, angina (due to RV ischemia), syncope, peripheral edema.

PHYSICAL EXAMINATION

Jugular venous distention, RV lift, increased P₂, right-sided S₃ or S₄, tricuspid regurgitation. Peripheral cyanosis and edema are late manifestations.

LABORATORY FINDINGS

CXR shows enlarged central PA; may demonstrate vascular “pruning.” ECG typically indicates RV hypertrophy and RA enlargement. *Echocardiogram* shows RV and RA enlargement, RV hypertrophy; RV systolic pressure can be estimated from Doppler velocity of tricuspid regurgitation; echo “bubble study” identifies right-to-left intracardiac shunts that can cause Group 1 PH. *Pulmonary function tests (PFTs)* identify underlying obstructive or restrictive lung disease; impaired CO diffusion capacity is common. *Chest CT* identifies contributing interstitial lung disease or pulmonary thromboembolic disease (note that ventilation-perfusion [V/Q] scan is more sensitive for detection of chronic thromboembolism as cause of Group 4 PH). *ANA titer*, rheumatoid factor, anti-Scl-70 antibodies are elevated in specific collagen vascular conditions that can result in PH. *HIV testing* should be performed in individuals at risk. *Cardiopulmonary exercise testing* can differentiate pulmonary from cardiac contributions to dyspnea. *Right heart catheterization* assesses PA pressures, cardiac output, and pulmonary vascular resistance, quantifies underlying congenital vascular shunts, and

TABLE 129-1 Classification of Pulmonary Hypertension**1. Pulmonary Arterial Hypertension**

- Idiopathic
- Heritable (mutations/familial cases)
- Collagen vascular diseases (e.g., scleroderma, SLE, rheumatoid arthritis)
- Congenital systemic to pulmonary shunts (e.g., ventricular septal defect, patent ductus arteriosus, atrial septal defect)
- Portal hypertension
- HIV infection
- Drugs or toxins (e.g., fenfluramine)

2. Pulmonary Hypertension Due to Left Heart Disease

- LV systolic or diastolic dysfunction
- Left-sided valvular disease

3. Pulmonary Hypertension Due to Lung Disease or Hypoxia

- Chronic obstructive lung disease
- Interstitial lung disease
- Sleep-disordered breathing
- Chronic hypoventilation

4. Chronic Pulmonary Thromboembolic Disease

- Chronic pulmonary embolism

5. Miscellaneous

- Systemic conditions (e.g., sarcoidosis, pulmonary histiocytosis)
- Hematologic conditions (e.g., myeloproliferative diseases)

distinguishes left-sided heart disease from pulmonary causes of PH; during procedure, response to short-acting vasodilators can be tested. Serum brain natriuretic peptide (BNP) and NT-proBNP elevation correlate with RV dysfunction and hemodynamic severity of PH.

Figure 129-1 summarizes a testing approach for pts with unexplained PH.

PULMONARY ARTERIAL HYPERTENSION (PAH)

Represents Group 1 PH (Table 129-1), an uncommon but very serious form of PH, for which advanced pharmacologic therapies are available. Most pts with idiopathic PAH present in fourth and fifth decades, female > male predominance; may be familial. Major symptom is dyspnea, often with insidious onset. *Right heart catheterization* demonstrates a mean pulmonary artery pressure ≥ 25 mmHg, pulmonary vascular resistance >240 dyne-s/cm⁵, with a mean pulmonary capillary wedge pressure ≤ 15 mmHg. Mean survival of PAH is 5–6 years, even with therapy.

TREATMENT**Pulmonary Arterial Hypertension**

Limit physical activities, use diuretics for peripheral edema, O₂ supplementation if PO₂ reduced.

If short-acting vasodilators are beneficial during right heart catheterization, pt may benefit from high-dose *calcium channel blocker* (e.g., nifedipine, up to 240 mg/d, or amlodipine up to 20 mg/d); monitor for hypotension or worsening of right heart failure during such therapy.

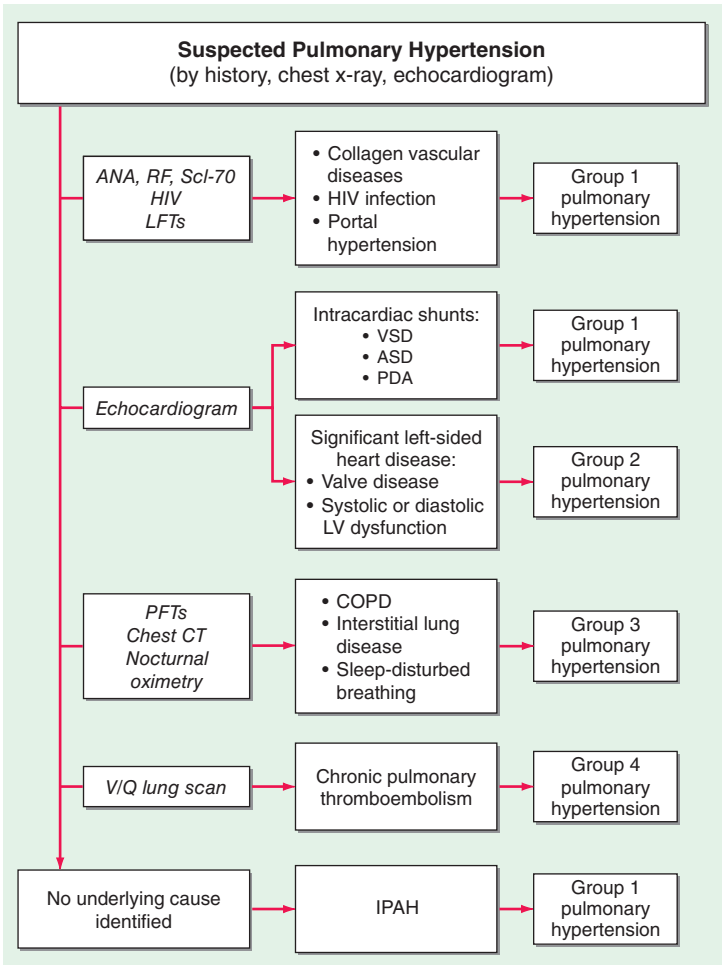


FIGURE 129-1 An algorithm to assess for causes of pulmonary hypertension. In the absence of an identifiable etiology, idiopathic pulmonary arterial hypertension would be suspected. ASD, atrial septal defect; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IPAH, idiopathic pulmonary arterial hypertension; PDA, patent ductus arteriosus; PFTs, pulmonary function tests; RF, rheumatoid factor; Scl-70, anti-topoisomerase 1 antibodies; V/Q, ventilation/perfusion; VSD, ventricular septal defect.

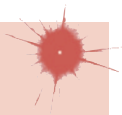
Additional approved therapies for PAH include:

1. Endothelin receptor antagonists: *bosentan* (62.5 mg PO bid × 1 month, then 125 mg PO bid), *macitentan* (10 mg once daily) and *ambrisentan* (5–10 mg daily) significantly improve pulmonary vascular resistance and exercise tolerance.
2. Phosphodiesterase type 5 inhibitors: *sildenafil* (20–80 mg PO tid) and *tadalafil* (40 mg daily) also improve exercise tolerance in PAH. Do not prescribe concurrently with nitrates; the combination could result in marked hypotension.

3. Prostaglandins (*iloprost* by inhalation, *epoprostenol* by continuous IV infusion, and *treprostinil* by IV, SC, or inhalation routes) improve symptoms, exercise tolerance, and, in the case of *epoprostenol*, survival. The most common side effect is flushing.
4. The oral soluble guanylyl cyclase stimulator *riociguat* has been shown to improve exertional capacity in pts with PAH.
5. The oral prostaglandin I₂ receptor *selexipag* reduces the frequency of hospitalization and disease progression in pts being treated with an endothelin receptor antagonist, *sildenafil*, or both.

For selected pts with persistent right heart failure, lung transplantation may be considered.

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Diagnostic Procedures in
Respiratory Disease

Diagnostic modalities for assessing respiratory diseases include imaging studies and techniques for acquiring biological specimens.

IMAGING STUDIES**■ RADIOGRAPHIC STUDIES**

The chest x-ray (CXR), generally including both posteroanterior and lateral views, is often the first diagnostic study in pts presenting with respiratory symptoms. With some exceptions (e.g., pneumothorax), the CXR pattern is usually not sufficiently specific to *establish* a diagnosis; instead, the CXR serves to *detect* disease, assess magnitude, and guide further diagnostic investigation. With diffuse lung disease, CXR can detect an alveolar, interstitial, or nodular pattern. CXR can also detect pleural effusion and pneumothorax, as well as abnormalities in the hila and mediastinum. Lateral decubitus views can be used to estimate the size of freely flowing pleural effusions.

Chest computed tomography (CT), typically performed with helical scanning and multiple detectors, is widely used to clarify radiographic abnormalities detected by CXR. Advantages of chest CT compared with CXR include (1) ability to distinguish superimposed structures due to cross-sectional imaging; (2) superior assessment of tissue density, permitting accurate assessment of the size and density of pulmonary nodules and improved identification of abnormalities adjacent to the chest wall, such as pleural disease; (3) with the use of IV contrast, ability to distinguish vascular from nonvascular structures, which is especially useful in assessing hilar and mediastinal abnormalities (including staging of lung cancer); (4) with CT angiography, ability to detect pulmonary emboli; and (5) due to superior visible detail, improved recognition of parenchymal and airway diseases, including emphysema, bronchiectasis, lymphangitic carcinoma, and interstitial lung disease. In the appropriate clinical context, idiopathic pulmonary fibrosis can be reliably diagnosed based on chest CT. Low dose chest CT is recommended for lung cancer screening among pts aged 55–80 with at least a 30 pack-year smoking history, who have smoked in the past 15 years. With appropriate data reanalysis, chest CT scans can provide a three-dimensional reconstruction of the airways down to at least the sixth generation, providing a virtual bronchoscopy. Virtual bronchoscopies may be helpful in assessing stenotic airways and in planning therapeutic bronchoscopy procedures.

■ ULTRASOUND (US)

Diagnostic US is not useful for assessing the pulmonary parenchyma, but it can detect and localize pleural abnormalities and guide thoracentesis of a pleural effusion. As a nonionizing imaging approach, it is safe to perform on pregnant women and children. Real-time US imaging can assess diaphragmatic mobility. Portable US is useful to monitor resolution of pneumothorax and pleural effusion.

■ NUCLEAR MEDICINE IMAGING

Ventilation-perfusion lung scans can be used to assess for pulmonary thromboembolism but have largely been replaced by CT angiography. Positron emission tomographic (PET) scanning assesses the uptake and metabolism

of a radiolabeled glucose analogue. Because malignant lesions usually have increased metabolic activity, PET scanning, especially when combined with CT images in PET/CT, is useful to assess pulmonary nodules for potential malignancy and to stage lung cancer. PET studies are limited in assessing lesions <1 cm in diameter; false-negative screening for malignancy can result from lesions with low metabolic activity, such as carcinoid tumors or bronchioloalveolar cell carcinoma. False-positive PET signals can be observed in inflammatory conditions such as pneumonia.

■ OTHER IMAGING TECHNIQUES

A variety of other imaging techniques are used less commonly to assess respiratory disease. Magnetic resonance imaging (MRI) is generally less useful than CT for evaluation of the respiratory system but can be helpful to assist in the evaluation of intrathoracic cardiovascular pathology without radiation exposure and to distinguish vascular and nonvascular structures without IV contrast. MRI can also distinguish tumor from post-stenotic atelectasis and assess tumor infiltration of the chest wall or mediastinum. However, the presence of metallic foreign bodies, pacemakers, and intracranial aneurysm clips preclude the use of MRI. Pulmonary angiography can assess the pulmonary arterial system for venous thromboembolism but has largely been replaced by CT angiography.

PROCEDURES TO OBTAIN BIOSPECIMENS

■ BLOOD SAMPLES

Blood samples are useful for testing biomarkers of systemic illnesses, such as autoantibodies. Alpha-1 antitrypsin deficiency, which is a genetic syndrome associated with COPD and liver disease, can be detected through protein levels, protein phenotype, and genotype assessed in blood samples. Blood sources of DNA can also be used for other types of genetic testing.

■ SPUTUM EXAMINATION

Sputum can be obtained by spontaneous expectoration or induced by inhalation of an irritating aerosol-like hypertonic saline. Sputum is distinguished from saliva by the presence of alveolar macrophages and other inflammatory cells as opposed to squamous epithelial cells. Sputum examination should include gross inspection for blood and color, as well as Gram's stain and routine bacterial culture. Bacterial culture of expectorated sputum may be misleading due to contamination with oropharyngeal flora. Sputum samples can also be assessed for a variety of other pathogens, including mycobacteria, fungi, and viruses. Sputum samples induced by hypertonic saline can be stained for the presence of *Pneumocystis jirovecii*. Cytologic examination of sputum samples can be used as an initial screen for malignancy.

■ BRONCHOSCOPY

Bronchoscopy is a procedure that provides direct visualization of the tracheobronchial tree, typically to the subsegmental level. The fiberoptic bronchoscope is used in most cases, but rigid bronchoscopy is valuable in specific circumstances, including massive hemorrhage and foreign body removal. Flexible fiberoptic bronchoscopy allows visualization of the airways; identification of endobronchial abnormalities, including tumors and sites of bleeding; and collection of diagnostic specimens by washing, brushing, biopsy, or lavage. Washing involves instilling sterile saline through the bronchoscope channel onto the surface of a lesion; part of the saline is suctioned back through the bronchoscope and processed for cytology and microorganisms. Bronchial brushings can be obtained from the surface of an endobronchial lesion or from a more distal mass

or infiltrate (potentially with fluoroscopic guidance) for cytologic and microbiologic studies. Biopsy forceps can be used to obtain biopsies of endobronchial lesions or passed into peribronchial alveolar tissue (often with fluoroscopic guidance) to obtain transbronchial biopsies of more distal lung tissue. Transbronchial biopsy is particularly useful in diagnosing diffuse infectious processes, lymphangitic spread of cancer, and granulomatous diseases. Complications of transbronchial biopsy include hemorrhage and pneumothorax.

Bronchoalveolar lavage (BAL) is an adjunct to fiberoptic bronchoscopy, permitting collection of cells and fluid from distal air spaces. After wedging the bronchoscope in a subsegmental airway, saline is instilled and then suctioned back through the bronchoscope for analyses, which can include cytology, microbiology, and cell counts. BAL is especially useful in the diagnosis of *P. jirovecii* pneumonia and some other infections. Immunofluorescent staining with antibodies of nucleic acid analysis with PCR can facilitate rapid diagnosis of some infections.

Additional bronchoscopic approaches to obtain tissue samples from locations adjacent to the trachea or large bronchi for cytologic assessment of malignancy include transbronchial needle aspiration (TBNA). TBNA can be supplemented with endobronchial US (EBUS), which can allow guided aspiration of hilar and mediastinal lymph nodes based on real-time US images. Radial probe EBUS has improved the bronchoscopic diagnostic yield for peripheral pulmonary nodules.

■ PERCUTANEOUS NEEDLE ASPIRATION OF THE LUNG

A needle can be inserted through the chest wall and into a pulmonary lesion to aspirate material for cytologic and microbiologic studies. Percutaneous needle aspiration is usually performed under CT or US guidance. Owing to the small size of the sample obtained, sampling error is a limitation of the procedure.

■ THORACENTESIS

Thoracentesis should be performed as an early step in the evaluation of a pleural effusion of uncertain etiology. Analysis of pleural fluid can determine the etiology of the effusion ([Chap. 137](#)). Large-volume thoracentesis can be therapeutic by palliating dyspnea.

■ MEDIASTINOSCOPY

Tissue biopsy of mediastinal masses or lymph nodes is often required for cancer diagnosis and staging. Mediastinoscopy is performed from a suprasternal approach, and a rigid mediastinoscope is inserted—from which biopsies can be obtained. Lymph nodes in the aortopulmonary location typically require a parasternal mediastinotomy to provide access for biopsy.

■ MEDICAL THORACOSCOPY

Medical thoracoscopy, also known as pleuroscopy, focuses on pleural-based diseases. Medical thoracoscopy is commonly used to evaluate pleural effusions or to obtain biopsies from the parietal pleura. General anesthesia is typically not required.

■ VIDEO-ASSISTED THORACIC SURGERY (VATS)

VATS, also known as thoracoscopy, is widely used for the diagnosis of pleural lesions as well as peripheral parenchymal infiltrates and nodules. VATS, which requires that the pt tolerate single-lung ventilation during the procedure, involves passing a rigid scope with a camera through a trocar and into the pleural space; instruments can be inserted and manipulated through separate intercostal incisions. VATS has largely replaced “open biopsy,” which requires a thoracotomy.

131 Asthma



■ DEFINITION AND EPIDEMIOLOGY

Asthma is a syndrome characterized by airflow obstruction that varies both spontaneously and with specific treatment. Chronic airway inflammation causes airway hyperresponsiveness to a variety of triggers, leading to airflow obstruction and respiratory symptoms including dyspnea and wheezing. Although asthmatics typically have periods of normal lung function with intermittent airflow obstruction, a subset of pts develop chronic airflow obstruction.

The prevalence of asthma has increased markedly over the past 30 years. In developed countries, approximately 10% of adults and 15% of children have asthma. The majority of asthmatics have childhood-onset disease. Most asthmatics have atopy, and they often have atopic dermatitis (eczema) and/or allergic rhinitis. A minority of asthmatic pts do not have atopy (negative skin prick tests to common allergens and normal serum total IgE levels). These individuals, occasionally referred to as *intrinsic asthmatics*, often have adult-onset disease. Occupational asthma can result from a variety of chemicals, including toluene diisocyanate and trimellitic anhydride, and often has onset in adulthood.

Asthmatics can develop increased airflow obstruction and respiratory symptoms in response to a variety of different triggers. Inhaled allergens can be potent asthma triggers for individuals with specific sensitivity to those agents. Viral upper respiratory infections (URIs) commonly trigger asthma exacerbations. β -Adrenergic blocking medications can markedly worsen asthma symptoms and should typically be avoided in asthmatics. Exercise often triggers increased asthma symptoms, which usually begin after exercise has ended. Other triggers of increased asthma symptoms include air pollution, cold air, occupational exposures, and stress.

■ CLINICAL EVALUATION OF THE PT HISTORY

Common respiratory symptoms in asthma include wheezing, dyspnea, and cough. These symptoms often vary widely within a particular individual, and they can change spontaneously or with age, season of the year, and treatment. Symptoms may be worse at night, and nocturnal awakenings are an indicator of inadequate asthma control. The severity of a pt's asthmatic symptoms, as well as the pt's previous need for systemic steroid treatment, hospitalization, and intensive care treatment, are important to ascertain. Types of asthmatic triggers for the particular pt, and their recent exposure to them, should be determined. Approximately 1–5% of asthmatics have sensitivity to aspirin and other cyclooxygenase inhibitors; they typically are nonatopic and have nasal polyps. Cigarette smoking leads to more hospital admissions and more rapid decline in lung function in asthmatics; smoking cessation is essential.

■ PHYSICAL EXAMINATION

It is important to assess for signs of respiratory distress, including tachypnea, use of accessory respiratory muscles, and cyanosis. On lung examination, there may be wheezing and rhonchi throughout the chest, typically more prominent in expiration than inspiration. Localized wheezing may indicate an endobronchial lesion. Evidence of allergic nasal, sinus, or skin disease should be assessed. When asthma is adequately controlled, the physical examination may be normal.

■ PULMONARY FUNCTION TESTS

Spirometry often shows airflow obstruction, with a reduction in forced expiratory volume in 1 s (FEV_1) and FEV_1 /forced vital capacity (FVC) ratio. However,

spirometry may be normal, especially if asthma symptoms are adequately treated. Bronchodilator reversibility is demonstrated by an increase in FEV₁ by ≥ 200 mL and $\geq 12\%$ from baseline FEV₁ 15 min after a short-acting β agonist (often albuterol metered-dose inhaler two puffs or 180 μg). Many but not all asthmatics will demonstrate significant bronchodilator reversibility; optimal pharmacologic treatment may reduce bronchodilator reversibility. Airway hyperresponsiveness is characteristic of asthma; it can be assessed by exposure to direct bronchoconstrictors such as methacholine or histamine. Greater airway responsiveness is associated with increased asthmatic symptoms. The peak expiratory flow rate (PEFR) can be used by the pt to track asthma control objectively at home. Measurement of lung volumes is not typically performed, but increases in total lung capacity and residual volume may be observed. The diffusing capacity for carbon monoxide is usually normal.

■ OTHER LABORATORY TESTS

Blood tests are usually not helpful. Specific IgE measurements for inhaled allergens (radioallergosorbent test [RAST]) or allergy skin testing may assist in determining allergic triggers. Total serum IgE is markedly elevated in bronchopulmonary aspergillosis (BPA). Exhaled nitric oxide levels can provide an assessment of eosinophilic airway inflammation.

■ RADIOGRAPHIC FINDINGS

Chest x-ray is usually normal. In acute exacerbations, pneumothorax may be identified. In BPA, eosinophilic pulmonary infiltrates may be observed. Chest CT scan is not typically performed in routine asthma but may show central bronchiectasis in BPA.

■ DIFFERENTIAL DIAGNOSIS

The differential diagnosis of asthma includes other disorders that can cause wheezing and dyspnea. Upper airway obstruction by tumor or laryngeal edema can mimic asthma, but stridor in the large airways is typically noted on physical examination. Localized wheezing in the chest may indicate an endobronchial tumor or foreign body. Congestive heart failure can cause wheezing but is typically accompanied by bibasilar crackles. Eosinophilic pneumonias and Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis) may present with wheezing. Vocal cord dysfunction can mimic severe asthma and may require direct laryngoscopy to assess. When asthma involves chronic air-flow obstruction, distinguishing it from chronic obstructive pulmonary disease (COPD) can be very difficult, and some pts have both asthma and COPD (asthma-COPD overlap syndrome).

TREATMENT

Chronic Asthma

If a specific inciting agent for asthmatic symptoms can be identified and eliminated, that is an optimal part of treatment. In most cases, pharmacologic therapy is required. The two major classes of drugs are bronchodilators, which provide rapid symptomatic relief by relaxing airway smooth muscle, and controllers, which limit airway inflammation.

BRONCHODILATORS

The most widely used class of bronchodilators is β_2 -adrenergic agonists, which relax airway smooth muscle by activating β_2 -adrenergic receptors. Two types of inhaled β_2 agonists are widely used in asthma treatment: short-acting β_2 agonists (SABAs) and long-acting β_2 agonists (LABAs). SABAs, which include albuterol,

have rapid onset of action and last for up to 6 h. SABAs are effective rescue medications, but excessive use indicates inadequate asthma control. SABAs can prevent exercise-induced asthma if administered before exercise. LABAs, which include salmeterol and formoterol, have a slower onset of action but last for >12 h. LABAs have replaced regularly scheduled use of SABAs, but they do not control airway inflammation and should not be used without inhaled corticosteroid (ICS) therapy. Combinations of LABAs with ICS reduce asthma exacerbations and provide an excellent long-term treatment option for asthma severity of moderate persistent degree or greater.

Common side effects of β_2 -adrenergic agonists include muscle tremors and palpitations. These side effects are more prominent with oral formulations, which should not generally be used. There have been ongoing concerns about mortality risks associated with β_2 -adrenergic agonists, which have not been completely resolved. LABAs taken without concomitant inhaled steroid treatment may increase this risk.

Other available bronchodilator medications include anticholinergics and theophylline. Anticholinergics, which are available in short-acting and long-acting inhaled formulations, are commonly used in COPD. They appear to be less effective than β_2 -adrenergic agonists in asthma, and they are typically considered as an additional treatment option only if other asthma medications do not provide adequate asthma control. Theophylline may have both bronchodilator and anti-inflammatory effects; it is not widely used due to the potential toxicities associated with high plasma levels. Low doses of theophylline may have additive effects with ICS at levels below the standard therapeutic range, and this can be a useful treatment option for severe asthma.

CONTROLLER THERAPIES

ICSs are the most effective controller treatments for asthma. ICSs are usually given twice daily; a variety of ICS medications are available. Although they do not provide immediate symptom relief, respiratory symptoms and lung function often begin to improve within several days of initiating treatment. ICS reduces exercise-induced symptoms, nocturnal symptoms, and acute exacerbations. ICS treatment typically leads to reductions in airway hyperresponsiveness.

ICS side effects include hoarseness and oral candidiasis; these effects may be minimized by use of a spacer device and by rinsing out the mouth after taking ICS.

Other available controller therapies for asthma include systemic corticosteroids. Although quite helpful in the management of acute asthma exacerbations, systemic steroid use should be avoided if at all possible in the chronic management of asthma due to multiple potential side effects. Antileukotrienes, such as montelukast, may be quite beneficial in some pts. Cromolyn sodium and nedocromil sodium are not widely used due to their brief durations of action and typically modest effects. Omalizumab is a blocking antibody that neutralizes IgE; with SC injection every 2–4 weeks, it appears to reduce acute asthma exacerbation frequency in severe asthmatics. However, it is expensive and considered only for highly selected pts with elevated total serum IgE levels and refractory asthma symptoms despite maximal inhaled bronchodilator and ICS therapy. Antibodies that block IL-5 (mepolizumab, reslizumab) or its receptor (benralizumab) markedly reduce blood and tissue eosinophils and reduce exacerbations in pts who have persistently increased sputum eosinophils despite maximal ICS therapy.

OVERALL TREATMENT APPROACH

In addition to limiting exposure to their environmental triggers for asthma, pts should receive stepwise therapy appropriate for their disease severity

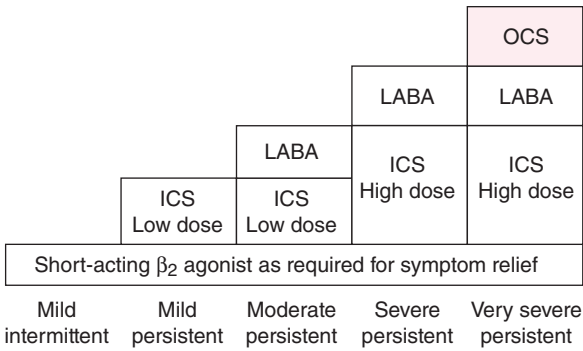


FIGURE 131-1 Stepwise approach to asthma therapy according to the severity of asthma and ability to control symptoms. ICS, inhaled corticosteroid; LABA, long-acting β_2 agonists; OCS, oral corticosteroid.

(Fig. 131-1). Asthmatics with mild intermittent symptoms are typically managed adequately with SABAs taken on an as-needed basis. Use of SABAs more than two times a week suggests that controller therapy, typically with an ICS twice per day, is required. If symptoms are not adequately controlled with ICS, LABAs can be added. If symptoms are still not adequately controlled, higher doses of ICS and/or alternative controller therapies should be considered. In highly selected pts not controlled by other therapies, bronchial thermoplasty may be considered.

ASTHMA EXACERBATIONS

■ CLINICAL FEATURES

Asthma exacerbations are periods of acute worsening of asthma symptoms that may be life-threatening. Exacerbations are commonly triggered by viral URIs, but other triggers also can be involved. Symptoms often include increased dyspnea, wheezing, and chest tightness. Physical examination can reveal tachypnea, tachycardia, and lung hyperinflation. Pulmonary function testing reveals a reduction in FEV₁ and PEF. Hypoxemia can result; Pco₂ is usually reduced due to hyperventilation. Normal or rising Pco₂ can signal impending respiratory failure.

TREATMENT

Asthma Exacerbations

The mainstays of asthma exacerbation treatment are high doses of SABAs and systemic corticosteroids. SABAs may be administered by nebulizer or metered-dose inhaler with a spacer; very frequent dosing (q1h or more often) may be required initially. Inhaled anticholinergic bronchodilator medication can be added to the SABAs. IV corticosteroids, such as methylprednisolone (e.g., 80 mg IV q8h), may be used, although oral corticosteroids (e.g., prednisone 30–45 mg once daily for 5–10 days) also may be used. Supplemental oxygen should be provided to maintain adequate oxygen saturation (>90%). If respiratory failure occurs, mechanical ventilation should be instituted, with care to minimize airway pressures and auto-PEEP. Because bacterial infections rarely trigger asthma

exacerbations, antibiotics are not routinely administered unless there are signs of pneumonia.

In an effort to treat asthma exacerbations before they become severe, asthma pts should receive written action plans with instructions for self-initiation of treatment based on respiratory symptoms and reductions in PEF.

132 Environmental Lung Diseases



The susceptibility to develop many pulmonary diseases is influenced by environmental factors. This chapter will focus on occupational and toxic chemical exposures. However, a variety of nonoccupational indoor exposures such as environmental tobacco smoke exposure (lung cancer), radon gas (lung cancer), and biomass fuel cooking (chronic obstructive pulmonary disease [COPD]) also should be considered. Particle size is an important determinant of the impact of inhaled environmental exposures on the respiratory system. Particles $>10\ \mu\text{m}$ in diameter typically are captured by the upper airway. Particles $2.5\text{--}10\ \mu\text{m}$ in diameter will likely deposit in the upper tracheobronchial tree, while smaller particles (including nanoparticles) will reach the alveoli. Water-soluble gases like ammonia are absorbed in the upper airways and produce irritative and bronchoconstrictive responses, while less water-soluble gases (e.g., phosgene) may reach the alveoli and cause a life-threatening acute chemical pneumonitis.

APPROACH TO THE PATIENT

Environmental Lung Diseases

Because there are many types of occupational lung disease (pneumoconiosis) that can mimic diseases not known to relate to environmental factors, obtaining a careful occupational history is essential. In addition to the types of occupation performed by the pt, the specific environmental exposures, use of protective respiratory devices, and ventilation of the work environment can provide key information. Assessing the temporal development of symptoms relative to the pt's work schedule also can be very useful.

The physical examination may indicate the type and severity of lung disease, but usually does not assist in identifying a specific environmental etiology. Pulmonary function tests should be used to assess the severity of impairment, but they typically do not suggest a specific diagnosis. Changes in spirometry before and after a work shift can provide strong evidence for bronchoconstriction in suspected occupational asthma. Chest x-ray is helpful in the assessment of environmental lung disease, but it may over- or underestimate the functional impact of pneumoconioses. Some chest x-ray patterns are distinctive for certain occupational lung diseases; chest CT scans can provide a more detailed evaluation. Specific laboratory tests can be invaluable for diagnosing certain environmental lung diseases, such as evaluation of urinary heavy metal concentrations to assess cadmium in battery plant workers.

OCCUPATIONAL EXPOSURES AND PULMONARY DISEASE

■ INORGANIC DUSTS

Asbestos-Related Diseases

In addition to exposures to asbestos that may occur during the production of asbestos products (from mining to manufacturing), common occupational asbestos exposures occur in shipbuilding and other construction trades (e.g., pipe-fitting, boilermaking) and in the manufacture of safety garments and friction materials (e.g., brake and clutch linings). Along with worker exposure in these areas, bystander exposure (e.g., spouses) can be responsible for some asbestos-related lung diseases.

A range of respiratory diseases has been associated with asbestos exposure. Pleural plaques indicate that asbestos exposure has occurred, but they are typically not symptomatic. Interstitial lung disease, often referred to as asbestosis, is pathologically and radiologically similar to idiopathic pulmonary fibrosis; it is typically accompanied by a restrictive ventilatory defect with reduced diffusing capacity of the lung for carbon monoxide (DLCO) on pulmonary function testing. Asbestosis, which is directly related to the intensity and duration of exposure, usually develops at least 10 years after exposure, and no specific therapy is available.

Benign pleural effusions can also occur from asbestos exposure. Lung cancer is clearly associated with asbestos exposure but does not typically present for at least 15 years after initial exposure. The lung cancer risk increases multiplicatively with cigarette smoking. In addition, mesotheliomas (both pleural and peritoneal) are strongly associated with asbestos exposure, but they are not related to smoking. Relatively brief asbestos exposures may lead to mesotheliomas, which typically do not develop for decades after the initial exposure. Biopsy of pleural tissue, typically by thoracoscopic surgery, is required for diagnosing mesothelioma.

Silicosis

Silicosis results from exposure to free silica (crystalline quartz), which occurs in mining, stone cutting, sand blasting, abrasive industries (e.g., glass and cement manufacturing), foundry work, and quarrying. Heavy exposures over relatively brief time periods (as little as 10 months) can cause acute silicosis—which is pathologically similar to pulmonary alveolar proteinosis and associated with a characteristic chest CT pattern known as “crazy paving.” Acute silicosis can be severe and progressive; whole lung lavage may be of some therapeutic benefit.

Longer-term exposures can result in simple silicosis, with small rounded opacities in the upper lobes of the lungs. Calcification of hilar lymph nodes can give a characteristic “eggshell” appearance on radiographic studies. Progressive nodular fibrosis can result in masses >1 cm in diameter in complicated silicosis. When such masses become very large, the term *progressive massive fibrosis* is used to describe the condition. Due to impaired cell-mediated immunity, silicosis pts are at increased risk of tuberculosis, atypical mycobacterial infections, and fungal infections. Silica may also be a lung carcinogen.

Coal Worker's Pneumoconiosis (CWP)

Occupational exposure to coal dust predisposes to coal worker's CWP, which is less common among coal workers in the western United States due to a lower risk from the bituminous coal found in that region. Simple CWP is defined radiologically by small nodular opacities and is not typically symptomatic. The development of larger nodules (>1 cm in diameter), usually in the upper lobes, characterizes complicated CWP. Complicated CWP is often symptomatic and is associated with reduced pulmonary function and increased mortality. In addition to CWP, coal dust exposure can cause COPD.

Berylliosis

Beryllium exposure may occur in the manufacturing of alloys, ceramics, and electronic devices. Although acute beryllium exposure can rarely produce acute pneumonitis, a chronic granulomatous disease very similar to sarcoidosis is much more common. Radiologically, chronic beryllium disease, like sarcoidosis, is characterized by pulmonary nodules along septal lines. As in sarcoidosis, either a restrictive or obstructive ventilatory pattern with reduced diffusing capacity (DLCO) on pulmonary function testing can be seen. Bronchoscopy with transbronchial biopsy is typically required to diagnose chronic beryllium disease. The most effective way to distinguish chronic beryllium disease from sarcoidosis is to assess for delayed hypersensitivity to beryllium by performing a lymphocyte proliferation test using blood or bronchoalveolar lavage lymphocytes. Removal from further beryllium exposure is required, and corticosteroids may be beneficial.

■ ORGANIC DUSTS**Cotton Dust (Byssinosis)**

Cotton dust exposures occur in the production of yarns for textiles and rope making. At the early stages of byssinosis, chest tightness occurs near the end of the first day of the workweek. In progressive cases, symptoms are present throughout the workweek. After at least 10 years of exposure, chronic airflow obstruction can develop. In symptomatic individuals, limiting further exposure is essential.

Grain Dust

Farmers and grain elevator operators are at risk for grain dust–related lung disease, which is similar to COPD. Symptoms include productive cough, wheezing, and dyspnea. Pulmonary function tests typically show airflow obstruction.

Farmer's Lung

Exposure to moldy hay containing spores of thermophilic actinomycetes can lead to the development of hypersensitivity pneumonitis. Within 8 h after exposure, the acute presentation of farmer's lung includes fever, cough, and dyspnea. With repeated exposures, chronic and patchy interstitial lung disease can develop.

Toxic Chemicals

Many toxic chemicals can affect the lung in the form of vapors and gases. For example, smoke inhalation can be lethal to firefighters and fire victims through a variety of mechanisms; carbon monoxide poisoning can cause life-threatening hypoxemia, while combustion of plastics and polyurethanes can release toxic agents including cyanide. Occupational asthma can result from exposure to diisocyanates in polyurethanes and acid anhydrides in epoxies. Occupational exposures to many toxic chemicals, including arsenic, chromium, and formaldehyde, increase the risk of lung cancer. Radon gas, released from earth materials and concentrated within buildings, and second-hand tobacco smoke are also risk factors for lung cancer.

PRINCIPLES OF MANAGEMENT

Treatment of environmental lung diseases typically involves limiting or avoiding exposures to the toxic substance. Chronic interstitial lung diseases (e.g., asbestosis, CWP) are not responsive to glucocorticoids, but acute organic dust exposures may respond to corticosteroids. Therapy of occupational asthma (e.g., diisocyanates) follows usual asthma guidelines ([Chap. 131](#)), and therapy of occupational COPD (e.g., byssinosis) follows usual COPD guidelines ([Chap. 133](#)).

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Chronic Obstructive
Pulmonary Disease

DEFINITION AND EPIDEMIOLOGY

Chronic obstructive pulmonary disease (COPD) is a syndrome characterized by chronic airflow obstruction. COPD includes emphysema (lung parenchymal destruction), chronic bronchitis (chronic cough and phlegm production), and small airway disease (fibrosis and destruction of small airways) in varying combinations in different pts. The presence of airflow obstruction is determined by a reduced ratio of the forced expiratory volume in 1 s (FEV_1) to the forced vital capacity (FVC). Among individuals with a reduced FEV_1/FVC ratio, the severity of airflow obstruction is determined by the level of reduction in FEV_1 (Table 133-1): $\geq 80\%$ is stage I, 50–80% is stage II, 30–50% is stage III, and $<30\%$ is stage IV. Pts who do not meet these classic thresholds for airflow obstruction may have emphysema, chronic bronchitis, and respiratory symptoms suggestive of COPD.

Cigarette smoking is the major environmental risk factor for COPD. The risk of COPD increases with cigarette smoking intensity, which is typically quantified as pack-years. (One pack of cigarettes smoked per day for 1 year equals 1 pack-year.) Individuals with airway hyperresponsiveness and certain occupational exposures (e.g., coal mining, gold mining, and cotton textiles) are likely also at increased risk for COPD. In countries in which biomass combustion with poor ventilation is used for cooking, an increased risk of COPD among women has been reported. The impact of electronic cigarettes on the development and progression of COPD is uncertain.

COPD is a progressive disorder; however, the rate of loss of lung function often slows markedly if smoking cessation occurs. In normal individuals, FEV_1 reaches a lifetime peak at around age 25 years, enters a plateau phase, and subsequently declines gradually and progressively. Subjects can develop COPD by having reduced maximally attained lung function, shortened plateau phase, or accelerated decline in lung function.

Symptoms may occur only when COPD is advanced; thus, early detection requires spirometric testing. The PaO_2 typically remains near normal until the FEV_1 falls to $<50\%$ of the predicted value. Hypercarbia and pulmonary hypertension are most common after FEV_1 has fallen to $<25\%$ of predicted. COPD pts with similar FEV_1 values can vary markedly in their respiratory symptoms and functional impairment. COPD often includes periods of increased respiratory symptoms, such as dyspnea, cough, and phlegm production, which are known as exacerbations. Exacerbations are often triggered by bacterial and/or viral respiratory infections. These exacerbations become more common as COPD

TABLE 133-1 GOLD Spirometric Grading Criteria for COPD Severity

GOLD STAGE	SEVERITY	SPIROMETRY
I	Mild	$FEV_1/FVC < 0.7$ and $FEV_1 \geq 80\%$ predicted
II	Moderate	$FEV_1/FVC < 0.7$ and $FEV_1 \geq 50\%$ but $< 80\%$ predicted
III	Severe	$FEV_1/FVC < 0.7$ and $FEV_1 \geq 30\%$ but $< 50\%$ predicted
IV	Very severe	$FEV_1/FVC < 0.7$ and $FEV_1 < 30\%$ predicted

Abbreviation: GOLD, Global Initiative for Lung Disease.

Source: From the Global Strategy for Diagnosis, Management and Prevention of COPD 2014. Available from <http://www.goldcopd.org>; with permission.

severity increases, but some individuals are much more susceptible to developing exacerbations than others with similar degrees of airflow obstruction.

■ CLINICAL MANIFESTATIONS

History

Common symptoms in COPD pts include cough and phlegm production; individuals with chronic productive cough for 3 months per year for two consecutive years have chronic bronchitis. However, chronic bronchitis without airflow obstruction is not included within COPD. Exertional dyspnea is a common and potentially disabling symptom in COPD pts. Exercise involving upper-body activity is especially difficult for severe COPD pts. Weight loss and cachexia are common in advanced disease.

Exacerbations are more frequent as disease progresses and are most often triggered by respiratory infections, often with a bacterial component. The history of prior exacerbations is a strong predictor of future exacerbations.

Physical Findings

The physical examination may be normal until COPD is fairly advanced. As disease progresses, signs of hyperinflation may become more prominent, including barrel chest and poor diaphragmatic excursion. Expiratory wheezing may be observed, but it does not predict the severity of obstruction or response to therapy. Digital clubbing raises the possibility of lung cancer, since it is not a sign of COPD.

During COPD exacerbations, signs of respiratory distress may be prominent, including tachycardia, tachypnea, use of accessory muscles of respiration, and cyanosis.

Radiographic Findings

Plain chest x-ray may show hyperinflation, emphysema, and pulmonary hypertension. It is typically performed to exclude other disease processes during routine evaluation and to exclude pneumonia and pneumothorax during exacerbations. Chest CT scanning has much greater sensitivity for detecting emphysema but is typically reserved for the evaluation of advanced disease when surgical options such as lung volume reduction and lung transplantation are being considered, or as part of lung cancer screening in smokers.

Pulmonary Function Tests

Objective documentation of airflow obstruction is essential for diagnosing COPD. Standardized staging of COPD is based on post-bronchodilator spirometry. In COPD, the FEV_1/FVC ratio is reduced to <0.7 . Increases in total lung capacity and residual volume, as well as reduced diffusing capacity for carbon monoxide (DLCO), are typically seen in emphysema.

Laboratory Tests

α_1 Antitrypsin (α_1AT) testing, typically by measurement of the protein level in the bloodstream, is recommended to exclude severe α_1AT deficiency. Augmentation therapy (a weekly IV infusion) is available for individuals with severe α_1AT deficiency (e.g., PI Z) who have developed airflow obstruction and/or emphysema. Pulse oximetry can determine the O_2 saturation. However, arterial blood gases remain useful to assess the severity of CO_2 retention as well as acid-base disorders. During acute exacerbations, arterial blood gases should be considered in pts with mental status changes, significant respiratory distress, very severe COPD, or a history of hypercarbia. Complete blood counts are useful in advanced disease to assess for erythrocytosis, which can occur secondary to hypoxemia, and anemia, which can worsen dyspnea.

TREATMENT**COPD****OUTPATIENT MANAGEMENT**

In addition to the severity of airflow obstruction, respiratory symptoms and exacerbation history are used to individualize management in COPD pts.

Smoking Cessation

Elimination of tobacco smoking has been convincingly shown to reduce decline in pulmonary function and to prolong survival in pts with COPD; complete smoking cessation is essential for all COPD pts. Although lung function does not typically improve substantially after smoking cessation, the rate of decline in FEV₁ often reverts to that of nonsmokers. Pharmacologic treatment to assist with smoking cessation is often beneficial. Use of nicotine replacement therapy (available as a transdermal patch, gum, lozenge, nasal spray, and oral inhaler) can increase rates of smoking cessation; oral bupropion also produces significant benefit and can be combined successfully with nicotine replacement. Varenicline, a partial agonist for nicotinic acetylcholine receptors, also can promote smoking cessation. All adult, nonpregnant smokers without specific contraindications should be offered pharmacologic treatment to assist with smoking cessation.

Nonpharmacologic Treatment

Pulmonary rehabilitation improves dyspnea and functional status and reduces hospitalizations. Annual influenza vaccinations are strongly recommended; in addition, pneumococcal and pertussis vaccinations are recommended.

Bronchodilators

Although inhaled bronchodilator medications have not been proven to increase longevity in COPD, they may significantly reduce respiratory symptoms and exacerbations. Short- and long-acting β -adrenergic agonists, short- and long-acting anticholinergics, and theophylline derivatives all may be used. Inhaled bronchodilator medications generally have fewer side effects than oral bronchodilator medications.

Pts with mild symptoms and infrequent exacerbations can usually be managed with an inhaled short-acting anticholinergic such as ipratropium or a short-acting β agonist such as albuterol. Combination therapy with long-acting β agonists and/or long-acting anticholinergics should be added in pts with significant respiratory symptoms and/or frequent exacerbations. The narrow toxic-therapeutic ratio of theophylline compounds limits their use, and monitoring of serum levels is required.

Corticosteroids

Chronic systemic corticosteroid treatment is not recommended in COPD pts due to the risk of multiple complications, including osteoporosis, weight gain, cataracts, and glucose intolerance. Although inhaled steroids have not been proven to reduce the rate of decline of FEV₁ in COPD, inhaled steroid medications (typically given in combination with a long-acting β agonist and/or long-acting anticholinergic) likely reduce the frequency of COPD exacerbations. Inhaled steroids have been associated with an increased risk of pneumonia.

PDE4 Inhibitors

Roflumilast reduces exacerbation frequency in severe COPD pts with chronic bronchitis and a prior history of exacerbations; however, side effects including nausea often limit its use.

Antibiotics

Chronic treatment with azithromycin has been demonstrated to reduce exacerbation frequency and should be considered in COPD pts with frequent exacerbations.

Oxygen

Long-term supplemental oxygen therapy has been shown to reduce symptoms and improve survival in COPD pts who are chronically hypoxemic. Documentation of the need for O_2 requires a measurement of PaO_2 or oxygen saturation (SaO_2) after a period of stability. Pts with a $PaO_2 \leq 55$ mmHg or $SaO_2 \leq 88\%$ should receive O_2 to raise the SaO_2 to $\geq 90\%$. O_2 is also indicated for pts with PaO_2 of 56–59 mmHg or $SaO_2 < 90\%$ if associated with signs and symptoms of pulmonary hypertension or cor pulmonale. For individuals who meet these guidelines, continuous O_2 therapy is recommended because the number of hours per day of oxygen use is directly related to the mortality benefit. Supplemental oxygen may also be prescribed for selected COPD pts who desaturate only with exercise or during sleep, although the evidence for benefit is much less compelling.

Surgical Options for Severe COPD

Two main types of surgical options are available for end-stage COPD. Lung volume reduction surgery can reduce mortality and improve lung function in selected pts with upper lobe–predominant emphysema and low exercise capacity (after pulmonary rehabilitation). Individuals who meet the criteria for the high-risk group ($FEV_1 < 20\%$ predicted and either a diffuse distribution of emphysema or $DLCO < 20\%$ predicted) should not be considered for lung volume reduction surgery. Lung transplantation should be considered for COPD pts who have very severe chronic airflow obstruction and disability at a relatively young age despite maximal medical therapy.

MANAGEMENT OF COPD EXACERBATIONS

COPD exacerbations are a major cause of morbidity and mortality. Critical decisions in management include whether hospitalization is required. Although there are no definitive guidelines to determine which COPD pts require hospitalization for an exacerbation, the development of respiratory acidosis, worsening hypoxemia, severe underlying COPD, pneumonia, or social situations without adequate home support for the treatment required should prompt consideration of hospitalization.

Key components of COPD exacerbation treatment include bronchodilators, antibiotics, and short courses of systemic glucocorticoids.

Antibiotics

Because bacterial infections often trigger COPD exacerbations, antibiotic therapy should be strongly considered, especially with increased sputum volume or change in sputum color. Common pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Antibiotic choice should depend on the local antibiotic sensitivity patterns and the severity of disease.

Bronchodilators

Bronchodilator therapy is essential during COPD exacerbations. Short-acting β -adrenergic agonists (e.g., albuterol) and anticholinergics (e.g., ipratropium) are typically used. Administration of bronchodilators by nebulizer is often used initially because it is easier to administer to pts in respiratory distress. Conversion to metered-dose inhaler administration can be successfully achieved with appropriate training of the pt and staff.

Glucocorticoids

Systemic steroids hasten resolution of symptoms and reduce relapses. Dosing is not well worked out, but 30–40 mg of prednisolone daily (or IV equivalent) is standard, with a total course of 5–10 days in outpatients. Hyperglycemia is the most commonly reported complication.

Oxygen

Hypoxemia often worsens during COPD exacerbations. Supplemental O₂ should be administered to maintain SaO₂ ≥90%. Very high O₂ delivery can worsen hypercarbia, primarily due to increasing ventilation-perfusion mismatch. However, providing adequate O₂ to obtain saturation of ~90% is the key goal. Therefore, supplemental O₂ delivery should be focused on providing adequate oxygenation without providing unnecessarily high O₂ saturations. Pts may require use of supplemental O₂ after hospital discharge until the exacerbation completely resolves.

Ventilatory Support

Numerous studies suggest that noninvasive mask ventilation (noninvasive ventilation [NIV]) can improve outcomes in acute COPD exacerbations with respiratory failure (PaCO₂ >45 mmHg). Contraindications to NIV include cardiovascular instability, impaired mental status, inability to cooperate, copious secretions, craniofacial abnormalities or facial trauma, extreme obesity, or significant burns. Progressive hypercarbia, refractory hypoxemia, or alterations in mental status that compromise ability to comply with NIV therapy, hemodynamic instability, and respiratory arrest may necessitate endotracheal intubation for mechanical ventilation. Sufficient expiratory time during mechanical ventilatory support is required to avoid the development of auto-PEEP.

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Pneumonia, Bronchiectasis, and Lung Abscess



PNEUMONIA

Pneumonia, an infection of the lung parenchyma, is classified as community-acquired (CAP), hospital-acquired (HAP), ventilator-associated (VAP), or health care-associated (HCAP). Although the HCAP category initially referred to CAP caused by a multidrug-resistant (MDR) pathogen, it now describes pts with at least two or three risk factors for infection with MDR pathogens ([Table 134-1](#)).

■ PATHOPHYSIOLOGY

- Microorganisms gain access to the lower respiratory tract via microaspiration from the oropharynx (the most common route), hematogenous spread, or contiguous extension from an infected pleural or mediastinal space.
- Many CAP pathogens are components of the normal alveolar microbiota, which is similar to the oropharyngeal microbiota. This observation suggests that alterations in host defenses (e.g., alveolar macrophage activity, surfactant proteins A and D, mucociliary elevator function) allow overgrowth of one or more components of the normal bacterial microbiota. The two most likely sources of an altered alveolar microbiota are viral upper respiratory tract infections for CAP and antibiotic therapy for HAP/VAP.

TABLE 134-1 Risk Factors for Pathogens Resistant to Usual Therapy for Community-Acquired Pneumonia^a

MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA AND MRSA	NOSOCOMIAL MRSA	COMMUNITY-ACQUIRED MRSA
Hospitalization ≥ 2 days in previous 90 days	Hospitalization ≥ 2 days in previous 90 days	Cavitary infiltrate or necrosis
Use of antibiotics in previous 90 days	Use of antibiotics in previous 90 days	Gross hemoptysis
Immunosuppression	Chronic hemodialysis in previous 30 days	Neutropenia
Nonambulatory status	Documented prior MRSA colonization	Erythematous rash
Tube feedings	Congestive heart failure	Concurrent influenza
Gastric acid suppression	Gastric acid suppression	Young, previously healthy status
Severe COPD or bronchiectasis ^b		Summer-month onset

^aCephalosporin/macrolide or respiratory fluoroquinolone.

^bRisk for *Pseudomonas aeruginosa* infection.

Abbreviations: COPD, chronic obstructive pulmonary disease; MRSA, methicillin-resistant *Staphylococcus aureus*.

- Classic pneumonia (typified by that due to *Streptococcus pneumoniae*) presents as a lobar pattern and evolves through four phases characterized by changes in the alveoli:
 - *Edema*: Proteinaceous exudates are present in the alveoli.
 - *Red hepatization*: Erythrocytes and neutrophils are present in the intra-alveolar exudate.
 - *Gray hepatization*: Neutrophils and fibrin deposition are abundant.
 - *Resolution*: Macrophages are the dominant cell type.
- In VAP, respiratory bronchiolitis can precede a radiologically apparent infiltrate.

■ COMMUNITY-ACQUIRED PNEUMONIA

Microbiology

Although many bacteria, viruses, fungi, and protozoa can cause CAP, most cases are caused by relatively few pathogens. In >50% of cases, a specific etiology is never determined.

- Typical bacterial pathogens include *S. pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and gram-negative bacteria such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.
 - The incidence of pneumococcal pneumonia is decreasing because of the increasing use of pneumococcal vaccines.
- Atypical organisms include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella* spp., and respiratory viruses (e.g., influenza viruses, adenoviruses, human metapneumovirus, respiratory syncytial viruses).
 - A virus may be responsible for a large proportion of CAP cases that require hospital admission, even in adults.
 - Of CAP cases, 10–15% are polymicrobial and involve a combination of typical and atypical organisms.
 - The incidences of cases due to *M. pneumoniae* and *C. pneumoniae* are increasing, particularly among young adults.

- Involvement of anaerobes, which play a significant role in CAP only when aspiration precedes presentation by days or weeks, often results in significant empyemas.

Epidemiology

CAP affects >5 million adults each year in the United States, 80% of whom are treated on an outpatient basis. CAP causes >55,000 deaths annually and is associated with an overall yearly cost of ~\$17 billion.

- The incidence of CAP is highest at the extremes of age (i.e., <4 and >60 years).
- Risk factors for CAP include alcoholism, asthma, immunosuppression, institutionalization, and an age of ≥ 70 years (vs 60–69 years).
- Many factors—e.g., tobacco smoking, chronic obstructive pulmonary disease, colonization with methicillin-resistant *S. aureus* (MRSA), recent hospitalization or antibiotic therapy—influence the types of pathogens that should be considered in the etiologic diagnosis.

Clinical Manifestations

Pts frequently have fever, chills, sweats, cough (either nonproductive or productive of mucoid, purulent, or blood-tinged sputum), pleuritic chest pain, and dyspnea.

- Other common symptoms include nausea, vomiting, diarrhea, fatigue, headache, myalgias, and arthralgias.
- Elderly pts may present atypically, with confusion but few other manifestations.
- Physical examination often reveals tachypnea; increased or decreased tactile fremitus; dull or flat percussion reflecting consolidation and pleural fluid, respectively; crackles; bronchial breath sounds; or a pleural friction rub.

Diagnosis

Both confirmation of the diagnosis and assessment of the likely etiology are required. Although no data have demonstrated that treatment directed at a specific pathogen is superior to empirical treatment, an etiologic diagnosis allows narrowing of the empirical regimen, identification of organisms with public safety implications (e.g., *Mycobacterium tuberculosis*, influenza virus), and monitoring of antibiotic susceptibility trends.

- CXR is often required to differentiate CAP from other conditions, particularly since the sensitivity and specificity of physical examination findings for CAP are only 58% and 67%, respectively.
 - CT of the chest may be helpful for pts with suspected postobstructive pneumonia or suspected cavitory disease.
 - Some radiographic patterns suggest an etiology; e.g., pneumatoceles suggest *S. aureus*.
- Sputum samples must have >25 WBCs and <10 squamous epithelial cells per high-power field to be appropriate for culture. The sensitivity of sputum cultures is highly variable; in cases of proven bacteremic pneumococcal pneumonia, the yield of positive cultures from sputum samples is $\leq 50\%$.
- Blood cultures are positive in 5–14% of cases, most commonly yielding *S. pneumoniae*. Blood cultures are optional for most CAP pts but should be performed for high-risk pts (e.g., pts with chronic liver disease or asplenia).
- Urine antigen tests for *S. pneumoniae* and *Legionella pneumophila* type 1 can be helpful.
- PCR of nasopharyngeal swabs has become the standard for diagnosis of respiratory viral infection and is also useful for detection of many atypical bacteria.

- **Serology:** A fourfold rise in titer of specific IgM antibody can assist in the diagnosis of pneumonia due to some pathogens; however, the time required to obtain a final result and difficulty of interpretation limits the clinical utility of serology.
- **Biomarkers:** Serial measurements of C-reactive protein (CRP) levels in serum may help identify worsening disease or treatment failure. Measurement of serum procalcitonin (PCT) levels can help distinguish bacterial from viral infection, determine the need for antibacterial therapy, or determine when to discontinue treatment.

TREATMENT

Community-Acquired Pneumonia

DECIDING WHETHER TO HOSPITALIZE PTS

- Two sets of criteria identify pts who will benefit from hospital care. It is not clear which set is superior, and application of each tool should be tempered by a consideration of factors relevant to the individual pt.
 - **Pneumonia Severity Index (PSI):** Points are given for 20 variables, including age, coexisting illness, and abnormal physical and laboratory findings. On this basis, pts are assigned to one of five classes of mortality risk.
 - **CURB-65:** Five variables are included: confusion (C); urea >7 mmol/L (U); respiratory rate ≥ 30 /min (R); blood pressure, systolic ≤ 90 mmHg or diastolic ≤ 60 mmHg (B); and age ≥ 65 years (65). Pts with a score of 0 can be treated at home, pts with a score of 1 or 2 (not counting any point given for age ≥ 65 years) should be hospitalized, and pts with a score of ≥ 3 may require management in the ICU.

SELECTING ANTIBIOTIC THERAPY

- For recommendations on empirical antibiotic treatment of CAP, see [Table 134-2](#). U.S. guidelines always target *S. pneumoniae* and atypical pathogens. Retrospective data suggest that this approach lowers the mortality rate.
- Pts initially treated with IV antibiotics can be switched to oral agents when they can ingest and absorb drugs, are hemodynamically stable, and are improving clinically.
- A 5-day course of a fluoroquinolone is sufficient for cases of uncomplicated CAP, but a longer course may be required for pts with bacteremia, metastatic infection, or infection with a particularly virulent pathogen (e.g., *P. aeruginosa*, community-acquired MRSA).
- Fever and leukocytosis usually resolve within 2–4 days. Pts who have not responded to therapy by day 3 should be reevaluated, with consideration of alternative diagnoses, antibiotic resistance in the pathogen, and the possibility that the wrong drug is being given.

Complications

Common complications of severe CAP include respiratory failure, shock and multiorgan failure, coagulopathy, cardiac complications (e.g., MI, CHF, arrhythmias), and exacerbation of comorbid disease. Metastatic infection (e.g., brain abscess, endocarditis) occurs rarely and requires immediate attention.

- Lung abscess (see below) may occur in association with aspiration or infection caused by single CAP pathogens (e.g., community-acquired MRSA)

TABLE 134-2 Empirical Antibiotic Treatment of Community-Acquired Pneumonia**Outpatients**

1. Previously healthy and no antibiotics in past 3 months
 - A macrolide (clarithromycin [500 mg PO bid] or azithromycin [500 mg PO once, then 250 mg qd]) *or*
 - Doxycycline (100 mg PO bid)
2. Comorbidities or antibiotics in past 3 months: select an alternative from a different class
 - A respiratory fluoroquinolone (moxifloxacin [400 mg PO qd], gemifloxacin [320 mg PO qd], levofloxacin [750 mg PO qd]) *or*
 - A β -lactam (preferred: high-dose amoxicillin [1 g tid] or amoxicillin/clavulanate [2 g bid]; alternatives: ceftriaxone [1–2 g IV qd], cefpodoxime [200 mg PO bid], or cefuroxime [500 mg PO bid]) *plus* a macrolide^a
3. In regions with a high rate of “high-level” pneumococcal macrolide resistance,^b consider alternatives listed earlier for pts with comorbidities.

Inpatients, Non-ICU

- A respiratory fluoroquinolone (e.g., moxifloxacin [400 mg PO or IV qd] or levofloxacin [750 mg PO or IV qd])
- A β -lactam^c (e.g., ceftriaxone [1–2 g IV qd], ampicillin [1–2 g IV q4–6h], cefotaxime [1–2 g IV q8h], ertapenem [1 g IV qd]) *plus* a macrolide^d (e.g., oral clarithromycin or azithromycin as listed earlier or IV azithromycin [1 g once, then 500 mg qd])

Inpatients, ICU

- A β -lactam^e (e.g., ceftriaxone [2 g IV qd], ampicillin-sulbactam [2 g IV q8h], or cefotaxime [1–2 g IV q8h]) *plus* either azithromycin or a fluoroquinolone (as listed earlier for inpatients, non-ICU)

Special Concerns

If Pseudomonas is a consideration:

- An antipseudomonal β -lactam (e.g., piperacillin/tazobactam [4.5 g IV q6h], ceftipime [1–2 g IV q12h], imipenem [500 mg IV q6h], meropenem [1 g IV q8h]) *plus* either ciprofloxacin (400 mg IV q12h) or levofloxacin (750 mg IV qd)
- The earlier β -lactams *plus* an aminoglycoside (amikacin [15 mg/kg qd] or tobramycin [1.7 mg/kg qd]) *plus* azithromycin
- The earlier β -lactams^f *plus* an aminoglycoside *plus* an antipneumococcal fluoroquinolone

If CA-MRSA is a consideration:

- Add linezolid (600 mg IV q12h) or vancomycin (15 mg/kg q12h initially, with adjusted doses) *plus* clindamycin (300 mg q6h)

^aDoxycycline (100 mg PO bid) is an alternative to the macrolide.

^bMICs >16 μ g/mL in 25% of isolates.

^cA respiratory fluoroquinolone should be used for penicillin-allergic pts.

^dDoxycycline (100 mg IV q12h) is an alternative to the macrolide.

^eFor penicillin-allergic pts, use a respiratory fluoroquinolone and aztreonam (2 g IV q8h).

^fFor penicillin-allergic pts, substitute aztreonam.

Abbreviations: CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit.

or *P. aeruginosa*). Drainage should be established and proper antibiotics administered.

- Any significant pleural effusion should be tapped for diagnostic and therapeutic purposes. If the fluid has a pH <7, a glucose level <2.2 mmol/L, and an LDH content >1000 U or if bacteria are seen or cultured, fluid should be drained; a chest tube is usually required.

Follow-Up

CXR abnormalities may require 4–12 weeks to clear. Pts should receive influenza and pneumococcal vaccines, as appropriate.

HEALTH CARE–ASSOCIATED PNEUMONIA (SEE ALSO CHAP. 81)

■ VENTILATOR-ASSOCIATED PNEUMONIA

Microbiology

Potential etiologic agents of VAP include MDR and non-MDR pathogens; the prominence of the various pathogens depends on the length of hospital stay at the time of infection and the presence of other risk factors.

Epidemiology, Pathogenesis, and Clinical Manifestations

Prevalence estimates of VAP are 6–52 cases per 100 pts, with the highest hazard ratio in the first 5 days of mechanical ventilation.

- Three factors important in the pathogenesis of VAP are colonization of the oropharynx with pathogenic microorganisms, aspiration of these organisms to the lower respiratory tract, and compromise of normal host defense mechanisms.
- Clinical manifestations are similar to those in other forms of pneumonia.

Diagnosis

Application of clinical criteria consistently results in overdiagnosis of VAP. Use of quantitative cultures to discriminate between colonization and true infection by determining bacterial burden results in less antibiotic use and lower mortality. The more distal in the respiratory tree the diagnostic sampling, the more specific the results.

TREATMENT

Ventilator-Associated Pneumonia

- See [Table 134-3](#) for recommended options for empirical therapy for VAP.
 - Higher mortality rates are associated with inappropriate initial empirical treatment.
 - Broad-spectrum treatment should be modified when a pathogen is identified.
 - Clinical improvement, if it occurs, is usually evident within 48–72 h of the initiation of antimicrobial treatment.
- Treatment failure in VAP is not uncommon, especially when MDR pathogens are involved; MRSA and *P. aeruginosa* are associated with high failure rates.
- VAP complications include prolongation of mechanical ventilation, increased length of ICU stay, and necrotizing pneumonia with pulmonary hemorrhage or bronchiectasis. VAP is associated with significant mortality risk.
- Strategies effective for the prevention of VAP are listed in [Table 134-4](#).

TABLE 134-3 Empirical Antibiotic Treatment of Hospital-Acquired and Ventilator-Associated Pneumonia

NO RISK FACTORS FOR RESISTANT GRAM-NEGATIVE PATHOGEN	RISK FACTORS FOR RESISTANT GRAM-NEGATIVE PATHOGEN ^a (CHOOSE ONE FROM EACH COLUMN)	
Piperacillin-tazobactam (4.5 g IV q6h ^b) Cefepime (2 g IV q8h) Levofloxacin (750 mg IV q24h)	Piperacillin-tazobactam (4.5 g IV q6h ^b) Cefepime (2 g IV q8h) Ceftazidime (2 g IV q8h) Imipenem (500 mg IV q6h ^b) Meropenem (1 g IV q8h)	Amikacin (15–20 mg/kg IV q24h) Gentamicin (5–7 mg/kg IV q24h) Tobramycin (5–7 mg/kg IV q24h) Ciprofloxacin (400 mg IV q8h) Levofloxacin (750 mg IV q24h) Colistin (loading dose of 5 mg/kg IV followed by maintenance doses of 2.5 mg × [1.5 × CrCl + 30] IV q12h) Polymyxin B (2.5–3.0 mg/kg per day IV in 2 divided doses)
Risk factors for MRSA^b (add to above)		
Linezolid (600 mg IV q12h) or Adjusted-dose vancomycin (trough level, 15–20 mg/dL)		

^aPrior antibiotic therapy, prior hospitalization, local antibiogram.

^bPrior antibiotic therapy, prior hospitalization, known MRSA colonization, chronic hemodialysis, local documented MRSA pneumonia rate >10% (or local rate unknown).

Abbreviations: CrCl, creatinine clearance rate; MRSA, methicillin-resistant *Staphylococcus aureus*.

■ HOSPITAL-ACQUIRED PNEUMONIA

Less well studied than VAP, HAP more commonly involves non-MDR pathogens. Anaerobes may also be more commonly involved in non-VAP pts because of the increased risk of macroaspiration in pts who are not intubated.

■ BRONCHIECTASIS

Etiology and Epidemiology

Bronchiectasis is an irreversible airway dilation that involves the lung in either a focal (due to obstruction) or a diffuse (due to a systemic or infectious process) manner. Bronchiectasis can arise from infectious or noninfectious causes.

- The epidemiology varies greatly with the underlying etiology; in general, the incidence of bronchiectasis increases with age and is higher among women than among men.
- Of pts with bronchiectasis, 25–50% have idiopathic disease.

Pathogenesis

The most widely cited mechanism of infectious bronchiectasis is the “vicious cycle hypothesis,” in which susceptibility to infection and poor mucociliary clearance result in microbial colonization of the bronchial tree. Proposed mechanisms for noninfectious bronchiectasis include immune-mediated reactions that

TABLE 134-4 Pathogenic Mechanisms and Corresponding Prevention Strategies for Ventilator-Associated Pneumonia

PATHOGENIC MECHANISM	PREVENTION STRATEGY
Oropharyngeal colonization with pathogenic bacteria	
Elimination of normal flora	Avoidance of prolonged antibiotic courses
Large-volume oropharyngeal aspiration around time of intubation	Short course of prophylactic antibiotics for comatose pts ^a
Gastroesophageal reflux	Postpyloric enteral feeding ^b ; avoidance of high gastric residuals, prokinetic agents
Bacterial overgrowth of stomach	Avoidance of prophylactic agents that raise gastric pH ^b ; selective decontamination of digestive tract with nonabsorbable antibiotics ^b
Cross-infection from other colonized pts	Hand washing, especially with alcohol-based hand rub; intensive infection control education ^a ; isolation; proper cleaning of reusable equipment
Large-volume aspiration	Endotracheal intubation; rapid-sequence intubation technique; avoidance of sedation; decompression of small-bowel obstruction
Microaspiration around endotracheal tube	
Endotracheal intubation	Noninvasive ventilation ^a
Prolonged duration of ventilation	Daily awakening from sedation, ^a weaning protocols ^a
Abnormal swallowing function	Early percutaneous tracheostomy ^a
Secretions pooled above endotracheal tube	Head of bed elevated ^a ; continuous aspiration of subglottic secretions with specialized endotracheal tube ^a ; avoidance of reintubation; minimization of sedation and pt transport
Altered lower respiratory host defenses	Tight glycemic control ^b ; lowering of hemoglobin transfusion threshold

^aStrategies demonstrated to be effective in at least one randomized controlled trial.

^bStrategies with negative randomized trials or conflicting results.

damage the bronchial wall and parenchymal distortion as a result of lung fibrosis (e.g., postradiation fibrosis or idiopathic pulmonary fibrosis).

Clinical Manifestations

Presenting pts typically have a persistent productive cough with ongoing production of thick, tenacious sputum.

- Physical examination usually reveals crackles and wheezing on lung auscultation and occasionally reveals digital clubbing.
- Acute exacerbations are associated with increased production of purulent sputum.

Diagnosis

The diagnosis of bronchiectasis is based on clinical presentation with consistent CXR findings, such as parallel “tram tracks,” a “signet-ring sign” (a cross-sectional area of the airway with a diameter at least 1.5 times that of the adjacent vessel), lack of bronchial tapering, bronchial wall thickening, or cysts emanating from the bronchial wall.

TREATMENT**Bronchiectasis**

Treatment of infectious bronchiectasis is directed at the control of active infection and at improvements in secretion clearance and bronchial hygiene.

- Acute exacerbations should be treated with a 7- to 10-day course of antibiotics targeting the causative or presumptive pathogen; *H. influenzae* and *P. aeruginosa* are isolated commonly.
- Hydration and mucolytic administration, aerosolization of bronchodilators and hyperosmolar agents (e.g., hypertonic saline), and chest physiotherapy can be used to enhance secretion clearance.
- For pts with three or more recurrences per year, suppressive antibiotic treatment to minimize the microbial load and reduce the frequency of exacerbations has been proposed.
- In select cases, surgery (including lung transplantation) should be considered.

LUNG ABSCESS**Microbiology**

Lung abscess—necrosis and cavitation of the lung following microbial infection—can be categorized as primary (~80% of cases) or secondary; alternatively, it can be categorized as acute (<4–6 weeks in duration) or chronic (~40% of cases).

- Primary lung abscesses usually arise from aspiration in the absence of an underlying pulmonary or systemic condition, are often polymicrobial (primarily including anaerobic organisms and microaerophilic streptococci), and occur preferentially in dependent segments (posterior upper and superior lower lobes) of the right lung.
- Secondary lung abscesses arise in the setting of an underlying condition (e.g., a postobstructive process, an immunocompromising condition) and can be due to a number of different organisms, among which *P. aeruginosa* and other gram-negative rods are most common.

Clinical Manifestations

Initial presentation of lung abscess may be similar to that of pneumonia.

- Anaerobic lung abscesses may have a more chronic and indolent presentation, with night sweats, fatigue, and anemia; in addition, pts may have discolored phlegm and foul-tasting or foul-smelling sputum.
- Pts with lung abscesses due to non-anaerobic organisms (e.g., *S. aureus*) may present with a more fulminant course characterized by high fevers and rapid progression.

Diagnosis

Chest CT is the preferred radiographic study for precise delineation of the lesion.

- It is not clear whether invasive diagnostics (e.g., transtracheal aspiration) to identify an etiologic agent in primary lung abscesses is helpful.
- Sputum and blood cultures, serologic studies for opportunistic pathogens, and—if needed—more invasive methods of sample collection (e.g., bronchoalveolar lavage, CT-guided percutaneous aspiration) are recommended for secondary lung abscesses or when empirical therapy fails.

TREATMENT**Lung Abscess**

Treatment depends on the presumed or established etiology.

- For primary lung abscesses, the recommended regimens are clindamycin (600 mg IV tid) or an IV-administered β -lactam/ β -lactamase combination. After clinical improvement, the pt can be transitioned to an oral regimen (clindamycin, 300 mg qid; or amoxicillin/clavulanate).
- In secondary lung abscesses, antibiotic coverage should be directed at the identified pathogen.
- Continuation of oral treatment is recommended until imaging shows that the lung abscess has cleared or regressed to a small scar.
- Pts who continue to have fever ≥ 7 days after antibiotic initiation and whose additional diagnostic studies fail to identify another treatable pathogen may require surgical resection or percutaneous drainage of the abscess.

135**Pulmonary Thromboembolism and Deep-Vein Thrombosis****■ DEFINITION AND NATURAL HISTORY**

Venous thromboembolism (VTE) includes both deep-vein thrombosis (DVT) and pulmonary embolism (PE). DVT results from blood clot formation within large veins, usually in the legs. PE results from DVTs that have broken off and traveled to the pulmonary arterial circulation. Isolated calf vein thrombi have much lower risk of PE. Although DVTs are typically related to thrombus formation in the legs and/or pelvis, indwelling venous catheters, pacemakers, and internal cardiac defibrillators have increased the occurrence of upper extremity DVT. In the absence of PE, the major complication of DVT is postthrombotic syndrome, which causes chronic leg swelling and discomfort due to damage to the venous valves of the affected leg. In its most severe form, postthrombotic syndrome causes skin ulceration. PE is often fatal, usually due to progressive right ventricular failure. Chronic thromboembolic pulmonary hypertension is another long-term complication of PE.

Some genetic risk factors, including factor V Leiden and the prothrombin G20210A mutation, have been identified, but they account for only a minority of venous thromboembolic disease. Medical conditions that increase the risk of VTE include cancer and antiphospholipid antibody syndrome. A variety of other risk factors have been identified, including immobilization during prolonged travel, obesity, smoking, surgery, trauma, pregnancy, estrogen-containing contraceptives, postmenopausal hormone replacement, and inflammatory diseases (e.g., inflammatory bowel disease, psoriasis).

Massive PE, with thrombosis affecting at least half of the pulmonary vasculature, often includes dyspnea, syncope, hypotension, and cyanosis. Submassive PE includes RV dysfunction in the setting of normal systemic arterial pressure. Low-risk PE, which includes normal RV function and systemic arterial pressure, has an excellent prognosis.

■ CLINICAL EVALUATION

History

DVTs often present with progressive lower calf discomfort. For PE, unexplained dyspnea is the most common presenting symptom. Chest pain, cough, or hemoptysis can indicate pulmonary infarction with pleural irritation. A substantial fraction of pts hospitalized for syncope have PE.

Physical Examination

Tachypnea and tachycardia are common in PE. Low-grade fever, neck vein distention, and a loud P_2 on cardiac examination can be seen. Hypotension and cyanosis suggest massive PE. Physical examination with DVT may be notable only for mild calf tenderness. However, with massive DVT, marked thigh swelling and inguinal tenderness can be observed.

Laboratory Tests

Normal D-dimer level essentially rules out PE in pts with low-to-moderate likelihood of PE, although hospitalized pts often have elevated D-dimer levels due to other disease processes. Although hypoxemia and an increased alveolar-arterial O_2 gradient may be observed in PE, arterial blood gases are rarely useful in diagnosing PE. Elevated serum troponin, plasma heart-type fatty acid-binding protein, and brain natriuretic peptide levels can be seen in PE. The electrocardiogram can show an S1Q3T3 sign in PE, but that finding is not frequently observed.

Imaging Studies

Venous ultrasonography can detect DVT by demonstrating loss of normal venous compressibility. For pts with nondiagnostic venous ultrasound studies, CT or MRI can be used to assess for DVT. Many pts with PE have no imaging evidence for DVT.

In PE, a normal chest x-ray (CXR) is common. Although not commonly observed, focal oligemia and peripheral wedge-shaped densities on CXR are well-established findings in PE. Chest CT with IV contrast has become the primary diagnostic imaging test for PE. Ventilation-perfusion lung scanning is primarily used for subjects unable to tolerate IV contrast. Transthoracic echocardiography can identify right ventricular hypokinesis with moderate-to-large PE, but it is not typically useful for diagnosing the presence of a PE. Transesophageal echocardiography can be used to identify large central PE when IV contrast chest CT scans are not appropriate (e.g., renal failure or severe contrast allergy). With the advent of contrast chest CT scans for PE diagnosis, pulmonary angiography studies are rarely performed.

Integrated Diagnostic Approach

An integrated diagnostic approach that considers the clinical suspicion for DVT and PE is required. For individuals with a low clinical likelihood of DVT or with a low-to-moderate clinical likelihood of PE, the D-dimer level can be used to determine if further imaging studies are required. An algorithm for imaging studies in both DVT and PE is shown in [Fig. 135-1](#). The differential diagnosis of DVT includes a ruptured Baker's cyst and cellulitis. The differential diagnosis of PE is broad and includes pneumonia, acute myocardial infarction, and aortic dissection.

TREATMENT

Deep-Vein Thrombosis and Pulmonary Embolism

ANTICOAGULATION

Although anticoagulants do not dissolve existing clots in DVT or PE directly, they limit further thrombus formation and allow fibrinolysis to occur.

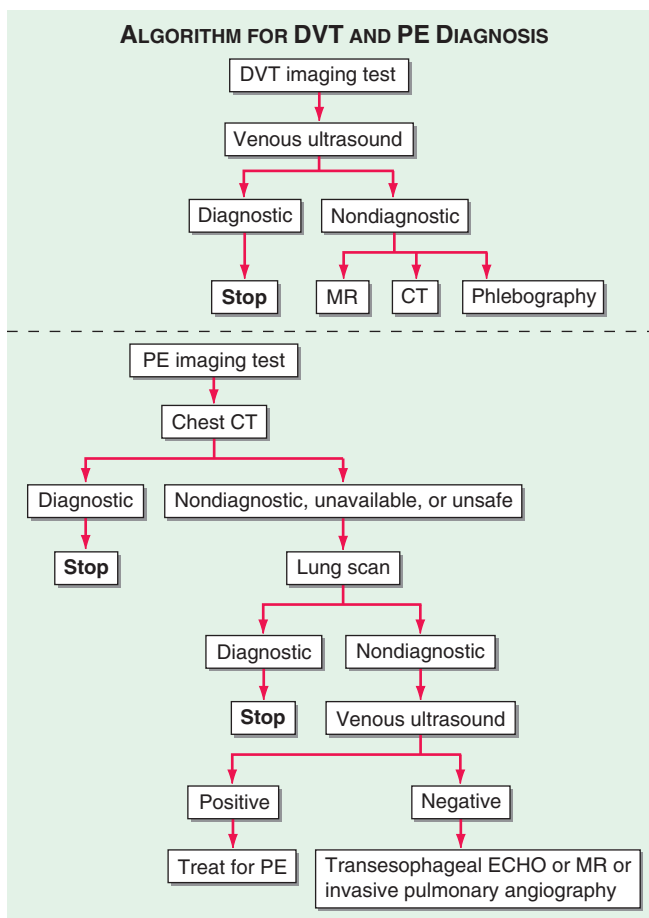


FIGURE 135-1 Imaging tests useful to diagnose DVT and PE. ECHO, echocardiogram.

Three general approaches can be used for anticoagulation in DVT and PE: (1) Parenteral therapy with unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux with overlapping transition to warfarin; (2) parenteral therapy switching after 5 days to an oral anticoagulant such as dabigatran or edoxaban; or (3) oral anticoagulation monotherapy with rivaroxaban or apixaban (both are anti-Xa agents) with a 3-week or 1-week loading dose, respectively, followed by a maintenance dose without parenteral anticoagulation.

The classical treatment approach of UFH with a target activated partial thromboplastin time (aPTT) of 60–80 s is being utilized less frequently. With that approach, UFH is typically administered with a bolus of 80 U/kg followed by a continuous infusion of approximately 18 U/kg per hour. Frequent dosage adjustments are often required to achieve and maintain a therapeutic aPTT with UFH. Heparin-induced thrombocytopenia can occur with UFH. However, the short half-life of UFH remains a significant advantage.

Alternatives to UFH for acute anticoagulation include LMWHs such as enoxaparin and dalteparin. Laboratory monitoring is not required, but doses are adjusted for renal impairment or obesity. Fondaparinux, a synthetic parenteral alternative to UFH, does not require laboratory monitoring but does require dose adjustment for body weight and renal insufficiency. Fondaparinux does not cause heparin-induced thrombocytopenia; alternatives for heparin-induced thrombocytopenia pts include direct thrombin inhibitors (e.g., argatroban or bivalirudin).

After initiating treatment with a parenteral agent, warfarin has traditionally been used for long-term oral anticoagulation. Warfarin can be initiated soon after a parenteral agent is given; however, at least 5 days are required for warfarin to achieve therapeutic anticoagulation. Warfarin is given to achieve a therapeutic international normalized ratio (INR) of the prothrombin time, which is typically an INR of 2.0–3.0. Pts vary widely in their required warfarin doses due to effects of genetics, diet, and other drugs; dosing often begins at 5 mg/d, with adjustment based on the INR. Warfarin should be avoided in pregnant pts.

Rivaroxaban and apixaban, direct factor Xa inhibitors, are approved as monotherapy for acute and extended treatment of DVT and PE, without a parenteral “bridging” anticoagulant. Dabigatran, a direct thrombin inhibitor, and edoxaban, a factor Xa inhibitor, are approved for treatment of VTE after an initial 5-day course of parenteral anticoagulation. Novel oral anticoagulants, including rivaroxaban, apixaban, and dabigatran, have the advantages of fixed dose regimens, rapid onset of effective anticoagulation, no laboratory monitoring, and fewer drug and dietary interactions.

The most troublesome adverse event from anticoagulation treatment is hemorrhage. For severe hemorrhage while undergoing treatment with UFH or LMWH, protamine can be given to reverse anticoagulation. There is no specific reversal agent for bleeding caused by fondaparinux or factor Xa inhibitors. However, the dabigatran antibody, idarucizumab, is a rapidly acting antidote for dabigatran. Severe bleeding while anticoagulated with warfarin can be treated with prothrombin complex concentrate; milder hemorrhage or markedly elevated INR values can be treated with vitamin K.

For DVT isolated to an upper extremity or calf that has been provoked by surgery, trauma, estrogen, or an indwelling central venous catheter or pacemaker, 3 months of anticoagulation is typically prescribed. For an initial episode of provoked or unprovoked proximal leg DVT or PE, the recurrence rate is high after cessation of anticoagulation. For pts with cancer and VTE, LMWH is typically used as monotherapy without warfarin and continued indefinitely unless the pt is rendered cancer-free. American College of Chest Physicians guidelines recommend considering anticoagulation for an indefinite duration with a target INR between 2 and 3 for pts with idiopathic VTE and a low bleeding risk. An alternative approach after the first 6 months of anticoagulation is to reduce the intensity of anticoagulation and to lower the target INR range to between 1.5 and 2. Another approach for pts at lower risk of recurrence, especially if there is an important reason to avoid long-term anticoagulation, is to consider low-dose aspirin after completing the initial period of standard anticoagulation.

OTHER TREATMENT MODALITIES

Although anticoagulation is the mainstay of therapy for venous thromboembolism, additional therapeutic modalities also can be employed, based on risk stratification (Fig. 135-2). Inferior vena cava filters can be used if thrombosis recurs despite adequate anticoagulation or if active bleeding precludes anticoagulation. Fibrinolytic therapy (often with tissue plasminogen activator) should be considered for massive PE, although the risk of hemorrhage is significant. Low-dose, ultrasound-facilitated, catheter-directed thrombolysis (potentially combined

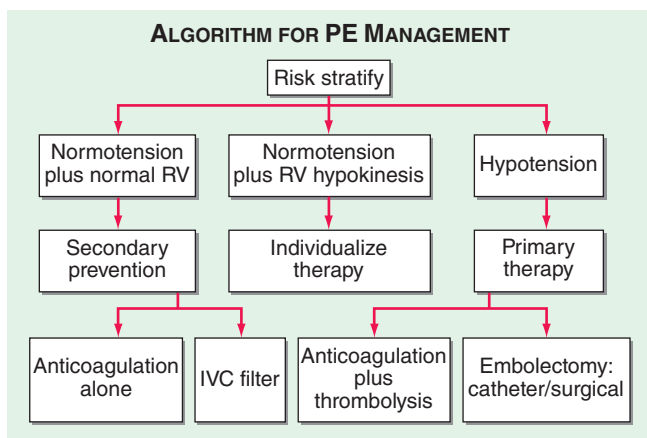


FIGURE 135-2 Acute management of pulmonary thromboembolism. IVC, inferior vena cava; RV, right ventricle.

with mechanical clot removal techniques) can be used for pts with submassive or massive PE or with extensive femoral, iliofemoral, or upper extremity DVT. Surgical embolectomy also can be considered for massive PE.

If PE pts develop chronic thromboembolic pulmonary hypertension, surgical intervention (pulmonary thromboendarterectomy) can be performed.

To reduce pt discomfort, below-knee graduated compression stockings can be used after a DVT.

Prevention of DVT and PE in hospitalized pts is often performed with low-dose UFH or LMWH. Betrixaban, a direct factor Xa inhibitor, is approved for VTE prophylaxis in acutely ill medical pts during hospitalization and continuing for a total duration of 5–6 weeks.

136 Interstitial Lung Disease

Interstitial lung diseases (ILDs) are a group of >200 disease entities characterized by diffuse lung parenchymal abnormalities. ILDs can be classified into two major groups: (1) diseases associated with predominant inflammation and fibrosis, and (2) diseases with predominantly granulomatous reaction in interstitial or vascular areas ([Table 136-1](#)). ILDs are nonmalignant and noninfectious, and they are typically chronic. The differential diagnosis of ILDs often includes infections (e.g., atypical mycobacteria, fungi), congestive heart failure, and malignancy (e.g., bronchoalveolar cell carcinoma). One of the most common ILDs associated with a granulomatous reaction, sarcoidosis, is discussed in [Chap. 169](#). Other common ILDs include idiopathic pulmonary fibrosis (IPF) and ILDs related to connective tissue diseases. Many ILDs are of unknown etiology; however, some ILDs are known to be associated with specific environmental exposures including asbestos, radiation therapy, and organic dusts.

TABLE 136-1 Major Categories of Alveolar and Interstitial Inflammatory Lung Disease

Lung response: Alveolitis, interstitial inflammation, and fibrosis

Known Cause

Asbestos	Radiation Aspiration pneumonia
Drugs (e.g., nitrofurantoin, amiodarone, methotrexate, rituximab) and chemotherapy drugs	Residual of adult respiratory distress syndrome
Smoking-related Desquamative interstitial pneumonia Respiratory bronchiolitis-associated interstitial lung disease Langerhans cell granulomatosis (eosinophilic granulomatosis of the lung)	

Unknown Cause

Idiopathic interstitial pneumonias	Pulmonary alveolar proteinosis
Idiopathic pulmonary fibrosis (usual interstitial pneumonia)	Lymphocytic infiltrative disorders (lymphocytic interstitial pneumonitis associated with connective tissue disease) Eosinophilic pneumonias
Acute interstitial pneumonia (diffuse alveolar damage)	Lymphangioleiomyomatosis Amyloidosis
Cryptogenic organizing pneumonia (bronchiolitis obliterans with organizing pneumonia) Nonspecific interstitial pneumonia	Inherited diseases Tuberous sclerosis, neurofibromatosis, Niemann-Pick disease, Gaucher disease, Hermansky-Pudlak syndrome
Connective tissue diseases Systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, Sjögren syndrome, polymyositis-dermatomyositis	Gastrointestinal or liver diseases (Crohn disease, primary biliary cirrhosis, chronic active hepatitis, ulcerative colitis) Graft-versus-host disease (bone marrow transplantation; solid organ transplantation)
Pulmonary hemorrhage syndromes Goodpasture syndrome, idiopathic pulmonary hemosiderosis, isolated pulmonary capillaritis	

Lung response: Granulomatous

Known Cause

Hypersensitivity pneumonitis (organic dusts)	Inorganic dusts: beryllium, silica
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Unknown Cause

Sarcoidosis	Bronchocentric granulomatosis
Granulomatous vasculitides	Lymphomatoid granulomatosis
Granulomatosis with polyangiitis (Wegener's), allergic granulomatosis of Churg-Strauss	

APPROACH TO THE PATIENT

Interstitial Lung Disease

History: Common presenting symptoms for pts with ILDs include dyspnea and nonproductive cough. Hemoptysis is uncommon in ILDs and could suggest diffuse alveolar hemorrhage, lymphangiomyomatosis (LAM), or granulomatosis with polyangiitis (GPA), as well as a secondary pulmonary infection. Assessment for connective tissue disease symptoms (e.g., Raynaud's) should be performed. Symptom onset and duration can assist in the differential diagnosis. Chronic symptoms (over months to years) are typically seen in most ILDs, including IPF, pneumoconioses, connective tissue diseases, and pulmonary Langerhans cell histiocytosis (PLCH or eosinophilic granuloma). Subacute symptoms (over weeks to months) can also be observed in many ILDs, especially in sarcoidosis, drug-induced ILDs, and cryptogenic organizing pneumonia (COP, also known as bronchiolitis obliterans with organizing pneumonia [BOOP]). Acute presentations are uncommon for ILDs but are typically observed with acute interstitial pneumonia (AIP), and they can also occur with eosinophilic pneumonia, GPA, and hypersensitivity pneumonitis (HP). Sudden onset of dyspnea can indicate a pneumothorax, which occurs in PLCH and tuberous sclerosis/LAM. Fatigue is common in all ILDs. Episodic presentations also are unusual, but they are more typical for eosinophilic pneumonia, HP, pulmonary hemorrhage, Churg-Strauss syndrome, and COP.

Age at presentation also can guide the differential diagnosis. IPF pts typically present at age >60, while sarcoidosis, PLCH, LAM, and connective tissue disease-related ILD often present between the ages of 20 and 40. LAM occurs exclusively in women, while IPF and ILD in rheumatoid arthritis (RA) occur more often in men. Cigarette smoking is a risk factor for several ILDs including IPF, PLCH, Goodpasture syndrome, pulmonary alveolar proteinosis (PAP), and respiratory bronchiolitis/desquamative interstitial pneumonia. Occupational exposures and hobbies can be important risk factors for many types of HP as well as pneumoconioses. Previous medical treatment with radiation and drugs also should be assessed. Family history of ILD should be obtained; variants in MUC5B and telomerase pathway genes are associated with IPF.

Physical examination: Bibasilar end-inspiratory crackles are commonly observed in inflammatory ILDs, but they are less frequent in granulomatous ILDs. Clubbing of the digits is observed in some pts with advanced ILD.

Laboratory studies: Testing can suggest an underlying connective tissue disorders (e.g., anti-cyclic citrullinated peptide antibody for RA). Specific serum antibodies can confirm exposure to relevant antigens in HP, but they do not prove causation. Anti-GM-CSF antibodies are diagnostic of acquired PAP.

Chest imaging: Chest x-ray (CXR) does not typically provide a specific diagnosis but often raises the possibility of ILD by demonstrating a bibasilar reticular pattern. Upper-lung-zone predominance of nodular opacities is noted in several ILDs, including PLCH, sarcoidosis, chronic HP, and silicosis. High-resolution chest CT scans provide improved sensitivity for the early detection of ILDs and may be sufficiently specific to allow a diagnosis to be made in ILDs such as IPF, PLCH, and asbestosis. Honeycombing is indicative of advanced fibrosis.

Pulmonary function testing: Lung function measurements can assess the extent of pulmonary involvement in pts with ILD. Most ILDs produce a restrictive

ventilatory defect with reduced total lung capacity. The forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) are typically reduced, but the ratio of FEV_1/FVC is usually normal to increased. Reduction in the diffusing capacity of the lung for carbon monoxide (DLCO) is commonly observed.

Tissue and cellular examination: In order to provide a specific diagnosis and assess disease activity, lung biopsy is often required. Bronchoscopy with transbronchial biopsies can be diagnostic in some ILDs, including sarcoidosis and eosinophilic pneumonia. In addition, bronchoscopy can assist by excluding chronic infections or lymphangitic carcinomatosis. However, the more extensive tissue samples provided by surgically obtained lung biopsies, typically obtained by video-assisted thoracic surgery, are often required to establish a specific diagnosis. Evidence for diffuse end-stage disease, such as widespread honeycombing, or other major operative risks are relative contraindications to lung biopsy procedures.

PRINCIPLES OF MANAGEMENT

If a causative agent can be identified (e.g., thermophilic actinomyces in HP), cessation of exposure to that agent is imperative. Because the response to treatment among different ILDs is so variable, identification of treatable causes is essential. Glucocorticoids can be highly effective for eosinophilic pneumonias, COP, HP, acute radiation pneumonitis, and drug-induced ILD. On the other hand, glucocorticoids are usually not beneficial in IPF. Smoking cessation is essential, especially for smoking-related ILDs such as PLCH and respiratory bronchiolitis.

Supportive therapeutic measures include providing supplemental O_2 for pts with significant hypoxemia ($PaO_2 < 55$ mmHg at rest and/or with exercise). Pulmonary rehabilitation is often beneficial. For younger pts with end-stage ILD, lung transplantation should be considered.

SELECTED INDIVIDUAL ILDS

Idiopathic Pulmonary Fibrosis

IPF, which typically includes a pathologic pattern known as usual interstitial pneumonia (UIP), is the most common idiopathic interstitial pneumonia. Cigarette smoking is a risk factor for IPF. Common respiratory symptoms include exertional dyspnea and a nonproductive cough. Physical examination is notable for inspiratory crackles at the lung bases. Clubbing may occur. High-resolution chest CT scans show subpleural reticular opacities predominantly in the lower lung fields, which are associated with honeycombing and traction bronchiectasis in advanced disease. Surgical lung biopsy is usually required to confirm the diagnosis, although pts with classic UIP patterns on CT scan may not require a biopsy. IPF can include acute exacerbations characterized by accelerated clinical deterioration over days to weeks; these exacerbations are associated with high mortality. Antifibrotic treatment with pirfenidone and nintedanib can slow the decline of pulmonary function in IPF, but immunosuppressive therapies are not effective.

Nonspecific Interstitial Pneumonia

Nonspecific interstitial pneumonia (NSIP) is a histologic pattern that can be observed in connective tissue disease, drug-induced ILD, and chronic HP. Idiopathic NSIP is a subacute restrictive process with similar presentation to IPF. High-resolution CT (HRCT) shows bilateral ground-glass opacities, and honeycombing is rare. Unlike IPF, NSIP pts have a good prognosis and typically respond well to systemic glucocorticoid treatment, cytotoxic agents, or biologics.

ILD Associated with Connective Tissue Disorders

ILDs commonly occur in scleroderma, RA, and polymyositis/dermatomyositis, but can also occur in Sjögren syndrome and systemic lupus erythematosus (SLE). Pulmonary manifestations may precede systemic manifestations of a connective tissue disorder. In addition to direct pulmonary involvement, it is necessary to consider complications of therapy (e.g., opportunistic infections), respiratory muscle weakness, esophageal dysfunction, and associated malignancies as contributors to pulmonary parenchymal abnormalities in pts with connective tissue disorders.

Progressive systemic sclerosis (scleroderma) commonly includes ILD as well as pulmonary vascular disease. Lung involvement tends to be highly resistant to available treatment, but cyclophosphamide and mycophenolate have modest benefits. Minimizing esophageal reflux with proton pump inhibitors or antireflux surgery should be considered if progressive ILD develops.

In addition to pulmonary fibrosis (ILD), RA pts can develop a range of pulmonary complications, including pleural effusions, pulmonary nodules, and pulmonary vasculitis. ILD in RA pts is more common in men. Immunosuppressive and cytotoxic agents have been used with variable success for RA-related ILD.

Dermatomyositis/polymyositis pts with anti-synthetase antibodies often have ILD. Multiple histopathologic subtypes of ILD may be present. Immunosuppressive and cytotoxic agents have been used in pts with progressive ILD.

SLE also can involve a range of pulmonary complications, including pleural effusions, pulmonary vascular disease, pulmonary hemorrhage, and BOOP. Chronic, progressive ILD is not commonly observed.

Cryptogenic Organizing Pneumonia

When the BOOP pathologic pattern occurs without another primary pulmonary disorder, the term *cryptogenic organizing pneumonia* is used. COP may present with a subacute flu-like illness. Recurrent and migratory patchy consolidative and ground glass pulmonary opacities are common. COP may occur secondary to a connective tissue disorder, medications, or an underlying malignancy; COP may also occur in isolation. Glucocorticoid therapy is often effective.

Desquamative Interstitial Pneumonia and Respiratory

Bronchiolitis-Associated ILD

Desquamative interstitial pneumonia (DIP) includes extensive macrophage accumulation in intraalveolar spaces with minimal fibrosis. It is seen almost exclusively in cigarette smokers and improves with smoking cessation. Respiratory bronchiolitis-associated ILD is a subset of DIP that includes central bronchial wall thickening, ground-glass opacities, and air trapping on HRCT; it also resolves in most pts after smoking cessation.

Acute Interstitial Pneumonia

Characterized by acute onset of hypoxemia and respiratory distress, AIP (Hamman-Rich syndrome) has high mortality with frequent recurrences among survivors. Chest imaging frequently shows patchy bilateral ground glass opacities and dependent air-space consolidation. Treatment is supportive and usually includes mechanical ventilation.

Granulomatous ILDs

Common granulomatous ILDs include sarcoidosis and HP. HP is an inflammatory lung disorder caused by repeated inhalation of an organic antigen in a susceptible individual. Treatment involves avoiding exposure to the causative antigen; systemic corticosteroids may be required in subacute or chronic HP. Granulomatous vasculitides include inflammatory infiltrates of blood vessels with associated granulomas. Hemoptysis is frequently observed. Granulomatosis with polyangiitis (Wegener's disease) commonly affects the lungs; chest

imaging abnormalities include lung nodules, patchy ground glass opacities, hilar lymphadenopathy, and consolidative opacities. Eosinophilic GPA (Churg-Strauss syndrome) frequently includes asthma, peripheral blood eosinophilia, and chronic sinusitis; common chest imaging abnormalities include consolidative opacities and small pleural effusions.

137 Diseases of the Pleura



PLEURAL EFFUSION

Pleural effusion is defined as excess fluid accumulation in the pleural space. Pleural effusions are typically detected by chest imaging (radiograph or CT); chest ultrasound can guide thoracentesis procedures. The two major classes of pleural effusions are transudates, which are caused by systemic influences on pleural fluid formation or resorption, and exudates, which are caused by local influences on pleural fluid formation and resorption. Common causes of transudative effusions are left ventricular heart failure, cirrhosis, and nephrotic syndrome. Common causes of exudative effusions are bacterial pneumonia, malignancy, viral infection, and pulmonary embolism. A more comprehensive list of the etiologies of transudative and exudative pleural effusions is provided in [Table 137-1](#). Additional diagnostic procedures are indicated with exudative effusions to define the cause of the local disease.

TABLE 137-1 Differential Diagnoses of Pleural Effusions

Transudative Pleural Effusions

1. Congestive heart failure
2. Cirrhosis
3. Nephrotic syndrome
4. Peritoneal dialysis
5. Superior vena cava obstruction
6. Myxedema
7. Urinothorax

Exudative Pleural Effusions

1. Neoplastic diseases
 - a. Metastatic disease
 - b. Mesothelioma
2. Infectious diseases
 - a. Bacterial infections
 - b. Tuberculosis
 - c. Fungal infections
 - d. Viral infections
 - e. Parasitic infections
3. Pulmonary embolism

(Continued)

TABLE 137-1 Differential Diagnoses of Pleural Effusions (Continued)

4. Gastrointestinal disease
 - a. Esophageal perforation
 - b. Pancreatic disease
 - c. Intraabdominal abscess
 - d. Diaphragmatic hernia
 - e. After abdominal surgery
 - f. Endoscopic variceal sclerotherapy
 - g. After liver transplant
5. Collagen-vascular diseases
 - a. Rheumatoid pleuritis
 - b. Systemic lupus erythematosus
 - c. Drug-induced lupus
 - d. Sjögren syndrome
 - e. Granulomatosis with polyangiitis (Wegener's)
 - f. Churg-Strauss syndrome
6. Post-coronary artery bypass surgery
7. Asbestos exposure
8. Sarcoidosis
9. Uremia
10. Meigs' syndrome
11. Yellow nail syndrome
12. Drug-induced pleural disease
 - a. Nitrofurantoin
 - b. Dantrolene
 - c. Methysergide
 - d. Bromocriptine
 - e. Procarbazine
 - f. Amiodarone
 - g. Dasatinib
13. Trapped lung
14. Radiation therapy
15. Post-cardiac injury syndrome
16. Hemothorax
17. Iatrogenic injury
18. Ovarian hyperstimulation syndrome
19. Pericardial disease
20. Chylothorax

Exudates fulfill at least one of the following three criteria: high pleural fluid/serum protein ratio (>0.5), pleural fluid lactate dehydrogenase (LDH) greater than two-thirds of the laboratory normal upper limit for serum LDH, or pleural/serum LDH ratio >0.6 . Transudative effusions typically do not meet any of these criteria. However, these criteria misidentify about 25% of transudates as exudates. For exudative effusions, pleural fluid should also be tested for pH, glucose, white blood cell count with differential, microbiologic studies, and cytology. An algorithm for determining the etiology of a pleural effusion is presented in [Fig. 137-1](#).

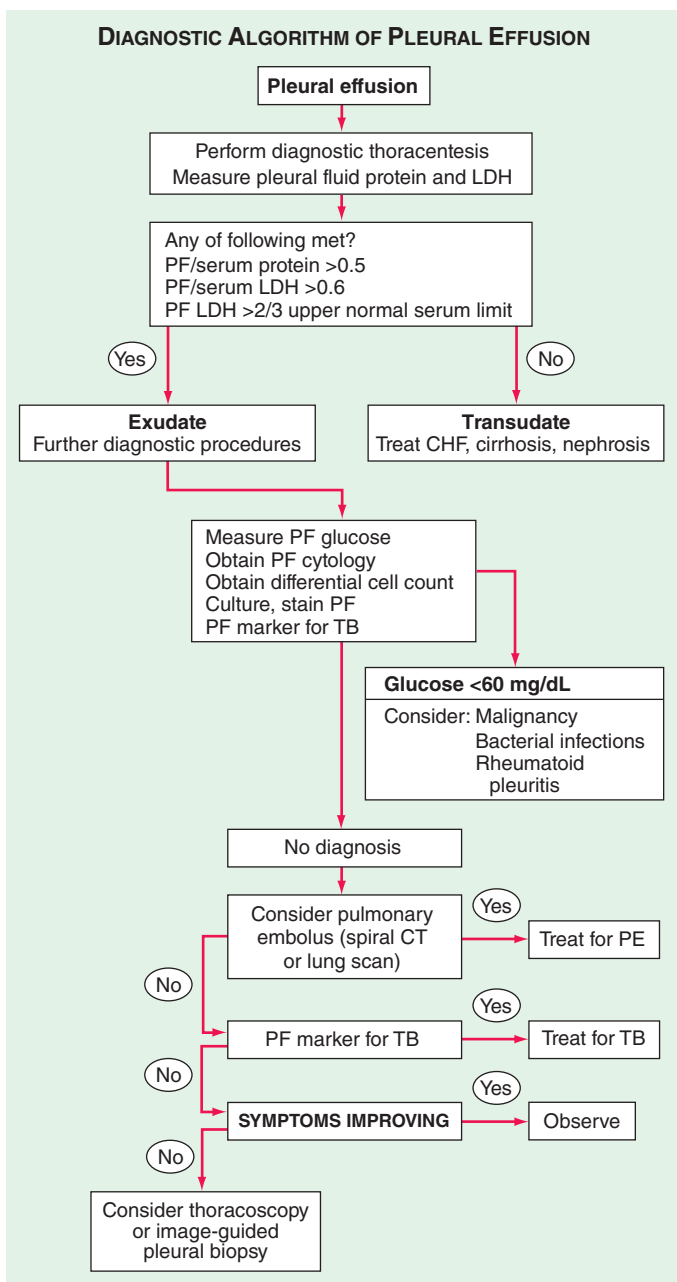


FIGURE 137-1 Approach to the diagnosis of pleural effusions. CHF, congestive heart failure; CT, computed tomography; LDH, lactate dehydrogenase; PE, pulmonary embolism; PF, pleural fluid; TB, tuberculosis.

PNEUMOTHORAX

Pneumothorax (Ptx) is defined as gas in the pleural space. Spontaneous Ptx occurs without trauma to the thorax. Primary spontaneous Ptx occurs in the absence of underlying lung disease and typically results from apical pleural blebs. Simple aspiration may be adequate treatment for an initial primary spontaneous Ptx, but recurrence typically requires thoracoscopic intervention. Secondary spontaneous Ptx occurs in the setting of underlying lung disease, most commonly chronic obstructive pulmonary disease. Chest tube placement is typically required for secondary spontaneous Ptx; thoracoscopy and/or pleurodesis (with pleural abrasion or a sclerosing agent) should also be considered.

Traumatic Ptx, resulting from either penetrating or nonpenetrating chest trauma, usually requires chest tube placement. Iatrogenic Ptx can occur from transthoracic needle biopsy, thoracentesis, placement of a central venous catheter, or transbronchial biopsy. Treatment with supplemental O₂ or aspiration is often adequate for iatrogenic Ptx, but chest tube placement may be required. Tension Ptx can result from trauma or mechanical ventilation. Positive pleural pressure in mechanical ventilation can rapidly lead to a tension Ptx with reduced cardiac output. Urgent treatment is required, either with a chest tube or, if not immediately available, with a large-bore needle inserted into the pleural space through the second anterior intercostal space.

138 Diseases of the Mediastinum



Key disease processes in the mediastinum include mediastinitis and mediastinal masses. Pneumomediastinum is an additional mediastinal abnormality that can result from alveolar rupture, esophageal perforation, or dissection of air from the neck or abdomen. Diagnosed by chest radiography, pneumomediastinum typically does not require specific treatment.

MEDIASTINITIS

Mediastinitis can be an acute or chronic process. Acute mediastinitis can result from esophageal perforation, following cardiac surgery with median sternotomy, or from infections in the neck, oral cavity, or face. Esophageal perforation can occur spontaneously or iatrogenically; surgical exploration of the mediastinum, repair of the esophageal perforation, and drainage of the pleural space and mediastinum are required. Mediastinitis after median sternotomy typically presents with wound drainage and is diagnosed by mediastinal needle aspiration. Treatment requires immediate drainage, debridement, and IV antibiotics.

Chronic mediastinitis can range from granulomatous lymph node inflammation to fibrosing mediastinitis. Most cases are due to tuberculosis or histoplasmosis.

MEDIASTINAL MASSES

Different types of mediastinal masses are found in the anterior, middle, and posterior mediastinal compartments. The most common mass lesions in the anterior mediastinum are thymomas, lymphomas, teratomas, and thyroid lesions. In the middle mediastinum, vascular masses, enlarged lymph nodes (e.g., metastatic cancer or granulomatous disease), and bronchogenic or pleuropericardial cysts are found. Posterior mediastinal masses include neurogenic tumors, gastroenteric cysts, and esophageal diverticula.

Chest CT scans are invaluable for evaluating mediastinal masses. Biopsy procedures are typically required to diagnose mediastinal masses; needle biopsy procedures (e.g., percutaneous or bronchoscopy), mediastinoscopy, and thoracoscopy are potential options.

139 Disorders of Ventilation



DEFINITION

Ventilatory disorders, reflected by abnormalities in PaCO_2 , include alterations in CO_2 production, minute ventilation, or respiratory system dead space. Many diseases can cause acute elevations in CO_2 production; chronic ventilatory disorders typically relate to reduced minute ventilation or increased respiratory dead space fraction.

HYPOVENTILATION

■ ETIOLOGY

Chronic hypoventilation can result from parenchymal lung diseases, chest wall abnormalities (e.g., severe kyphoscoliosis), sleep-disordered breathing, neuromuscular diseases, and abnormal respiratory drive. Obesity-hypoventilation syndrome (OHS) is diagnosed by body mass index $\geq 30 \text{ kg/m}^2$ and $\text{PaCO}_2 > 45 \text{ mmHg}$ in the absence of other causes of hypercapnia. Sleep-disordered breathing, typically obstructive sleep apnea, is seen in most OHS pts. Central hypoventilation syndrome is a rare disorder that includes a failure of the normal respiratory response to hypoxemia and/or hypercapnia.

■ CLINICAL ASSESSMENT

Key symptoms of hypoventilation can include dyspnea, reduced exercise capacity, orthopnea, daytime somnolence, morning headache, and anxiety. Parenchymal lung diseases, such as chronic obstructive pulmonary disease and interstitial lung disease, often include dyspnea and cough. Sleep-disordered breathing includes daytime somnolence, snoring, and fragmented sleep. Orthopnea is common in neuromuscular disorders, although weakness of the extremities or other muscle groups often precedes respiratory system muscular weakness. Hypoventilation related to neuromuscular and chest wall disorders typically begins with nocturnal hypoventilation and progresses to daytime hypercapnia. Chronic narcotic use and hypothyroidism can lead to reduced respiratory drive.

Physical examination, chest radiographic studies (CXR and possibly chest CT), and pulmonary function tests reveal most lung parenchymal and chest wall causes of hypoventilation. Measurements of maximal inspiratory and expiratory pressures or forced vital capacity can assess and monitor respiratory muscle strength. Polysomnography to assess for sleep-disordered breathing should also be considered. When pts have hypercapnia with normal pulmonary function, normal respiratory muscle strength, and normal alveolar-arterial PO_2 difference, respiratory drive abnormalities may be present, which can be revealed by polysomnography. Laboratory findings include increased PaCO_2 and often reduced PaO_2 as well. Compensatory increases in plasma bicarbonate levels and normal pH are seen in chronic hypoventilation. Eventually, pulmonary hypertension and cor pulmonale can develop. In central hypoventilation syndrome, hypercapnia worsens substantially during sleep.

TREATMENT**Hypoventilation**

In all forms of hypoventilation, if hypoxemia is present, supplemental oxygen should be considered. OHS is treated with weight reduction and nocturnal non-invasive positive pressure ventilation (NIPPV). Continuous positive airway pressure (CPAP) during sleep is adequate treatment for many OHS pts, but others require bilevel positive airway pressure (BiPAP).

NIPPV during sleep can provide ventilatory support and treat sleep apnea associated with neuromuscular disorders, chest wall disorders, and central hypoventilation. With progressive neuromuscular disorders, full-time mechanical ventilatory support is often required. Pts with respiratory drive disorders may benefit from phrenic nerve or diaphragm pacing.

HYPERVENTILATION**■ ETIOLOGY**

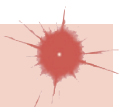
Hyperventilation is caused by ventilation in excess of requirements based on CO_2 production, leading to a reduced PaCO_2 . Although anxiety can contribute to the initiation and progression of hyperventilation, hyperventilation is not always related to anxiety. Hyperventilation can precede systemic illnesses such as diabetic ketoacidosis.

■ CLINICAL ASSESSMENT

Symptoms of chronic hyperventilation can include dyspnea, paresthesias, headache, tetany, visual disturbances, and atypical chest pain. Laboratory findings of chronic hyperventilation include a reduced PaCO_2 , but low serum bicarbonate level and near normal pH on arterial blood gas analysis.

TREATMENT**Hyperventilation**

Treatment of chronic hyperventilation is problematic. Identification of initiating factors and excluding alternative diagnoses can be helpful.

140 Sleep Apnea**■ DEFINITION AND ETIOLOGY**

Sleep apnea is defined by the presence of at least five episodes per hour of apnea (no airflow for ≥ 10 seconds) and/or hypopnea (reduction in airflow by at least 30% from baseline for ≥ 10 seconds accompanied by oxygen desaturation or arousal from sleep) in the presence of nocturnal breathing disturbance symptoms. Obstructive sleep apnea/hypopnea syndrome (OSAHS) is caused by upper airway closure during inspiration, punctuated by brief arousals that terminate apneic episodes. Risk factors for OSAHS include obesity, craniofacial factors such as micrognathia, family history of OSAHS, and male sex. Hypothyroidism

and acromegaly are systemic diseases associated with OSAHS. OSAHS increases the risk of multiple cardiovascular conditions, including coronary artery disease, heart failure, stroke, and arrhythmias.

Central sleep apnea (CSA) is characterized by respiratory pauses during sleep related to absence of respiratory effort. CSA is less common than OSAHS but may occur in conjunction with it. CSA is commonly found in heart failure and stroke pts, but may also occur from opioid medications and hypoxia (e.g., breathing at high altitudes).

■ CLINICAL ASSESSMENT

Key symptoms of OSAHS include daytime somnolence and nocturnal breathing disturbances (loud snoring, snorting, gasping, or breathing pauses). Other symptoms may include dry mouth, nocturia, morning headaches, and difficulty concentrating. Sleeping partners can provide essential historical information. Depression and hypertension are associated with OSAHS. Differential diagnosis of OSAHS includes insufficient amount of sleep, somnolence related to shift work, depression, drug effects (both stimulants and sedatives), narcolepsy, and idiopathic hypersomnolence.

Severity of OSAHS is based on the frequency of breathing disturbances (apnea-hypopnea index), duration of apneas and hypopneas, amount of oxygen desaturation during respiratory disturbances, degree of sleep fragmentation, and intensity of daytime somnolence.

Physical examination should include assessment of body mass index, waist and neck circumference, jaw and upper airway structure, nasal cavity, and blood pressure. Potentially related systemic illnesses, including acromegaly and hypothyroidism, should be considered.

Diagnostic testing often includes a polysomnogram in a sleep laboratory. However, home sleep studies without neurophysiologic monitoring may be used for screening. Significant daytime somnolence with a negative home screening study should be followed by a full polysomnogram.

TREATMENT

Sleep Apnea

In pts with OSAHS, efforts to reduce weight in obese pts, limit alcohol use, optimize sleep duration, regulate sleep schedules, treat nasal allergies, and carefully withdraw sedative medications should be pursued.

The primary therapy for OSAHS is continuous positive airway pressure (CPAP), delivered through a nasal or nasal-oral mask. Selecting a comfortable mask delivery system and titrating the appropriate amount of CPAP are essential. Airway drying related to CPAP can be reduced by including a heated humidification component in the CPAP system. Alternative OSAHS therapies include mandibular repositioning splints (oral devices), which hold the jaw and tongue forward to widen the pharyngeal airway. These devices are typically used for mild OSAHS pts or pts who do not tolerate CPAP. Several types of surgical procedures have been used in OSAHS, including bariatric surgery in obese pts, tonsillectomy, and pharyngeal surgery. Tracheostomy is curative since it bypasses the upper airway obstruction site, but it is rarely used. No drugs have been proven to reduce apneic events.

Treatment of CSA is challenging; it involves managing any predisposing conditions, such as congestive heart failure.

141 Acute Renal Failure

■ DEFINITION

Acute renal failure (ARF) or acute kidney injury (AKI), defined as a measurable increase in the serum creatinine (Cr) concentration (usually relative increase of 50% or absolute increase by 44–88 $\mu\text{mol/L}$ [0.5–1.0 mg/dL]), occurs in ~5–7% of hospitalized pts. It is associated with a substantial increase in in-hospital mortality and morbidity. AKI can be anticipated in some clinical circumstances (e.g., after radiocontrast exposure or major surgery), and there are no specific pharmacologic therapies proven helpful at preventing or reversing the condition. It is important to recognize that AKI is a clinical diagnosis and not a structural one. A pt may have AKI with or without injury to the kidney parenchyma. AKI can range in severity from asymptomatic and transient changes in laboratory parameters of glomerular filtration rate (GFR), to overwhelming and rapidly fatal derangements in effective circulating volume regulation and electrolyte and acid-base composition of the plasma. Maintaining optimal renal perfusion and intravascular volume is critical in most clinical circumstances; important cofactors in AKI include hypovolemia and drugs that interfere with renal perfusion and/or glomerular filtration (nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme [ACE] inhibitors, and angiotensin receptor blockers).

■ DIFFERENTIAL DIAGNOSIS

The separation into three broad categories (prerenal, intrinsic renal, and postrenal failure) is of considerable clinical utility (Table 141-1). *Prerenal failure* is most common among hospitalized pts. It may result from true volume depletion (e.g., diarrhea, vomiting, GI or other hemorrhage) or “arterial underfilling,” i.e., reduced renal perfusion in the setting of adequate or excess blood volume. Reduced renal perfusion may be seen in congestive heart failure (CHF) (due to reduced cardiac output and/or potent vasodilator therapy), hepatic cirrhosis (due mostly to peripheral vasodilation and arteriovenous shunting), nephrotic syndrome and other states of severe hypoproteinemia (total serum protein <54 g/L [<5.4 g/dL]), and renovascular disease (because of fixed stenosis at the level of the main renal artery or large branch vessels). Several drugs can reduce renal perfusion, most notably NSAIDs. ACE inhibitors and angiotensin II receptor antagonists may reduce GFR but do not tend to reduce renal perfusion.

Causes of *intrinsic renal failure* depend on the clinical setting. Among hospitalized pts, especially on surgical services or in intensive care units, acute tubular necrosis (ATN) is the most common diagnosis. A well-defined ischemic event or toxic exposure (e.g., aminoglycoside therapy) may lead to in-hospital ATN. Alternatively, pts may be admitted to the hospital with ATN associated with rhabdomyolysis; common predisposing factors in rhabdomyolysis include alcoholism, hypokalemia, and various drugs (e.g., statins). Allergic interstitial nephritis, usually due to antibiotics (e.g., penicillins, cephalosporins, sulfa drugs, quinolones, and rifampin), or NSAIDs, may also be responsible. More recently, the use of immune checkpoint inhibitors in cancer therapy has been linked to the development of interstitial nephritis. Radiographic contrast dyes may cause AKI in pts with preexisting kidney disease; the risk is substantially higher in diabetics

TABLE 141-1 Common Causes of Acute Kidney Injury**Prerenal**

Volume depletion

Blood loss

GI fluid loss (e.g., vomiting, diarrhea)

Overzealous diuretic use

Volume overload with reduced renal perfusion

Congestive heart failure

Low-output with systolic dysfunction

“High-output” (e.g., anemia, thyrotoxicosis)

Hepatic cirrhosis

Severe hypoproteinemia

Renovascular disease

Drugs

NSAIDs, cyclosporine, tacrolimus, ACE inhibitors, ARBs, cisplatin, aminoglycosides

Other

Hypercalcemia, “third spacing” (e.g., pancreatitis, systemic inflammatory response), hepatorenal syndrome

Intrinsic

ATN

Hypotension or shock, prolonged prerenal azotemia, postoperative sepsis syndrome, rhabdomyolysis, hemolysis, drugs

Radiocontrast, aminoglycosides, cisplatin

Other tubulointerstitial disease

Allergic interstitial nephritis

Pyelonephritis (bilateral, or unilateral in single functional kidney)

Heavy metal poisoning

Atheroembolic disease—after vascular procedures, thrombolysis, or anticoagulation

Glomerulonephritis

1. ANCA-associated: granulomatosis with polyangiitis (GPA), idiopathic pauci-immune GN, PAN

2. Anti-GBM disease; isolated or with pulmonary involvement (Goodpasture's syndrome)

3. Immune complex-mediated

Subacute bacterial endocarditis, SLE, cryoglobulinemia (with or without hepatitis C infection), postinfectious GN (classically poststreptococcal)

IgA nephropathy and Henoch-Schönlein purpura

Glomerular endotheliopathies

Thrombotic microangiopathy, malignant hypertension, scleroderma, antiphospholipid syndrome, preeclampsia

Postrenal (Urinary Tract Obstruction)

Bladder neck obstruction, bladder calculi

Prostatic hypertrophy

Ureteral obstruction due to compression

Pelvic or abdominal malignancy, retroperitoneal fibrosis

Nephrolithiasis

Papillary necrosis with obstruction

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; ARBs, angiotensin receptor blockers; ATN, acute tubular necrosis; GBM, glomerular basement membrane; GN, glomerulonephritis; GPA, granulomatosis with polyangiitis; PAN, polyarteritis nodosa.

with chronic kidney disease. Coronary angiography, other vascular procedures, thrombolysis, or anticoagulation may lead to atheroemboli, which cause AKI due to both hemodynamic and inflammatory effects; livedo reticularis, embolic phenomena with preserved peripheral pulses, and eosinophilia are important clues to this diagnosis. Acute glomerulonephritis (GN) ([Chap. 145](#)) and thrombotic microangiopathies may also cause AKI. Thrombotic microangiopathies can be clinically subdivided into renal-limited forms (e.g., *Escherichia coli*-associated hemolytic uremic syndrome [HUS]) and systemic forms (e.g., thrombotic thrombocytopenic purpura [TTP]). “Atypical HUS,” occurring in the absence of HUS-associated bacterial toxins, is associated with hereditary mutations in complement proteins or complement regulatory proteins, leading to exaggerated endothelial sensitivity to complement-mediated cytolysis. A variety of drugs can cause thrombotic microangiopathies, including calcineurin inhibitors (cyclosporine and tacrolimus), quinine, antiplatelet agents (e.g., ticlopidine), inhibitors of the action of vascular endothelial growth factor (VEGF), and chemotherapeutics (e.g., and gemcitabine). Important associated disorders in TTP include HIV infection, bone marrow transplantation, systemic lupus erythematosus (SLE), and antiphospholipid syndrome.

Postrenal failure is due to urinary tract obstruction, which is also more common among ambulatory rather than hospitalized pts. More common in men than women, it is most often caused by ureteral or urethral blockade. Occasionally, stones, sloughed renal papillae, or malignancy (primary or metastatic) may cause more proximal obstruction.

■ CHARACTERISTIC FINDINGS AND DIAGNOSTIC WORKUP

All pts with AKI manifest some degree of azotemia (increased blood urea nitrogen [BUN] and Cr). Other clinical features depend on the etiology of renal disease. Pts with *prerenal azotemia* due to volume depletion usually demonstrate orthostatic hypotension, tachycardia, low jugular venous pressure, and dry mucous membranes. Pts with prerenal azotemia and CHF (“cardiorenal syndrome”) may show jugular venous distention, an S₃ gallop, and peripheral and pulmonary edema. Therefore, the physical examination is critical in the workup of pts with prerenal AKI. In general, the BUN/Cr ratio tends to be high (>20:1), more so with volume depletion and CHF than with cirrhosis. The uric acid may also be disproportionately elevated in noncirrhotic prerenal states (due to increased proximal tubular absorption). Urine chemistries tend to show low urine [Na⁺] (<10–20 mmol/L, <10 with hepatorenal syndrome) and a fractional excretion of sodium (FE_{Na}) of <1% ([Table 141-2](#)). The urinalysis (UA) typically shows hyaline and a few granular casts, without cells or cellular casts. Renal ultrasonography is usually normal.

Pts with *intrinsic renal disease* present with varying complaints. GN is often accompanied by hypertension and mild to moderate edema (associated with Na retention and proteinuria, and sometimes with gross hematuria). An antecedent prodromal illness and/or prominent extrarenal symptoms and signs may occur if GN occurs in the context of a systemic illness, e.g., vasculitis or SLE; these may include hemoptysis or pulmonary hemorrhage (vasculitis and Goodpasture’s syndrome), arthralgias/arthritis (vasculitis or SLE), serositis (SLE), and unexplained sinusitis (vasculitis). The urine chemistries may be indistinguishable from those in pts with prerenal failure; in fact, some pts with GN have renal hypoperfusion (due to glomerular inflammation and ischemia) with resultant hyperreninemia leading to acute volume expansion and hypertension. The urine sediment can be very helpful in these cases. Red blood cell (RBC), white blood cell (WBC), and cellular casts are characteristic of GN; RBC casts are rarely seen in other conditions (i.e., they are highly specific). In the setting of inflammatory

TABLE 141-2 Urine Diagnostic Indices in Differentiation of Prerenal versus Intrinsic Renal Azotemia

DIAGNOSTIC INDEX	TYPICAL FINDINGS	
	PRERENAL AZOTEMIA	INTRINSIC RENAL AZOTEMIA
Fractional excretion of sodium (%) ^a $U_{Na} \times P_{Cr} / P_{Na} \times U_{Cr} \times 100$	<1	>1
Urine sodium concentration (mmol/L)	<10	>20
Urine creatinine to plasma creatinine ratio	>40	>20
Urine urea nitrogen to plasma urea nitrogen ratio	>8	<3
Urine specific gravity	>1.018	<1.015
Urine osmolality (mosmol/kg H ₂ O)	>500	<300
Plasma BUN/creatinine ratio	>20	<10–15
Renal failure index $U_{Na} / U_{Cr} / P_{Cr}$	<1	>1
Urinary sediment	Hyaline casts	Muddy brown granular casts

^aMost sensitive indices.

Abbreviations: P_{Cr}, plasma creatinine concentration; P_{Na}, plasma sodium concentration; U_{Cr}, urine creatinine concentration; U_{Na}, urine sodium concentration.

nephritis (GN or interstitial nephritis, see next), there may be increased renal echogenicity on ultrasonography. Unlike pts with GN, pts with interstitial diseases are less likely to have hypertension or proteinuria; a notable exception is NSAID-associated acute interstitial nephritis, which can be accompanied by proteinuria due to an associated minimal-change glomerular lesion. Hematuria and pyuria may present on UA. The classic sediment finding in allergic interstitial nephritis is a predominance (>10%) of urinary eosinophils with Wright's or Hansel's stain; however, urinary eosinophils can be increased in several other causes of AKI, such that measurement of urine eosinophils has no diagnostic utility in renal disease. WBC casts may also be seen, particularly in cases of pyelonephritis.

The urinary sediment of pts with ischemic or toxic ATN will characteristically contain pigmented "muddy-brown" granular casts and casts containing tubular epithelial cells; free tubular epithelial cells can also be seen. The FE_{Na} is typically >1% in ATN, but may be <1% in pts with milder, nonoliguric ATN (e.g., from rhabdomyolysis) and in pts with severe underlying "prerenal" disorders, such as CHF or cirrhosis.

Pts with *postrenal* AKI due to urinary tract obstruction are usually less severely ill than pts with prerenal or intrinsic renal disease, and their presentation may be delayed until azotemia is markedly advanced (BUN >54 μmol/L [150 mg/dL], Cr >1060–1325 μmol/L [12–15 mg/dL]). An associated impairment of urinary concentrating ability often "protects" the pt from complications of volume overload. Urinary electrolytes typically show an FE_{Na} >1%, and microscopic examination of the urinary sediment is usually bland. Ultrasonography is the key initial diagnostic tool. More than 90% of pts with postrenal AKI show obstruction of the urinary collection system on ultrasound (e.g., dilated ureter, calyces); false negatives include hyperacute obstruction and encasement of the ureter and/or kidney by tumor or of the ureter by retroperitoneal fibrosis, functionally obstructing urinary outflow without structural dilation. Other imaging techniques, such

as a furosemide renogram (MAG3 nuclear medicine study), may be required to define better the presence or absence of obstructive uropathy.

TREATMENT

Acute Renal Failure

Treatment should focus on providing etiology-specific supportive care. For example, pts with prerenal failure due to GI fluid loss may experience relatively rapid correction of AKI after the administration of IV fluid to expand volume. The same treatment in prerenal pts with CHF would be counterproductive; in this case, treatment of the underlying disease with vasodilators and/or inotropic agents would more likely be of benefit.

There are relatively few intrinsic renal causes of AKI for which there is safe and effective therapy. GN associated with vasculitis or SLE may respond to high-dose glucocorticoids and cytotoxic agents (e.g., cyclophosphamide), or high-dose glucocorticoids and monoclonal antibodies against the CD20 protein on B cells (rituximab and related agents); plasmapheresis and plasma exchange may be useful in other selected circumstances (e.g., Goodpasture's syndrome and TTP, respectively). Antibiotic therapy may be sufficient for the treatment of AKI associated with pyelonephritis or endocarditis. There are conflicting data regarding the utility of glucocorticoids in allergic interstitial nephritis. However, many practitioners advocate the use of glucocorticoids in pts with clinical evidence of progressive renal insufficiency despite discontinuation of the offending drug, or with history evidence of potentially reversible, severe disease.

The treatment of urinary tract obstruction often involves consultation with a urologist. Interventions as simple as Foley catheter placement or as complicated as multiple ureteral stents and/or nephrostomy tubes may be required.

DIALYSIS FOR AKI AND RECOVERY OF RENAL FUNCTION

Most cases of community- and hospital-acquired AKI resolve with conservative supportive measures, time, and patience. If nonprerenal AKI continues to progress, dialysis must be considered. The traditional indications for dialysis—volume overload refractory to diuretic agents; hyperkalemia; encephalopathy not otherwise explained; pericarditis, pleuritis, or other inflammatory serositis; and severe metabolic acidosis, compromising respiratory or circulatory function—can seriously compromise recovery from acute nonrenal illness. Therefore, dialysis should generally be provided in advance of these complications. The inability to provide requisite fluids for antibiotics, inotropes and other drugs, and/or nutrition should also be considered an indication for acute dialysis.

Dialytic options for AKI include (1) intermittent hemodialysis (IHD), (2) peritoneal dialysis (PD), and (3) continuous renal replacement therapy (CRRT, i.e., continuous arteriovenous or venovenous hemodiafiltration). Most pts are treated with IHD. It is unknown whether conventional thrice-weekly hemodialysis is sufficient or more frequent treatments are required. Few centers rely on PD for management of AKI (risks include infection associated with intraperitoneal catheter insertion and respiratory compromise due to abdominal distention). At some centers, CRRT is prescribed only in pts intolerant of IHD, usually because of hypotension; other centers use it as the modality of choice for pts in intensive care units. Hybrid hemodialysis techniques, such as slow low-efficiency dialysis (SLED), are equally effective and may be used in centers in which CRRT is not employed.

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Chronic Kidney Disease
and Uremia**■ EPIDEMIOLOGY**

The prevalence of chronic kidney disease (CKD), generally defined as a long-standing, irreversible impairment of kidney function, is substantially greater than the number of pts with end-stage renal disease (ESRD), now $\geq 500,000$ in the United States. There is a spectrum of disease related to decrements in renal function; clinical and therapeutic issues differ greatly depending on whether the glomerular filtration rate (GFR) reduction is moderate (stage 3 CKD, 30–59 mL/min per 1.73 m²) (see [Table 48-1](#)), severe (stage 4 CKD, 15–29 mL/min per 1.73 m²), or “end-stage renal disease” (stage 5 CKD, <15 mL/min per 1.73 m²). Dialysis is usually required once GFR <10 mL/min per 1.73 m². Common causes of CKD are outlined in [Table 142-1](#).

■ DIFFERENTIAL DIAGNOSIS

The first step in the differential diagnosis of CKD is establishing its chronicity, i.e., disproving a major acute component. The two most common means of determining disease chronicity are the history and prior laboratory data (if available) and the renal ultrasound, which is used to measure kidney size. In general, kidneys that have shrunk (<10–11.5 cm, depending on body size) are more likely affected by chronic disease. While reasonably specific (few false positives), reduced kidney size is only a moderately sensitive marker for CKD, i.e., there are several relatively common conditions in which kidney disease may be chronic without any reduction in renal size. Diabetic nephropathy, HIV-associated nephropathy, and infiltrative diseases such as multiple myeloma or amyloidosis may in fact be associated with relatively large kidneys despite chronicity. Renal biopsy, although rarely performed in pts with CKD, is a more reliable means of proving chronicity; a predominance of glomerulosclerosis or interstitial fibrosis argues strongly for chronic disease. Hyperphosphatemia, anemia, and other laboratory abnormalities are not reliable indicators in distinguishing acute from chronic disease.

Once chronicity has been established, clues from the physical examination, laboratory panel, and urine sediment evaluation can be used to determine etiology. A detailed history will identify important comorbid conditions, such as diabetes, HIV seropositivity, or peripheral vascular disease. The family history

TABLE 142-1 Common Causes of Chronic Renal Failure

Diabetic nephropathy
Hypertensive nephropathy ^a
Glomerulonephritis
Renovascular disease (ischemic nephropathy)
Polycystic kidney disease
Reflux nephropathy and other congenital renal diseases
Interstitial nephritis, including analgesic nephropathy
HIV-associated nephropathy
Transplant allograft failure (“chronic rejection”)

^aOften diagnosis of exclusion; very few pts undergo renal biopsy; may be occult renal disease with hypertension.

is paramount in the workup of autosomal dominant polycystic kidney disease or hereditary nephritis (Alport's syndrome). An occupational history may reveal exposure to environmental toxins or culprit drugs (including over-the-counter agents, such as analgesics or Chinese herbs).

Physical examination may demonstrate abdominal masses (i.e., polycystic kidneys), diminished pulses or femoral/carotid bruits (i.e., atherosclerotic peripheral vascular disease), or abdominal or femoral bruits (i.e., renovascular disease). The history and examination may also yield important data regarding severity of disease. Excoriations (uremic pruritus), pallor (anemia), muscle wasting, and a nitrogenous fetor are all signs of advanced CKD, as are pericarditis, pleuritis, and asterixis, complications of particular concern that usually prompt the initiation of dialysis.

Laboratory Findings

Serum and urine laboratory findings typically provide additional information useful in determining the etiology and severity of CKD; serial studies determine the pace of progression and/or whether the renal failure is in fact acute. Heavy proteinuria (>3.5 g/d), hypoalbuminemia, hypercholesterolemia, and edema suggest nephrotic syndrome ([Chap. 145](#)). Diabetic nephropathy, membranous nephropathy, focal segmental glomerulosclerosis, minimal change disease, amyloid, and HIV-associated nephropathy are principal causes. Proteinuria may decrease slightly with decreasing GFR, but rarely to normal levels. Hyperkalemia and metabolic acidosis may complicate all forms of CKD eventually, but can be more prominent in pts with interstitial renal diseases. Serum and urine protein electrophoresis, in addition to serum free light chains, should be obtained in all pts >35 years of age with CKD to exclude paraproteinemia-associated renal disease. If underlying glomerulonephritis is suspected, autoimmune disorders such as lupus and infectious etiologies such as hepatitis B and C should be assessed. Serum concentrations of calcium, phosphate, vitamin D, and parathyroid hormone (PTH) should be measured to evaluate metabolic bone disease. Hemoglobin, vitamin B₁₂, folate, and iron studies should be measured to evaluate anemia.

■ THE UREMIC SYNDROME

The culprit toxin(s) responsible for the uremic syndrome remain elusive. The serum creatinine (Cr) is the most common laboratory surrogate of renal function. GFR can be estimated using serum Cr-based equations derived from the Modification of Diet in Renal Disease Study. This "eGFR" is now reported with serum Cr by most clinical laboratories in the United States and is the basis for the National Kidney Foundation classification of CKD (see [Table 48-1](#)). In pts with low muscle mass, resulting in lesser generation of creatinine, creatinine-based measurement of GFR ("eGFR") may yield an overestimate of the actual GFR; measurement of cystatin-C may yield a more helpful, accurate estimate of eGFR under these circumstances.

Uremic symptoms tend to develop with serum Cr >530 – 710 $\mu\text{mol/L}$ (>6 – 8 mg/dL) or Cr_{Cl} <10 mL/min, although these values vary widely. Uremia is thus a clinical diagnosis made in pts with CKD. Symptoms of advanced uremia include anorexia, weight loss, dyspnea, fatigue, pruritus, sleep and taste disturbance, and confusion and other forms of encephalopathy. Key findings on physical examination include hypertension, jugular venous distention, pericardial and/or pleural friction rub, muscle wasting, asterixis, excoriations, and ecchymoses. Pts may suffer from excessive bleeding due to uremic platelet dysfunction. Laboratory abnormalities may include hyperkalemia, hyperphosphatemia, metabolic acidosis, hypocalcemia, hyperuricemia, anemia, and hypoalbuminemia. Most of these abnormalities eventually resolve with initiation of dialysis or renal transplantation ([Chaps. 143](#) and [144](#)) or with appropriate drug therapies (see next).

TREATMENT**Chronic Kidney Disease and Uremia**

Hypertension complicates many forms of CKD and warrants aggressive treatment to reduce the risk of stroke and potentially to slow the progression of CKD (see below). Volume overload contributes to hypertension in many cases, and potent diuretic agents are frequently required. Anemia can be ameliorated with recombinant human erythropoietin (rHuEPO); current practice is to target a hemoglobin concentration of 90–115 g/L. Iron deficiency and/or other causes of anemia can reduce the response to rHuEPO and should be investigated if present. Iron supplementation is often required; many pts require parenteral iron therapy, since intestinal iron absorption is reduced in CKD.

Hyperphosphatemia can be controlled with judicious restriction of dietary phosphorus and the use of postprandial phosphate binders, either calcium-based salts (calcium carbonate or acetate) or nonabsorbed agents (e.g., sevelamer). Hyperkalemia should be controlled with dietary potassium restriction or with potassium binders such as sodium zirconium cyclosilicate (ZS-9) or patiromer; the potassium binder kayexalate has been associated with colonic necrosis and is no longer recommended for chronic management of hyperkalemia. Dialysis should be considered if the potassium is >6 mmol/L on repeated occasions, despite these measures. Dialysis may also be necessary to manage diuretic-resistant hypervolemia. It is also advisable to begin dialysis if severe anorexia, weight loss, and/or hypoalbuminemia develop, as it has been definitively shown that outcomes for dialysis pts with malnutrition are particularly poor.

SLOWING PROGRESSION OF RENAL DISEASE

Prospective clinical trials have explored the roles of blood pressure control and dietary protein restriction on the rate of progression of renal failure. Control of hypertension is of benefit, although angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may exert unique beneficial effects, most likely due to their effects on intrarenal hemodynamics. The effects of ACE inhibitors and ARBs are most pronounced in pts with diabetic nephropathy and in those without diabetes but with significant proteinuria (>1 g/d). Diuretics and other antihypertensive agents are often required, in addition to ACE inhibitors and ARBs, to optimize hypertension control and attenuate disease progression; diuretics may also help control serum $[K^+]$.

143 Dialysis**OVERVIEW**

The decision to initiate dialysis for the management of end-stage renal disease (ESRD) usually depends on a combination of the pt's symptoms, comorbid conditions, and laboratory parameters. Unless a living donor is identified, transplantation is deferred by necessity, due to the scarcity of deceased donor organs (median waiting time, 3–6 years at most transplant centers). Dialytic options

include hemodialysis and peritoneal dialysis (PD). Roughly 85% of U.S. pts are started on hemodialysis. All three forms of “renal replacement therapy” (RRT) require planning and preparation months to years before ESRD occurs; early referral to a nephrologist is thus critical for successful RRT.

Absolute indications for dialysis include severe volume overload refractory to diuretic agents, severe hyperkalemia and/or acidosis, severe encephalopathy not otherwise explained, and pericarditis or other serositis. Additional indications for dialysis include symptomatic uremia (**Chap. 142**) (e.g., intractable fatigue, anorexia, dysgeusia, nausea, vomiting, pruritus, difficulty maintaining attention and concentration) and protein-energy malnutrition/failure to thrive without other overt cause. No absolute serum creatinine, blood urea nitrogen, creatinine or urea clearance, or glomerular filtration rate (GFR) is used as an absolute cutoff for requiring dialysis, although most individuals experience, or will soon develop, symptoms and complications when the GFR is below ~10 mL/min. However, the “pre-emptive” initiation of dialysis in such pts, prior to the onset of clinical indications, does not improve outcomes in ESRD.

HEMODIALYSIS

This requires direct access to the circulation, either via a native arteriovenous fistula (AVF—the preferred method of vascular access), usually at the wrist (a “Brescia-Cimino” fistula); an arteriovenous graft, usually made of polytetrafluoroethylene; a large-bore intravenous catheter; or a subcutaneous device attached to intravascular catheters. For pts with known, progressive CKD, planning of future dialysis is critical, involving creation of an AVF many months before dialysis is necessary so as to allow for healing and vascular maturation. Blood is pumped through hollow fibers of an artificial kidney (the “dialyzer”) and bathed with a solution of favorable chemical composition (isotonic, free of urea and other nitrogenous compounds, and generally low in potassium). Dialysate $[K^+]$ is varied from 1 to 4 mM, depending on predialysis $[K^+]$ and the clinical setting. Dialysate $[Ca^{2+}]$ is typically 2.5 mg/dL (1.25 mM), $[HCO_3^-]$ typically 35 meq/L, and dialysate $[Na^+]$ 140 mM; these can also be modified, depending on the clinical situation. Most pts undergo dialysis thrice weekly, usually for 3–4 h. The efficiency of dialysis is largely dependent on the duration of dialysis, blood flow rate, dialysate flow rate, and surface area of the dialyzer.

Complications of hemodialysis are outlined in **Table 143-1**. Many of these relate to the process of hemodialysis as an intense, intermittent therapy. In contrast to the native kidney or to PD, both major dialytic functions (i.e., clearance of solutes and fluid removal, or “ultrafiltration”) are accomplished over relatively short time periods. The rapid flux of fluid can cause hypotension, even without a pt reaching “dry weight.” Hemodialysis-related hypotension is common

TABLE 143-1 Complications of Hemodialysis

Hypotension	Dialysis-related amyloidosis
Accelerated vascular disease	Protein-energy malnutrition
Rapid loss of residual renal function	Hemorrhage
Access thrombosis	Anaphylactoid reaction ^a
Access or catheter sepsis	Thrombocytopenia ^b
Arrhythmia	

^aPrimarily with first use of “bioincompatible” modified cellulosic dialyzer membranes.

^bAssociated with the use of dialyzers sterilized by e-beam treatment.

in diabetic pts whose neuropathy prevents the compensatory responses (vasoconstriction and tachycardia) to intravascular volume depletion. Occasionally, confusion or other central nervous system symptoms will occur. The dialysis “disequilibrium syndrome” refers to the development of headache, confusion, and rarely seizures, in association with rapid solute removal early in the pt’s dialysis history, before adaptation to the procedure; this complication is largely avoided by an incremental induction of chronic dialytic therapy in uremic pts, starting with treatments of short duration, lower blood flows, and lower dialysate flow rates.

PERITONEAL DIALYSIS

PD does not require direct access to the circulation; rather, it obligates placement of a peritoneal catheter that allows infusion of a dialysate solution into the abdominal cavity; this allows transfer of solutes (i.e., urea, potassium, other uremic molecules) across the peritoneal membrane, which serves as the “artificial kidney.” This solution is similar to that used for hemodialysis, except that it must be sterile, and it uses lactate, rather than bicarbonate, to provide base equivalents. PD is far less efficient at cleansing the bloodstream than hemodialysis and therefore requires a much longer duration of therapy. Pts generally have the choice of performing their own “exchanges” (2–3 L of dialysate, 4–5 times during daytime hours) or using an automated device at night. Compared with hemodialysis, PD offers the major advantages of (1) independence and flexibility, and (2) a more gentle hemodynamic profile, with better preservation of residual renal function. Again, for pts with known, progressive CKD, planning of future PD is critical, often involving creation of an “embedded” PD catheter that can be utilized months or even years later at the onset of ESRD.

Complications are outlined in [Table 143-2](#). Peritonitis is the most important complication. The clinical presentation typically consists of abdominal pain and cloudy dialysate; peritoneal fluid leukocyte count is typically $>100/\mu\text{L}$, 50% neutrophils. In addition to the negative effects of the systemic inflammatory response, protein loss is magnified severalfold during the peritonitis episode. If severe or prolonged, an episode of peritonitis may prompt removal of the peritoneal catheter or even discontinuation of the modality (i.e., switch to hemodialysis). Gram-positive organisms (especially *Staphylococcus aureus* and other *Staphylococcus* spp.) predominate; *Pseudomonas* or fungal (usually *Candida*) infections tend to be more resistant to medical therapy and typically obligate catheter removal. Antibiotic administration may be intravenous or intraperitoneal when intensive therapy is required.

TABLE 143-2 Complications of Peritoneal Dialysis

PERITONITIS	DIALYSIS-RELATED AMYLOIDOSIS
Hyperglycemia	Insufficient clearance due to vascular disease or other factors
Hypertriglyceridemia	
Obesity	
Hypoproteinemia	Uremia secondary to loss of residual renal function
	Pleural effusion due to pleuro-peritoneal leak
Gastroesophageal reflux disease	Delayed gastric emptying

144 Renal Transplantation

With the advent of more potent and well-tolerated immunosuppressive regimens and further improvements in short-term graft survival, renal transplantation remains the treatment of choice for most pts with end-stage renal disease. Results are best with living-related transplantation, in part because of optimized tissue matching and in part because waiting time and ischemic time can be minimized; ideally, these pts are transplanted prior to the onset of symptomatic uremia or indications for dialysis. Transplant centers now also perform living-unrelated donor (e.g., spousal) transplants, often in “chains” involving multiple donors to optimize tissue matching. Graft survival in these cases is far superior to that observed with deceased donor transplants, although less favorable than with living-related transplants.

In 2014, there were >12,328 deceased-donor kidney transplants and 5574 living-donor transplants in the United States, with the ratio of deceased to living donors remaining stable over the last few years. As of 2015, there were 50,692 active adult candidates on the waiting list, and <18,000 pts were transplanted. This imbalance is set to worsen over the coming years with the predicted increased rates of obesity and diabetes worldwide. In an attempt to increase utilization of marginal kidneys while insuring longevity-matching, a new allocation system was developed and recently implemented. In an additional attempt to increase utilization of deceased-donor kidneys and reduce discard rates of organs, criteria for the use of so-called expanded criteria donor (ECD) kidneys and kidneys from donors after cardiac death (DCD) have been developed. ECD kidneys are usually used for older pts who are expected to fare less well on dialysis.

Factors that influence graft survival are outlined in [Table 144-1](#). Pretransplant blood transfusion should be avoided, so as to reduce the likelihood of sensitization to incompatible HLA antigens; if transfusion is necessary, leukocyte-reduced irradiated blood is preferred. Contraindications to renal transplantation are outlined in [Table 144-2](#). Overall, the current standard of care is that the pt should

TABLE 144-1 Some Factors That Influence Graft Survival in Renal Transplantation

HLA mismatch	↓
Presensitization (preformed antibodies)	↓
Very young or older donor age	↓
Female donor sex	↓
African-American donor race (compared with white)	↓
At-risk APOL1 donor genotype (two risk alleles for ESRD)	↓
Older recipient age	↑
African-American recipient race (compared with white)	↓
Recipient diabetes as the cause of end-stage renal disease	↓
Prolonged cold ischemia time	↓
Hepatitis C infection	↓
Large recipient body size	↓

TABLE 144-2 Contraindications to Renal Transplantation**Absolute Contraindications**

Active glomerulonephritis
Active bacterial or other infection
Active or very recent malignancy
Overt AIDS^a
Active hepatitis
Severe degrees of comorbidity (e.g., advanced atherosclerotic vascular disease)

Relative Contraindications

Severe psychiatric disease
Moderately severe degrees of comorbidity
Hepatitis C infection with chronic hepatitis or cirrhosis
Noncompliance with dialysis or other medical therapy
Primary renal diseases
 Primary focal sclerosis with prior recurrence in transplant
 Multiple myeloma
 Amyloid
 Oxalosis

^aMost centers consider overt AIDS a contraindication to transplantation; however, transplantation of HIV-positive pts is increasing in frequency.

have >5 years of life expectancy to be eligible for a renal transplant, since the benefits of transplantation are only realized after a perioperative period in which the mortality rate is higher than in comparable pts on dialysis.

REJECTION

Immunologic rejection is the major hazard to the short-term success of renal transplantation. Rejection may be (1) hyperacute (immediate graft dysfunction due to presensitization) or (2) acute (sudden change in renal function occurring within weeks to months). Rejection is usually detected by a rise in serum creatinine but may also lead to hypertension, fever, reduced urine output, and occasionally graft tenderness. A percutaneous renal transplant biopsy confirms the diagnosis. Treatment usually consists of a “pulse” of methylprednisolone. In refractory or particularly severe cases, 7–10 days of a monoclonal antibody directed at human T lymphocytes may be given. Antibody-mediated rejection may require the use of anti-B cell agents and/or plasmapheresis.

IMMUNOSUPPRESSION

Maintenance immunosuppressive therapy usually consists of a three-drug regimen, with each drug targeted at a different stage in the immune response. The calcineurin inhibitors cyclosporine and tacrolimus are the cornerstones of immunosuppressive therapy. The most potent of orally available agents, calcineurin inhibitors have vastly improved short-term graft survival. Side effects of cyclosporine include hypertension, hyperkalemia, resting tremor, hirsutism, gingival hypertrophy, hyperlipidemia, hyperuricemia and gout, and a slowly progressive loss of renal function with characteristic histopathologic patterns (also seen in exposed recipients of heart and liver transplants). *Tacrolimus* (previously called FK506) is a fungal macrolide that has the same mode of action as cyclosporine

as well as a similar side-effect profile; it does not, however, produce hirsutism or gingival hyperplasia. De novo diabetes mellitus is more common with tacrolimus. Recently, the U.S. Food and Drug Administration (FDA) approved a new costimulatory blocking antibody, belatacept, as a new strategy to prevent long-term calcineurin inhibitor toxicity.

Prednisone is frequently used in conjunction with cyclosporine, at least for the first several months following successful graft function. Side effects of prednisone include hypertension, glucose intolerance, cushingoid features, osteoporosis, hyperlipidemia, acne, and depression and other mood disturbances. Some centers have adopted “steroid-free” immunosuppressive regimens to avoid prednisone-associated side effects.

Mycophenolate mofetil has proved more effective than azathioprine in combination therapy with calcineurin inhibitors and prednisone. The major side effects of mycophenolate mofetil are gastrointestinal (diarrhea is most common); leukopenia (and thrombocytopenia to a lesser extent) develops in a fraction of pts.

Sirolimus is an alternative immunosuppressive agent often used in combination with other drugs, particularly when calcineurin inhibitors are reduced or eliminated. Side effects include hyperlipidemia and oral ulcers.

OTHER COMPLICATIONS

Infection and neoplasia are important complications of renal transplantation. Infection is common in the heavily immunosuppressed host (e.g., cadaveric transplant recipient with multiple episodes of rejection requiring steroid pulses or monoclonal antibody treatment). The culprit organism depends in part on characteristics of the donor and recipient and timing following transplantation (Table 144-3). In the first month, bacterial organisms predominate. After 1 month, there is a significant risk of systemic infection with cytomegalovirus (CMV), particularly in recipients without prior exposure whose donor was CMV positive. Prophylactic use of ganciclovir or valganciclovir can reduce the risk of CMV disease. Later on, there is a substantial risk of fungal and related infections, especially in pts who are unable to taper prednisone to <20–30 mg/d. Daily low-dose trimethoprim-sulfamethoxazole is effective at reducing the risk of *Pneumocystis carinii* infection.

The polyoma group of DNA viruses (BK, JC, SV40) can be activated by immunosuppression. Reactivation of BK is associated with a typical pattern of renal

TABLE 144-3 The Most Common Opportunistic Infections in Renal Transplant Recipients

Peritransplant (<1 month)	Late (>6 months)
Wound infections	<i>Aspergillus</i>
Herpesvirus	<i>Nocardia</i>
Oral candidiasis	BK virus (polyoma)
Urinary tract infection	Herpes zoster
Early (1–6 months)	Hepatitis B
<i>Pneumocystis carinii</i>	Hepatitis C
Cytomegalovirus	
<i>Legionella</i>	
<i>Listeria</i>	
Hepatitis B	
Hepatitis C	

inflammation, BK nephropathy, which can lead to loss of the allograft; therapy typically involves reduction of immunosuppression to aid in clearance of the reactivated virus.

Epstein-Barr virus–associated lymphoproliferative disease is the most important neoplastic complication of renal transplantation, especially in pts who receive polyclonal (antilymphocyte globulin, used at some centers for induction of immunosuppression) or monoclonal antibody therapy. Non-Hodgkin's lymphoma and squamous cell carcinoma of the skin are also more common in this population.

145 Glomerular Diseases



ACUTE GLOMERULONEPHRITIS (GN)

Historically called the “nephritic syndrome.” Characterized by development, over days, of azotemia, hypertension, edema, hematuria, proteinuria, and sometimes oliguria. Salt and water retention are due to reduced glomerular filtration rate (GFR) and may result in circulatory congestion. Red blood cell (RBC) casts on urinalysis confirm diagnosis. Proteinuria is usually <3 g/d. Most forms of acute GN are mediated by humoral immune mechanisms. Clinical course depends on underlying lesion ([Table 145-1](#)).

Acute Poststreptococcal GN

This is the prototype of the nephritic syndrome and the most common cause in childhood. Nephritis develops 1–3 weeks after pharyngeal or cutaneous

TABLE 145-1 Causes of Acute Glomerulonephritis

- I. Infectious diseases
 - A. Poststreptococcal glomerulonephritis^a
 - B. Nonstreptococcal postinfectious glomerulonephritis
 1. Bacterial: infective endocarditis, “shunt nephritis,” sepsis, pneumococcal pneumonia, typhoid fever, secondary syphilis, meningococemia
 2. Viral: hepatitis B, infectious mononucleosis, mumps, measles, varicella, vaccinia, echovirus, and coxsackievirus
 3. Parasitic: malaria, toxoplasmosis
 4. IgA dominant postinfectious glomerulonephritis—usually poststaphylococcal
- II. Multisystem diseases: SLE, vasculitis, Henoch-Schönlein purpura, Goodpasture's syndrome
- III. Primary glomerular diseases: mesangiocapillary glomerulonephritis, Berger's disease (IgA nephropathy), “pure” mesangial proliferative glomerulonephritis
- IV. Miscellaneous: Guillain-Barré syndrome, irradiation of Wilms' tumor, self-administered diphtheria-pertussis-tetanus vaccine, serum sickness

^aMost common cause.

Source: Glasscock RJ, Brenner BM: Harrison's Principles of Internal Medicine, 13th ed, 1995.

infection with “nephritogenic” strains of group A β -hemolytic streptococci. Diagnosis depends on a positive pharyngeal or skin culture (if available), positive titers for antistreptococcal antigens (ASO, anti-DNAse, or antihyaluronidase), and hypocomplementemia. Renal biopsy reveals diffuse proliferative GN. Treatment consists of correction of fluid and electrolyte imbalance. In most cases, the disease is self-limited, although the prognosis is less favorable and urinary abnormalities are more likely to persist in adults.

Postinfectious GN

May follow other bacterial, viral, and parasitic infections. Examples are bacterial endocarditis, sepsis, hepatitis B, and pneumococcal pneumonia. Features are milder than with poststreptococcal GN. A specific IgA-dominant acute postinfectious GN, with a dominance of IgA deposits on immunofluorescence, can be seen after staphylococcal infections, particularly in diabetics. Control of primary infection usually produces resolution of postinfectious GN, but steroids are often administered in severe cases to avoid dialysis.

RAPIDLY PROGRESSIVE GN

Defined as a subacute reduction in GFR of $>50\%$, with evidence of a proliferative GN; causes overlap with those of acute GN (Table 145-2). Broadly classified into three major subtypes on the basis of renal biopsy findings and pathophysiology: (1) immune complex-associated, e.g., in systemic lupus erythematosus (SLE); (2) “pauci-immune,” associated with antineutrophil cytoplasmic antibodies (ANCA); and (3) associated with anti-glomerular basement (anti-GBM) antibodies, e.g., in Goodpasture’s syndrome. All three forms will typically have a proliferative, crescentic GN by light microscopy but differ in the results of the immunofluorescence and electron microscopy components of the renal biopsy.

SLE (Lupus)

Renal involvement is due to deposition of circulating immune complexes. Clinical features of SLE with or without renal involvement include arthralgias, “butterfly” skin rash, serositis, alopecia (hair loss), and central nervous system disease. Nephrotic syndrome (NS) with renal insufficiency is common. Renal biopsy reveals mesangial, focal, or diffuse GN and/or membranous nephropathy. Diffuse GN, the most common finding in renal biopsy series, is typically characterized by an active sediment, severe proteinuria, and progressive renal insufficiency and may have an ominous prognosis. Pts have a positive antinuclear antibody test, anti-dsDNA antibodies, and hypocomplementemia. Treatment includes glucocorticoids, cytotoxic agents, and/or mycophenolate mofetil.

Antineutrophil Cytoplasmic Antibody (ANCA)–Associated, Pauci-Immune GN

May be renal-limited (idiopathic pauci-immune GN) or associated with systemic vasculitis (granulomatosis with polyangiitis [GPA, formerly known as Wegener’s] or microscopic polyarteritis nodosa). Defining characteristic is the presence of circulating ANCA. These are detected by immunofluorescence of alcohol-fixed neutrophils; a “perinuclear” pattern (pANCA) is usually due to antibodies against myeloperoxidase (MPO), whereas a “cytoplasmic” pattern (cANCA) is almost always due to reactivity against proteinase-3 (PR3). Confirmatory enzyme-linked immunosorbent assay testing against the MPO and PR3 antigens is mandatory, since the pANCA pattern can be caused by antibodies against other neutrophil components, e.g., lactoferrin; these do not have the same consistent relationship to vasculitis and pauci-immune GN. The anti-MPO or anti-PR3 titer does not always correlate with disease activity.

TABLE 145-2 Causes of Rapidly Progressive Glomerulonephritis

- I. Infectious diseases
 - A. Poststreptococcal glomerulonephritis^a
 - B. Infective endocarditis
 - C. Occult visceral sepsis
 - D. Hepatitis B infection (with vasculitis and/or cryoglobulinemia)
 - E. HIV infection
 - F. Hepatitis C infection (with cryoglobulinemia, membranoproliferative glomerulonephritis)
- II. Multisystem diseases
 - A. Systemic lupus erythematosus
 - B. Henoch-Schönlein purpura
 - C. Systemic necrotizing vasculitis (including granulomatosis with polyangiitis [Wegener's])
 - D. Goodpasture's syndrome
 - E. Essential mixed (IgG/IgM) cryoglobulinemia
 - F. Malignancy
 - G. Relapsing polychondritis
 - H. Rheumatoid arthritis (with vasculitis)
- III. Drugs
 - A. Penicillamine
 - B. Hydralazine
 - C. Allopurinol (with vasculitis)
 - D. Rifampin
 - E. Cocaine adulterated with levamisole (ANCA-associated)
- IV. Idiopathic or primary glomerular disease
 - A. Idiopathic crescentic glomerulonephritis
 1. Type I—with linear deposits of Ig (anti-GBM antibody-mediated)
 2. Type II—with granular deposits of Ig (immune complex-mediated)
 3. Type III—with few or no immune deposits of Ig ("pauci-immune")
 4. Antineutrophil cytoplasmic antibody-induced, forme fruste of vasculitis
 5. Immunotactoid glomerulonephritis
 6. Fibrillary glomerulonephritis
 - B. Superimposed on another primary glomerular disease
 1. Mesangiocapillary (membranoproliferative) glomerulonephritis (especially type II)
 2. Membranous glomerulonephritis
 3. Berger's disease (IgA nephropathy)

^aMost common cause.

Abbreviation: GBM, glomerular basement membrane.

Source: Glasscock RJ, Brenner BM: Harrison's Principles of Internal Medicine, 13th ed, 1995.

Pts typically have a prodromal, "flulike" syndrome, which may encompass myalgias, fever, arthralgias, anorexia, and weight loss. There may be associated cutaneous, pulmonary, upper respiratory (sinusitis), or neurologic (mononeuritis multiplex) complications of associated systemic vasculitis.

In particular, pulmonary necrotizing capillaritis can lead to hemoptysis and pulmonary hemorrhage.

Standard initial therapy for ANCA-associated rapidly progressive GN includes methylprednisolone and cyclophosphamide; more specific depletion of B cells by anti-CD20 antibody therapy with rituximab is a more widely used alternative. Most centers will also utilize plasmapheresis in the initial management of pts with a severe pulmonary-renal syndrome; however, plasmapheresis is no longer recommended for management of severe AKI in the absence of pulmonary hemorrhage. Steroids are quickly tapered soon after the acute inflammation subsides; cyclophosphamide is continued until a stable remission is achieved, typically within 3–6 months. Pts must receive prophylaxis for *Pneumocystis carinii* (*jiroveci*) pneumonia (PCP) with trimethoprim-sulfamethoxazole, atovaquone, or dapsone. Some form of maintenance immunosuppression is standard, typically for 12–18 months after achievement of a stable remission; drugs include methotrexate, mycophenolate mofetil, and azathioprine. Notably, however, pts treated with rituximab do not require maintenance oral immunosuppression, but instead require maintenance with regular rituximab infusions. Maintenance therapy with rituximab appears to be more successful than “conventional” oral maintenance immunosuppression at preventing a relapse.

Anti-Glomerular Basement Membrane Disease

Caused by antibodies against the $\alpha 3$ NCI (noncollagenous) domain of type IV collagen; circulating anti-GBM antibody and linear immunofluorescence on renal biopsy establish the diagnosis. Pts may have isolated GN; Goodpasture's syndrome encompasses GN and lung hemorrhage. Plasma exchange may produce remission; renal prognosis is worse in those who require dialytic support, with >50% crescents on renal biopsy, or creatinine >5–6 mg/dL. Severe lung hemorrhage is treated with IV glucocorticoids (e.g., 1 g/d \times 3 days). Approximately 10–15% will also have ANCA against MPO, some with evidence of vasculitis, e.g., leukocytoclastic vasculitis in the skin.

Henoch-Schönlein Purpura

A generalized vasculitis causing IgA nephropathy, purpura, arthralgias, and abdominal pain; occurs mainly in children. Renal involvement is manifested by hematuria and proteinuria. Serum IgA is increased in half of pts. Renal biopsy is useful for prognosis. Treatment is symptomatic.

NEPHROTIC SYNDROME

Characterized by albuminuria (>3.5 g/d) and hypoalbuminemia (<30 g/L) and accompanied by edema, hyperlipidemia, and lipiduria. Protein excretion should be quantified by 24-h urine collection, but can be monitored by measurement of the urine protein:creatinine ratio or albumin:creatinine ratio on a random spot urine. The measurement of creatinine excretion helps define the adequacy of 24-h urine collections: daily creatinine excretion should be 20–25 mg/kg lean body weight in men and 15–20 mg/kg lean body weight in women. For random urine samples, the ratio of protein or albumin to creatinine in mg/dL approximates the 24-h urine protein excretion, since creatinine excretion is only slightly >1000 mg/d per 1.73 m². A urine protein:creatinine ratio of 5 is thus consistent with 5 g/d per 1.73 m². Quantification of urine protein excretion on spot urines has largely supplanted formal 24-h urine collections for monitoring or screening, due to the greater ease and the need to verify a complete 24-h collection. The total protein:creatinine ratio does not detect microalbuminuria, a level of albumin excretion that is below the level of detection by tests for total protein; urine albumin:creatinine measurement is therefore preferred as a screening tool for lesser proteinuria.

TABLE 145-3 Causes of Nephrotic Syndrome (NS)

SYSTEMIC CAUSES	GLOMERULAR DISEASE
Diabetes mellitus, SLE, amyloidosis, HIV-associated nephropathy	Membranous Minimal change disease
Drugs: gold, penicillamine, probenecid, street heroin, NSAIDs, pamidronate, interferons	Focal glomerulosclerosis
Infections: bacterial endocarditis, hepatitis B, shunt infections, syphilis, malaria, hepatic schistosomiasis	Membranoproliferative GN
Malignancy: multiple myeloma, light chain deposition disease, Hodgkin's and other lymphomas, leukemia, carcinoma of breast and GI tract	Mesangioproliferative GN Immunotactoid and fibrillary GN

Abbreviation: GN, glomerulonephritis.

Source: Glasscock RJ, Brenner BM: *Harrison's Principles of Internal Medicine*, 13th ed, 1995.

In addition to edema, the complications of NS can include renal vein thrombosis and other thromboembolic events, infection, vitamin D deficiency, protein malnutrition, and drug toxicities due to decreased protein binding.

In adults, the most common cause of NS is diabetes. A minority of cases are secondary to SLE, amyloidosis, drugs, neoplasia, or other disorders (Table 145-3). By exclusion, the remainder are idiopathic. With the exception of diabetic nephropathy, suggested by a compatible natural history of proteinuria in a diabetic pt, a renal biopsy is required to make the diagnosis and determine therapy in NS.

Minimal Change Disease

Causes about 10–15% of idiopathic NS in adults, but 70–90% of NS in children. Blood pressure is normal; GFR is normal or slightly reduced; urinary sediment is benign or may show few RBCs. Protein selectivity is variable in adults. Recent upper respiratory infection, allergies, or immunizations are present in some cases; nonsteroidal anti-inflammatory drugs can cause minimal change disease with interstitial nephritis. Acute renal failure due to associated acute tubular necrosis may rarely occur, particularly among elderly persons. Renal biopsy shows only foot process fusion on electron microscopy. Remission of proteinuria with glucocorticoids carries a good prognosis; cytotoxic therapy or calcineurin inhibitor or anti-CD20 (e.g., rituximab) therapy may be required for relapsing pts. Progression to renal failure is uncommon. Focal sclerosis should be suspected in cases that are refractory to steroid therapy; these pts are more likely to progress to end-stage renal disease (ESRD). Children with steroid-resistant MCD/FSGS are more likely to have an underlying genetic cause.

Membranous GN

Characterized by subepithelial IgG deposits; accounts for ~30% of idiopathic adult NS. Pts present with edema and nephrotic proteinuria. Blood pressure, GFR, and urine sediment are usually normal at initial presentation. Hypertension, mild renal insufficiency, and abnormal urine sediment develop later. Renal vein thrombosis can occur, with low but greater frequency than with other forms of NS. Underlying diseases such as SLE, hepatitis B, and solid tumors and exposure to such drugs as high-dose captopril or penicillamine should be sought. The majority of pts with “primary” (previously “idiopathic”) membranous GN have detectable circulating autoantibodies to the M-type phospholipase A₂ (PLA₂R),

which is expressed in glomerular podocytes; the PLA2R titer can be monitored during therapy or utilized as a screening tool for idiopathic membranous GN in NS. Approximately 10% of pts with primary membranous GN who test negative for anti-PLA2R antibodies will have antibodies against the alternative podocyte antigen THSD7A (thrombospondin type-1 domain-containing 7A protein). Some pts progress to ESRD; however, 20–33% may experience a spontaneous remission. Male gender, older age, hypertension, and persistence of significant proteinuria (>6 g/d) are associated with a higher risk of progressive disease. Optimal immunosuppressive therapy is controversial. Glucocorticoids alone are ineffective. Cytotoxic agents may promote complete or partial remission in some pts, as may cyclosporine. Anti-CD20 antibody therapy with rituximab has recently shown considerable promise, consistent with a role for B cells and anti-podocyte antibodies in the pathophysiology. Reduction of proteinuria with angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) is also an important mainstay of therapy. Venous thromboembolic events (DVTs, renal vein thrombosis, etc.) occur in about 7% of pts with membranous nephropathy; hypoalbuminemia is the most significant independent predictor of venous thrombotic risk. Prophylactic anticoagulation is not recommended for all pts, but should be considered in pts at very high risk for venous thrombosis (albumin <2.0 g/dL) with low or intermediate bleeding risk.

Focal Glomerulosclerosis (FGS)

Can be primary or secondary. Primary tends to be more acute, similar to minimal change disease in abruptness of NS, but with added features of hypertension, renal insufficiency, and hematuria. Involves fibrosis of portions of some (primarily juxtamedullary) glomeruli and is found in ~35% of pts with NS. There are several different pathologic subtypes of idiopathic FGS, with prognostic implications. In particular, the “collapsing glomerulopathy” variant has pathologic similarity to HIV-associated nephropathy (HIVAN); both nephropathies cause rapidly progressive disease.

African Americans are disproportionately affected by FGS, HIVAN, and other nondiabetic renal disease, with higher incidence, greater susceptibility (HIVAN), and a much higher risk of developing ESRD. “African-specific” variants in the *APOL1* gene, which encodes apolipoprotein L1 expressed in glomerular podocytes, have recently been implicated in this enhanced genetic risk.

Treatment of primary FGS typically begins with an extended course of steroids; fewer than half of pts undergo remission. Cyclosporine is an alternative therapy for maintenance of remission and for steroid-resistant pts. As in other glomerulopathies, reduction of proteinuria with ACE inhibitors and/or ARBs is also an important component of therapy. Finally, primary FGS may recur after renal transplant, when it may lead to loss of the allograft.

Secondary FGS can occur in the late stages of any form of kidney disease associated with nephron loss (e.g., remote GN, prior severe pyelonephritis, sickle cell disease, vesicoureteral reflux). Treatment includes anti-proteinuric therapy with ACE inhibition and blood pressure control. There is no benefit of glucocorticoids or other immunosuppressive agents in secondary FGS. Clinical history, kidney size, biopsy findings, and associated conditions usually allow differentiation of primary versus secondary causes.

Membranoproliferative Glomerulonephritis (MPGN)

Mesangial expansion and proliferation extend into the capillary loop. Two ultrastructural variants exist. In MPGN I, subendothelial electron-dense deposits are present, C3 is deposited in a granular pattern indicative of immune-complex pathogenesis, and IgG and the early components of complement may or may not be present. In MPGN II, the lamina densa of the GBM is transformed into an

electron-dense character, as is the basement membrane in Bowman's capsule and tubules. C3 is found irregularly in the GBM. Small amounts of Ig (usually IgM) are present, but early components of complement are absent.

Pts with MPGN may have associated genetic mutations in complement components or complement regulatory factors. MPGN has been proposed to be reclassified into immunoglobulin-mediated disease (driven by the classical complement pathway) and non-immunoglobulin-mediated disease (driven by the alternative complement pathway).

Serum complement levels are usually decreased. MPGN affects young adults. Blood pressure and GFR are abnormal, and the urine sediment is active. Some have acute nephritis or hematuria. Similar lesions occur in SLE and hemolytic-uremic syndrome. Infection with hepatitis C virus (HCV) has been linked to MPGN, often with associated cryoglobulinemia. Glucocorticoids, cytotoxic agents, antiplatelet agents, and plasmapheresis have been used with limited success in HCV-associated MPGN; rituximab is a newer therapy with greater evident efficacy. Therapy with a direct-acting antiviral regimen should be considered in pts with MPGN and/or cryoglobulinemic vasculitis associated with HCV infection, once the vasculitis and/or MPGN has been controlled with rituximab. Some rare subsets of MPGN associated with activation of the alternative pathway of complement activation can be successfully treated with the C5a inhibitor eculizumab.

Diabetic Nephropathy

The most common cause of NS. Although prior duration of diabetes mellitus (DM) is variable, in type 1 DM proteinuria may develop 10–15 years after onset of diabetes, progress to NS, and then lead to renal failure over 3–5 years. Retinopathy is nearly universal in type 1 diabetics with nephropathy, so much so that the absence of retinopathy should prompt consideration of another glomerular lesion (e.g., membranous nephropathy). In contrast, only ~60% of type 2 diabetics with diabetic nephropathy have retinopathy. Clinical features include proteinuria, progressive hypertension, and progressive renal insufficiency. Pathologic changes include mesangial sclerosis, diffuse, and/or nodular (Kimmelstiel-Wilson) glomerulosclerosis. However, pts rarely undergo renal biopsy; to the extent that yearly measurement of microalbuminuria is routine management for all diabetics, the natural history is an important component of the diagnosis. Pts typically demonstrate progression from microalbuminuria (30–300 mg/24 h) to dipstick-positive proteinuria (>300 mg albuminuria) and then progressively overt proteinuria and chronic kidney disease. However, proteinuria can be quite variable in diabetic nephropathy, with as much as 25 g/24 h in the absence of profound renal insufficiency or alternatively with progressive renal insufficiency and stable, modest proteinuria.

Treatment with ACE inhibitors delays the onset of nephropathy and of ESRD in type 1 diabetics with microalbuminuria and/or declining renal function and should be instituted in all pts tolerant to that class of drug. If a cough develops in a pt treated with an ACE inhibitor, an ARB is the next best choice. Type 2 diabetics with microalbuminuria or proteinuria can be treated with ACE inhibitors or ARBs. Hyperkalemia, hypotension, and/or worsening GFR can limit single or combined therapy with renin-angiotensin-aldosterone (RAA) system inhibitors. If hyperkalemia develops and cannot be controlled with (1) optimizing glucose control, (2) loop diuretics (if otherwise appropriate), or (3) treatment of metabolic acidosis (if present), then potassium binder therapy with sodium zirconium cyclosilicate (ZS-9) or patiromer should be considered, so as to maintain RAA inhibition.

Evaluation of NS is shown in [Table 145-4](#).

TABLE 145-4 Evaluation of Nephrotic Syndrome

Random spot urine for protein and creatinine
Serum albumin, cholesterol, complement
Urine protein electrophoresis
Rule out SLE, diabetes mellitus
Review drug exposure
Renal biopsy
Consider malignancy (in elderly pt with membranous GN or minimal change disease)
Consider renal vein thrombosis (if membranous GN or symptoms of pulmonary embolism are present)

Abbreviation: GN, glomerulonephritis.

ASYMPTOMATIC URINARY ABNORMALITIES

Proteinuria in the nonnephrotic range and/or hematuria unaccompanied by edema, reduced GFR, or hypertension can be due to multiple causes (Table 145-5).

TABLE 145-5 Glomerular Causes of Asymptomatic Urinary Abnormalities

- I. Hematuria with or without proteinuria
 - A. Primary glomerular diseases
 1. Berger's disease (IgA nephropathy)^a
 2. Mesangiocapillary glomerulonephritis
 3. Other primary glomerular hematurias accompanied by "pure" mesangial proliferation, focal and segmental proliferative glomerulonephritis, or other lesions
 4. "Thin basement membrane" disease (? forme fruste of Alport's syndrome)
 - B. Associated with multisystem or hereditary diseases
 1. Alport's syndrome and other "benign" familial hematurias
 2. Fabry's disease
 3. Sickle cell disease
 - C. Associated with infections
 1. Resolving poststreptococcal glomerulonephritis
 2. Other postinfectious glomerulonephritides
- II. Isolated nonnephrotic proteinuria
 - A. Primary glomerular diseases
 1. "Orthostatic" proteinuria
 2. Focal and segmental glomerulosclerosis
 3. Membranous glomerulonephritis
 - B. Associated with multisystem or heredofamilial diseases
 1. Diabetes mellitus
 2. Amyloidosis
 3. Nail-patella syndrome

^aMost common.

Source: Glasscock RJ, Brenner BM: Harrison's Principles of Internal Medicine, 13th ed, 1995.

TABLE 145-6 Serologic Findings in Selected Multisystem Diseases Causing Glomerular Disease

DISEASE	C3	Ig	FANA	ANTI-dsDNA	ANTI-GBM	CRYO-Ig	CIC	ANCA
SLE	↓	↑ IgG	+++	++	–	++	+++	±
Goodpasture's syndrome	–	–	–	–	+++	–	±	+ (10–15%)
Henoch-Schönlein purpura	–	↑ IgA	–	–	–	±	++	–
Polyarteritis	↓↑	IgG	+	±	–	++	+++	+++
Granulomatosis with polyangiitis (Wegener's)	↓↑	↑ IgA, IgE	–	–	–	±	++	+++
Cryoglobulinemia	↓	±	–		–	+++	++	–
		↓↑ IgG						
		IgA, IgD						
Multiple myeloma	–	IgE	–		–	+	–	–
Waldenström's macroglobulinemia	–	↑ IgM	–	–	–	–	–	–
Amyloidosis	–	± Ig	–	–	–	–	–	–

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; anti-dsDNA, antibody to double-stranded (native) DNA; anti-GBM, antibody to glomerular basement membrane antigens; CIC, circulating immune complexes; cryo-Ig, cryoimmunoglobulin; C3, complement component 3; FANA, fluorescent antinuclear antibody assay; Ig, immunoglobulin levels; SLE, systemic lupus erythematosus; –, normal; +, occasionally slightly abnormal; ++, often abnormal; +++, severely abnormal.

Source: Glasscock RJ, Brenner BM: Harrison's Principles of Internal Medicine, 13th ed, 1995.

Thin Basement Membrane Nephropathy

Also known as benign familial hematuria, may cause up to 25% of isolated, sustained hematuria without proteinuria. Diffuse thinning of the glomerular basement membrane on renal biopsy, with minimal other changes. May be hereditary, caused in some instances by defects in type IV collagen. Pts have persistent glomerular hematuria, with minimal proteinuria. The renal prognosis is controversial but appears to be relatively benign.

IgA Nephropathy

Another very common cause of recurrent hematuria is of glomerular origin. Episodes of macroscopic hematuria are present with flulike symptoms, without skin rash, abdominal pain, or arthritis. Renal biopsy shows diffuse mesangial deposition of IgA, often with lesser amounts of IgG, nearly always by C3 and properdin but not by C1q or C4. Prognosis is variable; 50% develop ESRD within 25 years; men with hypertension and heavy proteinuria are at highest risk. Glucocorticoids and other immunosuppressive agents have not proved successful, except in pts who present with rapidly progressive GN and/or proliferative GN on renal biopsy. Rarely causes loss of allografts.

Glomerulopathies Associated with Multisystem Disease

(See [Table 145-6](#).)

146 Renal Tubular Disease



Tubulointerstitial diseases constitute a diverse group of acute and chronic, hereditary and acquired disorders involving the renal tubules and supporting structures ([Table 146-1](#)). Functionally, they may result in a wide variety of physiologic phenotypes, including nephrogenic diabetes insipidus (DI) with polyuria, non-anion-gap metabolic acidosis, salt wasting, and hypo- or hyperkalemia. Azotemia is common, owing to associated glomerular fibrosis and/or ischemia. Compared with glomerulopathies, proteinuria and hematuria are less dramatic, and hypertension is less common. The functional consequences of tubular dysfunction are outlined in [Table 146-2](#).

ACUTE INTERSTITIAL NEPHRITIS (AIN)

Drugs are a leading cause of this type of renal failure, usually identified by a gradual rise in the serum creatinine at least several days after the institution of therapy, occasionally accompanied by fever, eosinophilia, rash, and arthralgias. The onset of renal dysfunction may be very rapid in pts who have previously been sensitized to the offending agent; this is particularly true for rifampin, for which intermittent or interrupted therapy appears to be associated with the development of AIN. In addition to azotemia, there may be evidence of tubular dysfunction (e.g., hyperkalemia, metabolic acidosis). Urinalysis may show hematuria, pyuria, white cell casts, and eosinophiluria on Hansel's or Wright's stain; notably, however, eosinophiluria is not specific for AIN, occurring in other causes of acute kidney injury (AKI), including atheroemboli; "urine for eosinophils" is not a diagnostically useful test.

TABLE 146-1 Principal Causes of Tubulointerstitial Disease of the Kidney

Toxins	
Exogenous toxins	Metabolic toxins
Analgesic nephropathy ^a	Acute uric acid nephropathy
Lead nephropathy	Gouty nephropathy ^a
Chinese herb nephropathy	Hypercalcemic nephropathy
Balkan endemic nephropathy	Hypokalemic nephropathy
Miscellaneous nephrotoxins (e.g., antibiotics, cyclosporine, radiographic contrast media, heavy metals) ^{a,b}	Miscellaneous metabolic toxins (e.g., hyperoxaluria, cystinosis, Fabry's disease)
Neoplasia	
Lymphoma	
Leukemia	
Multiple myeloma (cast nephropathy, AL amyloidosis)	
Immune Disorders	
Acute (allergic) interstitial nephritis ^{a,b}	Transplant rejection
Sjögren's syndrome	HIV-associated nephropathy
Amyloidosis	
Vascular Disorders	
Arteriolar nephrosclerosis ^a	Sickle cell nephropathy
Atheroembolic disease	Acute tubular necrosis ^{a,b}
Hereditary Renal Diseases	
Disorders associated with renal failure	Hereditary tubular disorders
Autosomal dominant polycystic kidney disease	Barter's syndrome (hereditary hypokalemic alkalosis)
Autosomal recessive polycystic kidney disease	Gitelman's syndrome (hereditary hypokalemic alkalosis)
Medullary cystic kidney disease	Pseudohypoaldosteronism type I (hypotension/salt wasting and hyperkalemia)
Hereditary nephritis (Alport's syndrome)	Pseudohypoaldosteronism type II (hereditary hypertension and hyperkalemia)
	Liddle's syndrome (hypertension and hypokalemia)
	Hereditary hypomagnesemia
	Hereditary nephrogenic diabetes insipidus
	X-linked (AVP receptor dysfunction)
	Autosomal (aquaporin-2 dysfunction)
Infectious Injury	
Acute pyelonephritis ^{a,b}	
Chronic pyelonephritis	
Miscellaneous Disorders	
Chronic urinary tract obstruction ^a	
Vesicoureteral reflux ^a	
Radiation nephritis	

^aCommon.^bTypically acute.

TABLE 146-2 Transport Dysfunction in Tubulointerstitial Disease

DEFECT	CAUSE(S)
Reduced GFR ^a	Obliteration of microvasculature and obstruction of tubules
Fanconi syndrome	Damage to proximal tubular reabsorption of solutes, primarily glucose, amino acids, and phosphate; may also exhibit hypouricemia, proximal tubular acidosis, low-molecular-weight proteinuria
Hyperchloremic acidosis ^a	<ol style="list-style-type: none"> 1. Reduced ammonia production (CKD) or excretion (hyperkalemia) 2. Inability to acidify the collecting duct fluid (distal renal tubular acidosis) 3. Proximal bicarbonate wasting (proximal RTA)
Polyuria, isothermia ^a	Damage to medullary tubules (thick ascending limb and/or collecting duct) and vasculature
Hypokalemic alkalosis	Damage or hereditary dysfunction of the thick ascending limb or distal convoluted tubule (Bartter's and Gitelman's syndromes)
Magnesium wasting	Damage or hereditary dysfunction of the thick ascending limb or distal convoluted tubules
Hyperkalemia ^a	Potassium secretory defects including aldosterone resistance
Salt wasting	Distal tubular damage with impaired sodium reabsorption

^aCommon.

Abbreviations: CKD, chronic kidney disease; RTA, renal tubular acidosis.

Drugs that commonly cause AIN are listed in [Table 146-3](#). Some drugs have a particular predilection for causing AIN, e.g., nafcillin; however, less frequent causes may be apparent only from case reports, such that a detailed history and literature review may be required to make the association with AIN. Many drugs, nonsteroidal anti-inflammatory drugs (NSAIDs) in particular, may elicit a glomerular lesion with similarity to minimal change disease, in addition to AIN; these pts typically have nephrotic-range proteinuria, versus the modest proteinuria typically associated with tubulointerstitial disease. More recently, the increasing use of immune checkpoint inhibitor agents such as nivolumab in cancer care has revealed an important association between these agents and AIN.

Renal dysfunction in drug-associated AIN usually improves after withdrawal of the offending drug, but complete recovery may be delayed and incomplete. In uncontrolled studies, glucocorticoids have been shown to promote earlier recovery of renal function and reduce fibrosis; this therapy is generally reserved to avoid or reduce the duration of dialytic therapy in pts who fail to respond to medication withdrawal.

AIN may also occur in the context of systemic infections, classically leptospirosis, *Legionella* infection, and streptococcal bacterial infection. IN characterized by a dense infiltrate of IgG4-expressing plasma cells can occur as part of IgG4-related systemic disease; pancreatitis, retroperitoneal fibrosis, and a chronic sclerosing sialadenitis may variably be present. Sjögren's syndrome can also be associated with acute tubulointerstitial nephritis. Finally, the tubulointerstitial nephritis and uveitis syndrome (TINU) is another increasingly recognized form of AIN. In addition to uveitis, which may precede or follow the AIN in pts with TINU, systemic symptoms and signs are common, e.g., weight loss, fever,

TABLE 146-3 Causes of Acute Interstitial Nephritis

Drugs (70%, antibiotics in one-third)
Antibiotics
Methicillin, nafcillin, oxacillin
Rifampin
Penicillins, cephalosporins
Ciprofloxacin
Sulfamethoxazole and other sulfonamides
Proton pump inhibitors, e.g., omeprazole
H ₂ blockers, e.g., cimetidine
Allopurinol
5-Aminosalicylates
NSAIDs, including COX-2 inhibitors
Immune checkpoint inhibitors (e.g., nivolumab)
Infections (16%)
Leptospirosis, <i>Legionella</i> , streptococcal, tuberculosis
Tubulointerstitial nephritis and uveitis syndrome (TINU) (5%)
Idiopathic (8%)
Sarcoidosis (1%)
IgG4-related systemic disease

Abbreviation: COX-2, cyclooxygenase 2.

malaise, arthralgias, and an elevated erythrocyte sedimentation rate. The renal disease is typically self-limited; those with progressive disease are often treated with prednisone.

CHRONIC INTERSTITIAL NEPHRITIS

Analgesic nephropathy is an important cause of chronic kidney disease (CKD) that results from the cumulative (in quantity and duration) effects of combination analgesic agents, usually phenacetin and aspirin. It is thought to be a more common cause of end-stage renal disease (ESRD) in Australia/New Zealand than elsewhere owing to the larger per capita ingestion of analgesic agents in that region of the world. Transitional cell carcinoma may develop. Analgesic nephropathy should be suspected in pts with a history of chronic headache or back pain with CKD that is otherwise unexplained. Manifestations include papillary necrosis, calculi, sterile pyuria, and azotemia.

A severe form of chronic tubulointerstitial fibrosis has been associated with the ingestion of Chinese herbal medicines, typically employed as part of a dieting regimen; Balkan endemic nephropathy (BEN), geographically restricted to pts from this region of southeastern Europe, shares many similarities with Chinese herbal nephropathy. These disorders are thought to be caused by exposure to aristolochic acid and/or other plant, endemic (in BEN), and medical toxins (the appetite suppressants fenfluramine and diethylpropion, in Chinese herbal nephropathy). Like analgesic nephropathies, these syndromes are both characterized by a high incidence of genitourinary malignancy.

Chronic therapy with lithium can also cause a chronic tubulointerstitial nephritis, often accompanied by nephrogenic DI that persists following discontinuation of the medication. If at all feasible, lithium-treated pts with evolving CKD should be transitioned to alternative medications for their psychiatric

disease (e.g., valproic acid). Co-treatment with lithium and amiloride may prevent nephrogenic DI in these pts by blocking entry of lithium into principal cells via the amiloride-sensitive Na⁺ channel; however, there are no long-term studies on the effect of amiloride co-therapy on the development or progression of CKD.

Metabolic causes of chronic IN include hypercalcemia (with nephrocalcinosis), oxalosis (primary or secondary, e.g., with intestinal disease and hyperabsorption of dietary oxalate), hypokalemia, and hyperuricemia or hyperuricosuria. The renal pathology associated with chronic hypokalemia includes a relatively specific proximal tubular vacuolization, IN, and renal cysts; both chronic and acute renal failure have been described. Chronic IN can occur in association with several systemic diseases, including sarcoidosis, Sjögren's syndrome, and following radiation or chemotherapy exposure (e.g., ifosfamide, cisplatin).

MONOCLONAL IMMUNOGLOBULINS AND RENAL DISEASE

Monoclonal immunoglobulins are associated with a wide variety of renal manifestations (Table 146-4), of which myeloma-associated cast nephropathy is the most common. The physiochemical characteristics of the monoclonal immunoglobulin, or more commonly the monoclonal light or heavy chains, determine the clinical phenotype in individual pts, most commonly cast nephropathy, light chain deposition disease, and AL amyloidosis. In cast nephropathy, filtered light chains aggregate and cause tubular obstruction, tubular damage, and interstitial inflammation. Pts can present with CKD or with AKI; important predisposing factors in acute cast nephropathy include hypercalcemia and volume depletion.

Diagnosis of cast nephropathy relies on the detection of monoclonal light chains in serum and/or urine, typically by protein electrophoresis and immunofixation. Dipstick analysis of the urine for protein is classically negative in cast nephropathy, despite the excretion of up to several grams a day of light chain

TABLE 146-4 Renal Diseases Associated with Monoclonal Immunoglobulins

DISEASE	NOTES
Cast nephropathy	Most common cause of CKD in myeloma Tubular obstruction with light chains Interstitial inflammation Acute or chronic renal failure
Light chain deposition disease	Nephrotic syndrome, chronic renal failure, ~40% have associated myeloma
Heavy chain deposition disease	Nephrotic syndrome, chronic renal failure
Monoclonal immunoglobulin deposition disease	Nephrotic syndrome, chronic renal failure
AL amyloidosis	Nephrotic syndrome, cardiac/endocrine/ neuropathic involvement ~10% have associated myeloma Renal tubular dysfunction (RTA, nephrogenic DI, etc.)
Hypercalcemia	With myeloma
Hyperviscosity syndrome	With Waldenström's macroglobulinemia
Fanconi syndrome	Glucosuria, aminoaciduria, phosphaturia, ± hypouricemia, proximal RTA, etc.

Abbreviations: CKD, chronic kidney disease; DI, diabetes insipidus; RTA, renal tubular acidosis.

protein; light chains are not detected by this screening test, which tests only for albuminuria. In contrast, the glomerular deposition of light chains in light chain deposition disease or AL amyloidosis can result in nephrotic-range proteinuria (Table 146-4), with strongly *positive* urine dipstick for protein.

Management of cast nephropathy encompasses aggressive hydration, treatment of hypercalcemia if present, and chemotherapy for the associated multiple myeloma. Some experts advocate the use of plasmapheresis for pts with severe AKI, high levels of serum monoclonal light chains, and a renal biopsy demonstrating cast nephropathy.

Filtered light chains and multiple other low-molecular-weight proteins are also endocytosed and metabolized by the proximal tubule. Rarely, specific light chains generate crystalline depositions within proximal tubule cells, causing a Fanconi syndrome; again, this property appears to be caused by the specific physicochemical characteristics of the associated light chains. Fanconi syndrome or dysfunction of the distal nephron (hyperkalemic acidosis or nephrogenic DI) may also complicate renal amyloidosis.

POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening monogenic genetic disorder, caused by autosomal dominant mutations in the *PKD1* and *PKD2* genes; it is a quantitatively important cause of ESRD. Autosomal recessive polycystic disease is a less much common cause of renal failure, typically presenting in infancy; hepatic involvement is much more prominent. The massive renal cysts in ADPKD can lead to progressive CKD, episodic flank pain, hematuria (often gross), hypertension, and/or urinary tract infection. The kidneys are often palpable and occasionally of very large size. Hepatic cysts and intracranial aneurysms may also be present; pts with ADPKD and a family history of ruptured intracranial aneurysms should undergo presymptomatic screening. Other common extrarenal features include diverticulosis and mitral valve prolapse.

The expression of ADPKD is highly variable, even within individual families, with the age of onset of ESRD ranging from childhood to old age. The renal phenotype is more severe in pts with mutations in *PKD1*, who on average develop ESRD approximately 15 years earlier than those with *PKD2* mutations. Indeed, some pts with ADPKD discover the disease incidentally in late adult life, having had mild to moderate hypertension earlier.

The diagnosis is usually made by ultrasonography. In a 15- to 29-year-old at-risk individual from a family with ADPKD, the presence of at least two renal cysts (unilateral or bilateral) is sufficient for diagnosis. Notably, however, renal cysts are a common ultrasound finding in older pts without ADPKD, particularly those with CKD. Therefore, in at-risk individuals 30–59 years of age, the presence of at least two cysts in each kidney is required for the diagnosis; this increases to four cysts in each kidney for those aged >60. Conversely, the absence of at least two cysts in each kidney excludes the diagnosis of ADPKD in at-risk individuals between the ages of 30 and 59.

Hypertension is common in ADPKD, often in the absence of an apparent reduction in glomerular filtration rate. Activation of the renin-angiotensin system appears to play a dominant role; angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are the recommended antihypertensive agents, with a target blood pressure of <130/80 mmHg. Dual therapy with an ARB and ACE inhibitor does not confer additional benefit in slowing progression of ADPKD to ESRD. Promising treatment modalities for halting progression of CKD in ADPKD include vasopressin antagonists, somatostatin analogues, and inhibitors of cell proliferation.

Urinary tract infections are also common in ADPKD. In particular, pts may develop cyst infections, often with negative urine cultures and an absence of pyuria. Pts with an infected cyst may have a discrete area of tenderness, as opposed to the more diffuse discomfort of pyelonephritis; however, clinical distinction between these two possibilities can be problematic. Many commonly used antibiotics, including penicillins and aminoglycosides, fail to penetrate cysts and are ineffective; therapy of kidney infections in ADPKD should use an antibiotic that is known to penetrate cysts (e.g., quinolones), guided initially by local antimicrobial susceptibility patterns.

RENAL TUBULAR ACIDOSIS (RTA)

This describes a number of pathophysiologically distinct entities of tubular function whose common feature is the presence of a non-anion-gap metabolic acidosis. Diarrhea, CKD, and RTA together constitute the vast majority of cases of non-anion-gap metabolic acidosis. Pts with earlier stages of CKD (Table 48-1) typically develop a non-anion-gap acidosis, with a superimposed increase in the anion gap at later stages (Chap. 2). Acidosis may develop at an earlier stage of CKD in those with prominent injury to the distal nephron, as for example in reflux nephropathy.

Distal Hypokalemic (Type I) RTA

Pts are unable to acidify the urine despite systemic acidosis; the urinary anion gap is positive, reflective of a decrease in ammonium excretion (Chap. 2). Distal hypokalemic RTA may be inherited (both autosomal dominant and autosomal recessive) or acquired due to autoimmune and inflammatory diseases (e.g., Sjögren's syndrome, sarcoidosis), urinary tract obstruction, or amphotericin B therapy. Chronic type I RTA is typically associated with hypercalciuria and osteomalacia, a consequence of the long-term buffering of acidosis by bone.

Proximal (Type II) RTA

There is a defect in bicarbonate reabsorption, usually associated with features of Fanconi syndrome, including glycosuria, aminoaciduria, phosphaturia, and uricosuria (indicating proximal tubular dysfunction). Isolated proximal RTA is caused by hereditary dysfunction of the basolateral sodium-bicarbonate cotransporter. Fanconi syndrome may be inherited or acquired due to myeloma, chronic IN (e.g., Chinese herbal nephropathy), or drugs (e.g., ifosfamide, tenofovir). Treatment requires large doses of bicarbonate (5–15 mmol/kg per day), which may aggravate hypokalemia.

Type IV RTA

This may be due to hyporeninemic hypoaldosteronism or to resistance of the distal nephron to aldosterone. Hyporeninemic hypoaldosteronism is typically associated with volume expansion and most commonly seen in elderly and/or diabetic pts with CKD. The hyperkalemia associated with NSAIDs and cyclosporine is at least partially due to hyporeninemic hypoaldosteronism. Pts with hyporeninemic hypoaldosteronism are typically hyperkalemic; they may also exhibit a mild non-anion-gap acidosis, with urine pH <5.5 and a positive urinary anion gap. Acidosis often improves with reduction in serum $[K^+]$; hyperkalemia appears to interfere with medullary concentration of ammonium by the renal countercurrent mechanism. Should reduction in serum $[K^+]$ not improve acidosis, pts should be treated with oral bicarbonate or citrate. Finally, various forms of distal tubular injury and tubulointerstitial disease, e.g., IN, are associated with distal insensitivity to aldosterone; urine pH is classically >5.5, again with a positive urinary anion gap.

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Dysuria, Urinary Tract Infections, Bladder Pain, and Interstitial Cystitis



DYSURIA

Dysuria, or pain that occurs during urination, is commonly perceived as burning or stinging in the urethra and is a symptom of several syndromes that can be distinguished by the presence or absence of other symptoms.

■ EPIDEMIOLOGY

Approximately 50% of women experience dysuria at some time in their lives; ~20% report having had dysuria within the past year. Dysuria is less common among men.

■ CLINICAL MANIFESTATIONS

The underlying syndromes that cause dysuria differ somewhat between men and women.

- In women, most dysuria syndromes can be categorized as either bacterial cystitis or lower genital tract infection (e.g., vaginitis, urethritis, sexually transmitted infection [STI]) (see [Chap. 86](#)). The presence of urinary frequency, urinary urgency, suprapubic pain, and/or hematuria is more typical of bacterial cystitis than of STIs.
- In men, dysuria is often due to STIs or involvement of the prostate (e.g., acute or chronic bacterial prostatitis) (see [Chap. 86](#)). In addition, dysuria and other symptoms of cystitis can occur in the setting of significant benign prostatic hyperplasia that leads to urinary stasis with an accompanying bacterial infection.
- In both sexes, dysuria can result from noninfectious disorders. Noninfectious causes of acute dysuria include lower urinary tract stones, trauma, and urethral exposure to topical chemicals. Chronic dysuria may be attributable to lower urinary tract cancers, certain medications, Behçet's syndrome, or interstitial cystitis/bladder pain syndrome.

■ DIAGNOSIS

Among women presenting with dysuria, the probability of bacterial cystitis is ~50%. This figure rises to >90% if four criteria are fulfilled: (1) dysuria and (2) frequency without either (3) vaginal discharge or (4) irritation.

- Healthy, nonpregnant women who meet the earlier criteria can be diagnosed with uncomplicated bacterial cystitis; other women with dysuria should be further evaluated by urine dipstick, urine culture, and a pelvic examination.
- Men should be evaluated with urinalysis, urine culture, and prostate examination.

TREATMENT

Dysuria

Once the underlying cause of dysuria is identified, it should be treated appropriately, as outlined in other chapters.

URINARY TRACT INFECTIONS

DEFINITIONS

- The term *urinary tract infection* encompasses a variety of clinical entities.
 - *Cystitis*: symptomatic disease of the bladder
 - *Pyelonephritis*: symptomatic disease of the kidney
 - *Prostatitis*: symptomatic disease of the prostate
 - *Asymptomatic bacteriuria (ASB)*: asymptomatic infection identified by a screening urine culture unrelated to the genitourinary tract
- *Uncomplicated UTI* refers to acute disease in nonpregnant outpatient women without anatomic abnormalities or instrumentation of the urinary tract; *complicated UTI* refers to all other types of UTI.

EPIDEMIOLOGY

UTI occurs far more commonly in females than in males, although obstruction from prostatic hypertrophy causes men >50 years old to have an incidence of UTI comparable to that among women of the same age.

- Of women, 50–80% have at least one UTI during their lifetime and 20–30% have recurrent episodes.
- Risk factors for acute cystitis include recent use of a diaphragm with spermicide, frequent sexual intercourse, a history of UTI, diabetes mellitus, and incontinence; many of these factors also increase the risk of pyelonephritis.

MICROBIOLOGY

In the United States, *Escherichia coli* accounts for 75–90% of cystitis isolates; *Staphylococcus saprophyticus* for 5–15%; and *Klebsiella* spp., *Proteus* spp., *Enterococcus* spp., *Citrobacter* spp., and other organisms for 5–10%.

- The spectrum of organisms causing uncomplicated pyelonephritis is similar, with *E. coli* predominating.
- Gram-positive bacteria (e.g., enterococci and *Staphylococcus aureus*) and yeasts are also important pathogens in complicated UTI.

PATHOGENESIS

In the majority of UTIs, bacteria establish infection by ascending from the urethra to the bladder. Continuing ascent up the ureter to the kidney is the pathway for most renal parenchymal infections.

- The pathogenesis of candiduria is distinct in that the hematogenous route is common.
- The presence of *Candida* in the urine of a non-instrumented immunocompetent pt implies either genital contamination or potentially widespread visceral dissemination.

CLINICAL MANIFESTATIONS

When a UTI is suspected, the most important issue is to classify it as ASB; as uncomplicated cystitis, pyelonephritis, or prostatitis; or as complicated UTI.

- ASB is diagnosed when a screening urine culture performed for a reason unrelated to the genitourinary tract is incidentally found to contain bacteria, but the pt has no local or systemic symptoms referable to the urinary tract.
- *Cystitis* presents as dysuria, urinary frequency, and urgency; nocturia, hesitancy, suprapubic discomfort, and gross hematuria are often noted as well.

Unilateral back or flank pain and fever are signs that the upper urinary tract is involved.

- *Pyelonephritis* presents as fever, lower-back or costovertebral-angle pain, nausea, and vomiting. Bacteremia develops in 20–30% of cases.
 - *Papillary necrosis* can occur in pts with obstruction, diabetes, sickle cell disease, or analgesic nephropathy.
 - *Emphysematous pyelonephritis* is particularly severe, is associated with the production of gas in renal and perinephric tissues, and occurs almost exclusively in diabetic pts.
 - *Xanthogranulomatous pyelonephritis* occurs when chronic urinary obstruction (often by staghorn calculi), together with chronic infection, leads to suppurative destruction of renal tissue.
- *Prostatitis* can be either infectious or noninfectious; noninfectious cases are far more common. Acute bacterial prostatitis presents as dysuria, urinary frequency, fever, chills, symptoms of bladder outlet obstruction, and pain in the prostatic, pelvic, or perineal area.
- *Complicated UTI* presents as symptomatic disease in a man or woman with an anatomic predisposition to infection, with a foreign body in the urinary tract, or with factors predisposing to a delayed response to therapy.

■ DIAGNOSIS

The clinical history itself has a high predictive value in diagnosing uncomplicated cystitis; the likelihood of UTI is 96% in a pt presenting with both dysuria and urinary frequency in the absence of vaginal discharge.

- A urine dipstick test positive for nitrite or leukocyte esterase can confirm the diagnosis of uncomplicated cystitis in pts with a high pretest probability of disease.
- The detection of bacteria in a urine culture is the diagnostic gold standard for UTI. A colony-count threshold of $\geq 10^2$ bacteria/mL is more sensitive (95%) and specific (85%) than a threshold of 10^5 /mL for the diagnosis of acute cystitis in women with symptoms of cystitis. ASB requires $\geq 10^5$ bacteria/mL in the absence of clinical symptoms referable to cystitis.

TREATMENT

Urinary Tract Infections

- **Uncomplicated cystitis in women** See [Table 147-1](#) for effective therapeutic regimens.
 - Trimethoprim-sulfamethoxazole (TMP-SMX) has been recommended as first-line treatment for acute cystitis but should be avoided in regions with resistance rates $>20\%$.
 - Nitrofurantoin is another first-line agent with low rates of resistance.
 - Fluoroquinolones should be used only when other antibiotics are not suitable because of increasing resistance (in uropathogens and organisms at other sites), increased risk of Achilles tendon rupture, and irreversible neuropathy.
 - β -Lactam agents are associated with lower rates of pathogen eradication and higher rates of relapse.
- **Pyelonephritis** Given high rates of TMP-SMX-resistant *E. coli*, fluoroquinolones (e.g., ciprofloxacin, 500 mg PO bid for 7 days) are first-line agents for the treatment of acute uncomplicated pyelonephritis. Oral TMP-SMX

TABLE 147-1 Treatment Strategies for Acute Uncomplicated Cystitis

DRUG AND DOSE	ESTIMATED CLINICAL EFFICACY, %	ESTIMATED BACTERIAL EFFICACY, ^a %	COMMON SIDE EFFECTS
Nitrofurantoin, 100 mg bid × 5–7 d	87–95	82–92	Nausea, headache
TMP-SMX, 1 DS tablet bid × 3 d	86–100	85–100	Rash, urticaria, nausea, vomiting, hematologic abnormalities
Fosfomycin, 3-g single-dose sachet	83–95	78–98	Diarrhea, nausea, headache
Pivmecillinam, 400 mg bid × 3–7 d	55–82	74–84	Nausea, vomiting, diarrhea
Fluoroquinolones, dose varies by agent; 3-d regimen	81–98	78–96	Nausea, vomiting, diarrhea, headache, drowsiness, insomnia
β-Lactams, dose varies by agent; 5- to 7-d regimen	79–98	74–98	Diarrhea, nausea, vomiting, rash, urticaria

^aMicrobial response as measured by reduction of bacterial counts in the urine.

Note: Efficacy rates are averages or ranges calculated from the data and studies included in the 2010 Infectious Diseases Society of America/European Society of Clinical Microbiology and Infectious Diseases guideline for treatment of uncomplicated UTI and the 2014 JAMA systematic review on UTI in the outpatient setting. Ranges are estimates from published studies and may vary by specific agent and by rate of resistance.

Abbreviations: DS, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole.

(one double-strength tablet bid for 14 days) is effective against susceptible uropathogens.

- **UTI in pregnant women** Nitrofurantoin, ampicillin, and the cephalosporins are considered relatively safe in early pregnancy.
- **UTI in men** In men with apparently uncomplicated UTI, a 7- to 14-day course of a fluoroquinolone or TMP-SMX is recommended.
 - If acute bacterial prostatitis is suspected, antibiotics should be initiated after urine and blood are obtained for cultures.
 - Therapy can be tailored to urine culture results and should be continued for 2–4 weeks; a 4- to 6-week course is often necessary for chronic bacterial prostatitis.
- **Asymptomatic bacteriuria** ASB should be treated only in pregnant women, in pts undergoing urologic surgery, and perhaps in neutropenic pts and renal transplant recipients. Antibiotic choice is guided by culture results. Pregnant women with ASB are treated for 4–7 days.
- **Catheter-associated UTI** Urine culture results are essential to guide therapy.
 - Replacing the catheter during treatment is generally necessary. Candiduria, a common complication of indwelling catheterization, resolves in ~1/3 of asymptomatic cases with catheter removal.
 - Treatment of candiduria (fluconazole, 200–400 mg/d for 14 days) is recommended for pts who have symptomatic cystitis or pyelonephritis and for those who are at high risk for disseminated disease.

■ PREVENTION OF RECURRENT UTI

Women experiencing symptomatic UTIs ≥ 2 times a year are candidates for prophylaxis—either continuous or postcoital—or pt-initiated therapy. Continuous prophylaxis and postcoital prophylaxis usually entail low doses of TMP-SMX, a fluoroquinolone, or nitrofurantoin. Pt-initiated therapy involves supplying the pt with materials for urine culture and for self-medication with a course of antibiotics at the first symptoms of infection.

■ PROGNOSIS

In the absence of anatomic abnormalities, recurrent infection in children and adults does not lead to chronic pyelonephritis or to renal failure.

BLADDER PAIN

Pts perceive pain as coming from the urinary bladder if it is suprapubic in location, alters with bladder filling or emptying, and/or is associated with urinary symptoms such as urgency and frequency.

- Bladder pain occurring acutely (i.e., lasting ≤ 2 days) is helpful in distinguishing bacterial cystitis from lower genital tract infections.
- Chronic or recurrent bladder pain may accompany lower urinary tract stones, pelvic cancers, urethral diverticulum, cystitis induced by radiation or certain medications, tuberculous cystitis, bladder neck obstruction, neurogenic bladder, urogenital prolapse, or benign prostatic hyperplasia. The diagnosis of interstitial cystitis/bladder pain syndrome should be considered in pts who do not have one of these conditions.

INTERSTITIAL CYSTITIS

Interstitial cystitis (bladder pain syndrome) is a chronic condition characterized by pain perceived to be from the urinary bladder, urinary urgency and frequency, and nocturia.

■ EPIDEMIOLOGY

In the United States, 3–6% of women and 2–4% of men have interstitial cystitis. Among women, the average age at onset is the early forties, but the range is from childhood through the early sixties.

■ ETIOLOGY

The etiology of interstitial cystitis remains unknown.

- Theoretical possibilities include chronic bladder infection, inflammatory factors such as mast cells, autoimmunity, increased permeability of the bladder mucosa, and unusual pain sensitivity.
- However, few data support any of these factors as an inciting cause.

■ CLINICAL MANIFESTATIONS

The cardinal symptoms of pain, urinary urgency and frequency, and nocturia occur in no consistent order. Symptoms can begin acutely or gradually. Pain, which is often present at two or more sites, can affect the suprapubic area (80% of pts), the urethra, the vulva, and non-urogenital areas.

- Unlike pelvic pain arising from other sources, pain caused by interstitial cystitis is exacerbated by bladder filling and relieved by bladder emptying.
- Of pts with interstitial cystitis, 85% void >10 times per day; some do so as often as 60 times per day.

- Many pts with interstitial cystitis have comorbid functional somatic syndromes (e.g., fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome).

■ DIAGNOSIS

The diagnosis is based on the presence of appropriate symptoms and the exclusion of diseases with a similar presentation (e.g., diseases that manifest with pelvic pain and/or urinary symptoms; functional somatic syndromes with urinary symptoms)

- Physical examination and laboratory findings are insensitive and/or nonspecific.
- Cystoscopy may reveal an ulcer ($\leq 10\%$ of pts) or petechial hemorrhages after bladder distension, but neither of these findings is specific.

TREATMENT

Interstitial Cystitis

The goal of therapy is the relief of symptoms, which often requires a multifaceted approach (e.g., education, stress reduction, dietary changes, medications such as NSAIDs or amitriptyline, pelvic-floor physical therapy, and treatment of associated functional somatic syndromes).

148 Nephrolithiasis



Renal calculi are common, affecting $\sim 1\%$ of the population, and recurrent in more than half of pts. Stone formation begins when urine becomes supersaturated with insoluble components due to (1) low urinary volume, (2) excessive or insufficient excretion of selected compounds, or (3) other factors (e.g., urinary pH) that diminish solubility. Approximately 75% of stones are Ca-based (the majority Ca oxalate; also Ca phosphate and other mixed stones), 15% struvite (magnesium-ammonium-phosphate), 5% uric acid, and 1% cystine, reflecting the metabolic disturbance(s) from which they arise.

■ SIGNS AND SYMPTOMS

Stones in the renal pelvis may be asymptomatic or cause hematuria alone; with passage, obstruction may occur at any site along the collecting system. Obstruction related to the passing of a stone leads to severe pain, often radiating to the groin, sometimes accompanied by intense visceral symptoms (i.e., nausea, vomiting, diaphoresis, light-headedness), hematuria, pyuria, urinary tract infection (UTI), and, rarely, hydronephrosis. In contrast, staghorn calculi, associated with recurrent UTI with urea-splitting organisms (*Proteus*, *Klebsiella*, *Providencia*, *Morganella*, and others), may be completely asymptomatic, presenting with loss of renal function.

■ STONE COMPOSITION

Most stones are composed of Ca oxalate. These may be associated with hypercalciuria and/or hyperoxaluria. Hypercalciuria can be seen in association with a very high-Na diet, loop diuretic therapy, distal (type I) renal tubular acidosis (RTA), sarcoidosis, Cushing's syndrome, aldosterone excess, or conditions

associated with hypercalcemia (e.g., primary hyperparathyroidism, vitamin D excess, milk-alkali syndrome), or it may be idiopathic.

Hyperoxaluria may be seen with intestinal (especially ileal) malabsorption syndromes (e.g., inflammatory bowel disease, pancreatitis), due to reduced intestinal secretion of oxalate and/or the binding of intestinal Ca by fatty acids within the bowel lumen, with enhanced absorption of free oxalate and hyperoxaluria. Ca oxalate stones may also form due to (1) a deficiency of urinary citrate, an inhibitor of stone formation that is underexcreted with metabolic acidosis; and (2) hyperuricosuria (see below). Ca phosphate stones are much less common and tend to occur in the setting of an abnormally high urinary pH (7–8), usually in association with a complete or partial distal RTA.

Struvite stones form in the collecting system when infection with urea-splitting organisms is present. Struvite is the most common component of staghorn calculi and obstruction. Risk factors include previous UTI, nonstruvite stone disease, urinary catheters, neurogenic bladder (e.g., with diabetes or multiple sclerosis), and instrumentation.

Uric acid stones develop when the urine is saturated with uric acid in the presence of an acid urine pH; pts typically have underlying metabolic syndrome and insulin resistance, often with clinical gout, associated with a relative defect in ammoniogenesis and urine pH that is <5.4 and often <5.0. Pts with myeloproliferative disorders and other causes of secondary hyperuricemia and hyperuricosuria due to increased purine biosynthesis and/or urate production are at risk for stones if the urine volume diminishes. Hyperuricosuria without hyperuricemia may be seen in association with certain drugs (e.g., probenecid, high-dose salicylates).

Cystine stones are the result of a rare inherited defect in renal and intestinal transport of several dibasic amino acids; the overexcretion of cystine (cysteine disulfide), which is relatively insoluble, leads to nephrolithiasis. Stones begin in childhood and are a rare cause of staghorn calculi; they occasionally lead to end-stage renal disease. Cystine stones are more likely to form in acidic urinary pH.

■ WORKUP

Although some have advocated a complete workup after a first stone episode, others would defer that evaluation until there has been evidence of recurrence or if there is no obvious cause (e.g., low fluid intake during the summer months with obvious dehydration). [Table 148-1](#) outlines a reasonable workup for an outpatient with an uncomplicated kidney stone. On occasion, a stone is recovered and can be analyzed for content, yielding important clues to pathogenesis and management. For example, a predominance of Ca phosphate suggests underlying distal RTA or hyperparathyroidism.

TABLE 148-1 Workup for an Outpatient with a Renal Stone

1. Dietary and fluid intake history
2. Careful medical history and physical examination, focusing on systemic diseases
3. Noncontrast helical CT, with 5-mm CT cuts
4. Routine UA; presence of crystals, hematuria, measurement of urine pH
5. Serum chemistries: BUN, Cr, uric acid, calcium, phosphate, chloride, bicarbonate, PTH
6. Timed urine collections (at least 1 day during week, 1 day on weekend): Cr, Na, K, urea nitrogen, uric acid, calcium, phosphate, oxalate, citrate, pH

Abbreviations: Cr, creatinine; PTH, parathyroid hormone.

TABLE 148-2 Specific Therapies for Nephrolithiasis

STONE TYPE	DIETARY MODIFICATIONS	OTHER
Calcium oxalate	Increase fluid intake	Citrate supplementation (calcium or potassium salts > sodium)
	Moderate sodium intake	
	Moderate oxalate intake	Cholestyramine or other therapy for fat malabsorption
	Moderate protein intake	Thiazides if hypercalciuric
	Moderate fat intake	Allopurinol if hyperuricosuric
Calcium phosphate	Increase fluid intake	Thiazides if hypercalciuric
	Moderate sodium intake	Treat hyperparathyroidism if present
		Alkali for distal renal tubular acidosis
Struvite	Increase fluid intake; same as calcium oxalate if evidence of calcium oxalate nidus for struvite	Methenamine and vitamin C or daily suppressive antibiotic therapy (e.g., trimethoprim-sulfamethoxazole)
Uric acid	Increase fluid intake	Allopurinol
	Moderate dietary protein intake	Alkali therapy (K ⁺ citrate) to raise urine pH to 6.0–6.5
Cystine	Increase fluid intake	Alkali therapy Penicillamine

Note: Sodium excretion correlates with calcium excretion.

TREATMENT

Nephrolithiasis

Treatment of renal calculi is often empirical, based on odds (Ca oxalate stones most common), clinical history, and/or the metabolic workup. An increase in fluid intake to at least 2.5–3 L/d is perhaps the single most effective intervention, regardless of the type of stone. Conservative recommendations for pts with Ca oxalate stones (i.e., low-salt, low-fat, moderate-protein diet) are thought to be healthful in general and therefore advisable in pts whose condition is otherwise uncomplicated. In contrast to prior assumptions, dietary calcium intake does not contribute to stone risk; rather, dietary calcium may help to reduce oxalate absorption and reduce stone risk. [Table 148-2](#) outlines stone-specific therapies for pts with complex or recurrent nephrolithiasis.

149 Urinary Tract Obstruction



Urinary tract obstruction (UTO), a potentially reversible cause of renal failure (RF), should be considered in all cases of acute or abrupt worsening of chronic RF. Consequences depend on duration and severity and whether the obstruction is unilateral or bilateral. UTO may occur at any level from collecting tubule

to urethra. It is preponderant in women (pelvic tumors), elderly men (prostatic disease), diabetic pts (papillary necrosis), pts with neurologic diseases (spinal cord injury or multiple sclerosis, with neurogenic bladder), and individuals with retroperitoneal lymphadenopathy or fibrosis, vesicoureteral reflux, nephrolithiasis, or other causes of functional urinary retention (e.g., anticholinergic drugs).

■ CLINICAL MANIFESTATIONS

Pain can occur in some settings (obstruction due to stones) but is not common. In men, there is frequently a history of lower urinary tract symptoms, e.g., hesitancy, urgency, or frequent nocturia. Physical examination may reveal an enlarged bladder by percussion over the lower abdominal wall; bedside ultrasound assessment (“bladder scan”) can be helpful to assess the postvoid bladder volume. Other findings depend on the clinical scenario. Prostatic hypertrophy can be determined by digital rectal examination. A bimanual examination in women may show a pelvic or rectal mass. The workup of pts with RF suspected of having UTO is shown in [Fig. 149-1](#). Laboratory studies may show marked elevations of blood urea nitrogen and creatinine; if the obstruction has been of sufficient duration, there may be evidence of tubulointerstitial disease (e.g., hyperkalemia, non-anion-gap metabolic acidosis, mild hypernatremia). Urinalysis is most often benign or with a small number of cells; heavy proteinuria is rare. An obstructing stone may be visualized on abdominal radiography or helical noncontrast CT with 5-mm cuts.

Ultrasonography can be used to assess the degree of hydronephrosis and the integrity of the renal parenchyma; CT or IV urography may be required to localize the level of obstruction. Calyceal dilation is commonly seen; it may be absent with hyperacute obstruction, upper tract encasement by tumor or retroperitoneal fibrosis, or indwelling staghorn calculi. A nuclear renal scan to assess excretion of the radioisotope technetium Tc-99m mertiatide (Tc-99m MAG3), before and after administration of a loop diuretic may be helpful for functional assessment of obstruction; it can also identify a difference in function between the two kidneys. Imaging in retroperitoneal fibrosis with associated periaortitis classically reveals a periaortic, confluent mass encasing the anterior and lateral sides of the aorta. Kidney size may indicate the duration of obstruction. It should be noted that unilateral obstruction may be prolonged and severe (ultimately leading to loss of renal function in the obstructed kidney), with no hint of abnormality on physical examination and laboratory survey.

TREATMENT

Urinary Tract Obstruction

Management of acute RF associated with UTO is dictated by (1) the level of obstruction (upper vs lower tract), and (2) the acuity of the obstruction and its clinical consequences, including renal dysfunction and infection. Benign causes of UTO, including bladder outlet obstruction and nephrolithiasis, should be ruled out because conservative management, including Foley catheter placement and IV fluids, respectively, will usually relieve the obstruction in most cases.

Among more seriously ill pts, ureteral obstruction due to tumor is the most common and concerning cause of UTO. If technically feasible, ureteral obstruction due to tumor is best managed by cystoscopic placement of a ureteral stent. Otherwise, the placement of nephrostomy tubes with external drainage may be required. IV antibiotics should also be given if there are signs of pyelonephritis or urosepsis. In addition to ureteral stenting, pts with idiopathic retroperitoneal

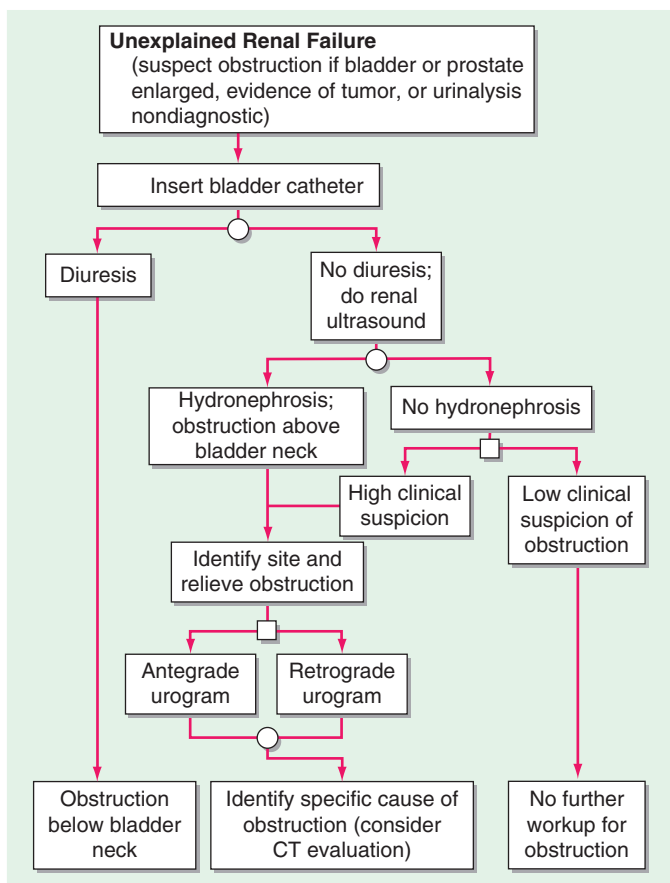


FIGURE 149-1 Diagnostic approach for urinary tract obstruction in unexplained renal failure. Circles represent diagnostic procedures, and squares indicate clinical decisions based on available data.

fibrosis are typically treated with immunosuppression (prednisone, mycophenolate mofetil, and/or tamoxifen).

Fluid and electrolyte status should be carefully monitored after obstruction is relieved. There may be a physiologic natriuresis/diuresis related to volume overload. However, there may be an "inappropriate" natriuresis/diuresis related to (1) elevated urea nitrogen, leading to an osmotic diuresis; and (2) acquired nephrogenic diabetes insipidus. Hyponatremia, sometimes of a severe degree, may develop.

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Peptic Ulcer and Related Disorders

**PEPTIC ULCER DISEASE**

Peptic ulcer disease (PUD) occurs most commonly in duodenal bulb (duodenal ulcer, DU) and stomach (gastric ulcer, GU). It may also occur in esophagus, pyloric channel, duodenal loop, jejunum, and Meckel's diverticulum. PUD results when "aggressive" factors (gastric acid, pepsin) overwhelm "defensive" factors involved in mucosal resistance (gastric mucus, bicarbonate, microcirculation, prostaglandins, mucosal "barrier") and from effects of *Helicobacter pylori*.

CAUSES AND RISK FACTORS**General**

H. pylori is a spiral urease-producing organism that colonizes gastric antral mucosa in up to 100% of persons with DU and 80% with GU. It is also found in normals (increasing prevalence with age) and in those of low socioeconomic status. *H. pylori* is invariably associated with histologic evidence of active chronic gastritis, which over years can lead to atrophic gastritis and gastric cancer. The other major cause of ulcers (those not due to *H. pylori*) is nonsteroidal anti-inflammatory drugs (NSAIDs). Fewer than 1% are due to gastrinoma (Zollinger-Ellison [Z-E] syndrome). Other risk factors and associations: hereditary (? increased parietal cell number), smoking, hypercalcemia, mastocytosis, blood group O (antigens may bind *H. pylori*). Unproven: stress, coffee, alcohol.

Duodenal Ulcer

Mild gastric acid hypersecretion resulting from (1) increased release of gastrin, presumably due to (a) stimulation of antral G cells by cytokines released by inflammatory cells and (b) diminished production of somatostatin by D cells, both resulting from *H. pylori* infection; and (2) an exaggerated acid response to gastrin due to an increased parietal cell mass resulting from gastrin stimulation. These abnormalities reverse rapidly with eradication of *H. pylori*. However, a mildly elevated maximum gastric acid output in response to exogenous gastrin persists in some pts long after eradication of *H. pylori*, suggesting that gastric acid hypersecretion may be, in part, genetically determined. *H. pylori* may also result in elevated serum pepsinogen levels. Mucosal defense in duodenum is compromised by toxic effects of *H. pylori* infection on patches of gastric metaplasia that result from gastric acid hypersecretion or rapid gastric emptying. Other risk factors include glucocorticoids, NSAIDs, chronic renal failure, renal transplantation, cirrhosis, and chronic lung disease.

Gastric Ulcer

H. pylori is also principal cause. Gastric acid secretory rates are usually normal or reduced, possibly reflecting earlier age of infection by *H. pylori* than in DU pts. Gastritis due to reflux of duodenal contents (including bile) may play a role. Chronic salicylate or NSAID use may account for 15–30% of GUs and increase risk of associated bleeding, perforation.

■ CLINICAL FEATURES

Duodenal Ulcer

Burning epigastric pain 90 min to 3 h after meals, often nocturnal, relieved by food.

Gastric Ulcer

Burning epigastric pain made worse by or unrelated to food; anorexia, food aversion, weight loss (in 40%). Great individual variation. Similar symptoms may occur in persons without demonstrated peptic ulcers (“nonulcer dyspepsia”); less responsive to standard therapy.

■ COMPLICATIONS

Bleeding, obstruction, penetration causing acute pancreatitis, perforation, intractability.

■ DIAGNOSIS

Duodenal Ulcer

Upper endoscopy or upper gastrointestinal (GI) barium radiography.

Gastric Ulcer

Upper endoscopy preferable to exclude possibility that ulcer is malignant (brush cytology, ≥ 6 pinch biopsies of ulcer margin). Radiographic features suggesting malignancy: ulcer within a mass, folds that do not radiate from ulcer margin, a large ulcer (>2.5 – 3 cm).

■ DETECTION OF *H. PYLORI*

Detection of antibodies in serum (inexpensive, preferred when endoscopy is not required); rapid urease test of antral biopsy (when endoscopy is required). Urea breath test generally used to confirm eradication of *H. pylori*, if necessary. The fecal antigen test is sensitive, specific, and inexpensive (Table 150-1).

TABLE 150-1 Tests for Detection of *H. pylori*

TEST	SENSITIVITY/ SPECIFICITY, %	COMMENTS
Invasive (endoscopy/biopsy required)		
Rapid urease	80–95/95–100	Simple, false negative with recent use of PPIs, antibiotics, or bismuth compounds
Histology	80–90/ >95	Requires pathology processing and staining; provides histologic information
Culture	—/—	Time consuming, expensive, dependent on experience; allows determination of antibiotic susceptibility
Noninvasive		
Serology	>80 / >90	Inexpensive, convenient; not useful for early follow-up
Urea breath test	>90 / >90	Simple, rapid; useful for early follow-up; false negatives with recent therapy (see rapid urease test); exposure to low-dose radiation with ^{14}C test
Stool antigen	>90 / >90	Inexpensive, convenient; not established for eradication but promising

Abbreviation: PPIs, proton pump inhibitors.

TREATMENT

Peptic Ulcer Disease

MEDICAL

Objectives: pain relief, healing, prevention of complications, prevention of recurrences. For GU, exclude malignancy (follow endoscopically to healing). Dietary restriction unnecessary with contemporary drugs; discontinue NSAIDs; smoking may prevent healing and should be stopped. Eradication of *H. pylori* markedly reduces rate of ulcer relapse and is indicated for all DUs and GUs associated with *H. pylori* (Table 150-2). Acid suppression is generally included in regimen. Reinfection rates are <1%/year. Standard drugs (H_2 receptor blockers, sucralfate, antacids) heal 80–90% of DUs and 60% of GUs in 6 weeks; healing is more rapid with omeprazole (20 mg/d).

TABLE 150-2 Recommended First-Line Therapies for *H. pylori* Infection

REGIMEN	DRUGS (DOSES)	DOSING FREQUENCY	DURATION (DAYS)	FDA APPROVAL
Clarithromycin triple	PPI (standard or double dose)	BID	14	Yes ^a
	Clarithromycin (500 mg) Amoxicillin (1 g) or Metronidazole (500 mg TID)			
Bismuth quadruple	PPI (standard dose)	BID	10–14	No ^b
	Bismuth subcitrate (120–300 mg) or Subsalicylate (300 mg)	QID		
	Tetracycline (500 mg) Metronidazole (250–500 mg)	QID QID (250) TID to QID (500)		
Concomitant	PPI (standard dose)	BID	10–14	No
	Clarithromycin (500 mg)			
	Amoxicillin (1 g)			
	Nitroimidazole (500 mg) ^c			
Sequential	PPI (standard dose)	BID	5–7	No
	PPI, Clarithromycin (500 mg) + Nitroimidazole (500 mg) ^c	BID	5–7	
Hybrid	PPI (standard dose) + Amox (1 g)	BID	7	No
	PPI, Amox, Clarithromycin (500 mg), Nitroimidazole (500 mg) ^c	BID	7	

(Continued)

TABLE 150-2 Recommended First-Line Therapies for *H. pylori* Infection (Continued)

REGIMEN	DRUGS (DOSES)	DOSING FREQUENCY	DURATION (DAYS)	FDA APPROVAL
Levofloxacin triple	PPI (standard or double dose) + Amox (1 g)	BID	5–7	No
	Levofloxacin (500 mg)	QD		
	Amox (1 g)	BID		
Levofloxacin sequential	PPI (standard or double dose) + Amox (1 g)	BID	5–7	No
	PPI, Amox, Levofloxacin (500 mg QD), Nitroimidazole (500 mg) ^c	BID	5–7	
LOAD	Levofloxacin (250 mg)	QD	7–10	No
	PPI (double dose)	QD		
	Nitazoxanide (500 mg)	BID		
	Doxycycline (100 mg)	QD		

^aSeveral PPI, clarithromycin, and amoxicillin combinations have achieved FDA approval. PPI, clarithromycin, and metronidazole is not an FDA-approved treatment regimen.

^bPPI, bismuth, tetracycline, and metronidazole combined with a PPI for 10 days is an FDA-approved treatment regimen.

^cMetronidazole or tinidazole.

Abbreviations: BID, twice daily; FDA, Food and Drug Administration; PPI, proton pump inhibitor; TID, three times daily; QD, once daily; QID, four times daily.

Source: Adapted with permission from Wolters Kluwer Health, Inc.: Chey WD et al: ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection. Am J Gastroenterol 112:212, 2017.

SURGERY

Used for complications (persistent or recurrent bleeding, obstruction, perforation) or, uncommonly, intractability (first screen for surreptitious NSAID use and gastrinoma). For DU, see [Table 150-3](#). For GU, perform subtotal gastrectomy.

COMPLICATIONS OF SURGERY

(1) Obstructed afferent loop (Billroth II), (2) bile reflux gastritis, (3) dumping syndrome (rapid gastric emptying with abdominal distress + postprandial vasomotor symptoms), (4) postvagotomy diarrhea, (5) bezoar, (6) anemia (iron, B₁₂, folate malabsorption), (7) malabsorption (poor mixing of gastric contents, pancreatic juices, bile; bacterial overgrowth), (8) osteomalacia and osteoporosis (vitamin D and Ca malabsorption), (9) gastric remnant carcinoma.

TABLE 150-3 Surgical Treatment of Duodenal Ulcer

OPERATION	RECURRENCE RATE	COMPLICATION RATE
Vagotomy + antrectomy (Billroth I or II) ^a	1%	Highest
Vagotomy and pyloroplasty	10%	Intermediate
Parietal cell (proximal gastric, superselective) vagotomy	≥10%	Lowest

^aBillroth I, gastroduodenostomy; Billroth II, gastrojejunostomy.

APPROACH TO THE PATIENT**Peptic Ulcer Disease**

Optimal approach is uncertain. Serologic testing for *H. pylori* and treating, if present, may be cost-effective. Other options include trial of acid-suppressive therapy, endoscopy only in treatment failures, or initial endoscopy in all cases.

GASTROPATHIES

The classification of gastritis is shown in [Table 150-4](#).

■ EROSIVE GASTROPATHIES

Hemorrhagic gastritis, multiple gastric erosions may be caused by aspirin and other NSAIDs (lower risk with newer agents, e.g., nabumetone and etodolac, which do not inhibit gastric mucosal prostaglandins) or severe stress (burns, sepsis, trauma, surgery, shock, or respiratory, renal, or liver failure). Pt may be asymptomatic or experience epigastric discomfort, nausea, hematemesis, or melena. Diagnosis is made by upper endoscopy.

TREATMENT**Erosive Gastropathies**

Removal of offending agent and maintenance of O₂ and blood volume as required. For prevention of stress ulcers in critically ill pts, hourly oral administration of liquid antacids (e.g., Maalox 30 mL), IV H₂ receptor antagonist

TABLE 150-4 Classification of Gastritis

- | |
|--|
| I. Acute gastritis |
| A. Acute <i>H. pylori</i> infection |
| B. Other acute infectious gastritides |
| 1. Bacterial (other than <i>H. pylori</i>) |
| 2. <i>H. heilmannii</i> |
| 3. Phlegmonous |
| 4. Mycobacterial |
| 5. Syphilitic |
| 6. Viral |
| 7. Parasitic |
| 8. Fungal |
| II. Chronic atrophic gastritis |
| A. Type A: Autoimmune, body-predominant |
| B. Type B: <i>H. pylori</i> -related, antral-predominant |
| C. Indeterminate |
| III. Uncommon forms of gastritis |
| A. Lymphocytic |
| B. Eosinophilic |
| C. Crohn's disease |
| D. Sarcoidosis |
| E. Isolated granulomatous gastritis |
| F. Russell body gastritis |

(e.g., cimetidine, 300-mg bolus + 37.5–50 mg/h IV), or both is recommended to maintain gastric pH > 4. Alternatively, sucralfate slurry, 1 g PO q6h, can be given; does not raise gastric pH and may thus avoid increased risk of aspiration pneumonia associated with liquid antacids. Pantoprazole can be administered IV to suppress gastric acid in the critically ill. Misoprostol, 200 µg PO qid, or profound acid suppression (e.g., famotidine, 40 mg PO bid) can be used with NSAIDs to prevent NSAID-induced ulcers.

■ CHRONIC GASTRITIS

Identified histologically by an inflammatory cell infiltrate dominated by lymphocytes and plasma cells with scant neutrophils. In its early stage, the changes are limited to the lamina propria (*superficial gastritis*). When the disease progresses to destroy glands, it becomes *atrophic gastritis*. The final stage is *gastric atrophy*, in which the mucosa is thin and the infiltrate sparse. Chronic gastritis can be classified based on predominant site of involvement.

Type A Gastritis

This is the body-predominant and less common form. Generally asymptomatic, common in elderly; autoimmune mechanism may be associated with achlorhydria, pernicious anemia, and increased risk of gastric cancer (value of screening endoscopy uncertain). Antibodies to parietal cells present in >90%.

Type B Gastritis

This is an antral-predominant disease and caused by *H. pylori*. Often asymptomatic but may be associated with dyspepsia. Atrophic gastritis, gastric atrophy, gastric lymphoid follicles, and gastric B cell lymphomas may occur. Infection early in life or in setting of malnutrition or low gastric acid output is associated with gastritis of entire stomach (including body) and increased risk of gastric cancer. Eradication of *H. pylori* (Table 150-2) is not routinely recommended unless PUD or gastric mucosa-associated lymphoid tissue (MALT) lymphoma is present.

■ SPECIFIC TYPES OF GASTROPATHY OR GASTRITIS

Alcoholic gastropathy (submucosal hemorrhages), Ménétrier's disease (hypertrophic gastropathy), eosinophilic gastritis, granulomatous gastritis, Crohn's disease, sarcoidosis, infections (tuberculosis, syphilis, fungi, viruses, parasites), pseudolymphoma, radiation, corrosive gastritis.

ZOLLINGER-ELLISON SYNDROME (GASTRINOMA)

Consider when ulcer disease is severe, refractory to therapy, associated with ulcers in atypical locations, or associated with diarrhea. Tumors are usually pancreatic or in duodenum (submucosal, often small), may be multiple, slowly growing; >60% malignant; 25% associated with MEN 1, i.e., multiple endocrine neoplasia type 1 (gastrinoma, hyperparathyroidism, pituitary neoplasm), often duodenal, small, multicentric, less likely to metastasize to liver than pancreatic gastrinomas but often metastasize to local lymph nodes.

■ DIAGNOSIS

Suggestive

Basal acid output >15 mmol/h; basal/maximal acid output >60%; large mucosal folds on endoscopy or upper GI radiograph.

Confirmatory

Serum gastrin >1000 ng/L or rise in gastrin of 200 ng/L following IV secretin and, if necessary, rise of 400 ng/L following IV calcium (Table 150-5).

TABLE 150-5 Differential Diagnostic Tests

CONDITION	FASTING GASTRIN	GASTRIN RESPONSE TO	
		IV SECRETIN	FOOD
DU	N (≤ 150 ng/L)	NC	Slight \uparrow
Z-E	$\uparrow\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	NC
Antral G (gastrin) cell hyperplasia	\uparrow	\uparrow , NC	$\uparrow\uparrow\uparrow$

Abbreviations: DU, duodenal ulcer; N, normal; NC, no change; Z-E, Zollinger-Ellison syndrome.

DIFFERENTIAL DIAGNOSIS

Increased Gastric Acid Secretion

Z-E syndrome, antral G-cell hyperplasia or hyperfunction (? due to *H. pylori*), postgastrectomy retained antrum, renal failure, massive small bowel resection, chronic gastric outlet obstruction.

Normal or Decreased Gastric Acid Secretion

Pernicious anemia, chronic gastritis, gastric cancer, vagotomy, pheochromocytoma.

TREATMENT

Zollinger-Ellison Syndrome

Omeprazole (or lansoprazole), beginning at 60 mg PO q A.M. and increasing until maximal gastric acid output is <10 mmol/h before next dose, is drug of choice during evaluation and in pts who are not surgical candidates; dose can often be reduced over time. Radiolabeled octreotide scanning has emerged as the most sensitive test for detecting primary tumors and metastases; may be supplemented by endoscopic ultrasonography. Exploratory laparotomy with resection of primary tumor and solitary metastases is done when possible. In pts with MEN 1, tumor is often multifocal and unresectable; treat hyperparathyroidism first (hypergastrinemia may improve). For unresectable tumors, parietal cell vagotomy may enhance control of ulcer disease by drugs. Chemotherapy or biologic therapy is used for metastatic tumor to control symptoms (e.g., streptozocin, 5-fluorouracil, doxorubicin, or interferon α); 40% partial response rate. Long-acting and radioactive somatostatin analogues and a combination of temozolomide plus capecitabine may produce regression or disease stabilization. VEGF antagonists and mTOR inhibitors are being tested.

151

Inflammatory Bowel Diseases



Inflammatory bowel diseases (IBDs) are chronic inflammatory disorders of unknown etiology involving the gastrointestinal (GI) tract. Peak occurrence is between ages 15 and 30 and between ages 60 and 80, but onset may occur at any age. Epidemiologic features are shown in [Table 151-1](#). Pathogenesis of IBD involves activation of immune cells by unknown inciting agent

TABLE 151-1 Epidemiology of IBD

	ULCERATIVE COLITIS	CROHN'S DISEASE
Incidence (North America) per person-years	0–19.2 per 100,000	0–20.2 per 100,000
Age of onset	15–30 and 60–80	15–30 and 60–80
Ethnicity	Jewish > non-Jewish white > African American > Hispanic > Asian	
Male/female ratio	0.51–1.58	0.34–1.65
Smoking	May prevent disease (OR 0.58)	May cause disease (OR 1.76)
Oral contraceptives	No increased risk	OR 2.82
Appendectomy	Protective (risk 13–26% lower)	Not protective
Monozygotic twins	6–18% concordance	38–58% concordance
Dizygotic twins	0–2% concordance	4% concordance
Antibiotic use in the first year of life	2.9× the risk of developing childhood IBD	

Abbreviations: IBD, inflammatory bowel disease; OR, odds ratio.

(? microorganism, dietary component, bacterial or self-antigen) leading to release of cytokines and inflammatory mediators. Genetic component suggested by increased risk in first-degree relatives of pts with IBD and concurrence of type of IBD, location of Crohn's disease (CD), and clinical course. Reported associations include HLA-DR2 in Japanese pts with ulcerative colitis (UC) and a CD-related gene called *CARD15* on chromosome 16p. *CARD15* mutations may account for 10% of CD risk. Other potential pathogenic factors include serum antineutrophil cytoplasmic antibodies (ANCA) in 70% of pts with UC (also in 5–10% of CD pts) and antibodies to *Saccharomyces cerevisiae* (ASCA) in 60–70% of CD pts (also in 10–15% of UC pts and 5% of normal controls). Granulomatous angitis (vasculitis) may occur in CD. Acute flares may be precipitated by infections, nonsteroidal anti-inflammatory drugs (NSAIDs), and stress. Onset of UC often follows cessation of smoking.

ULCERATIVE COLITIS

■ PATHOLOGY

Colonic mucosal inflammation; rectum almost always involved, with inflammation extending continuously (no skip areas) proximally for a variable extent; histologic features include epithelial damage, inflammation, crypt abscesses, loss of goblet cells.

■ CLINICAL MANIFESTATIONS

Bloody diarrhea, mucus, fever, abdominal pain, tenesmus, weight loss; spectrum of severity (majority of cases are mild, limited to rectosigmoid). In severe cases, dehydration, anemia, hypokalemia, hypoalbuminemia.

■ COMPLICATIONS

Toxic megacolon, colonic perforation; cancer risk related to extent and duration of colitis; often preceded by or coincident with dysplasia, which may be detected on surveillance colonoscopic biopsies.

■ DIAGNOSIS

Sigmoidoscopy/colonoscopy: mucosal erythema, granularity, friability, exudate, hemorrhage, ulcers, inflammatory polyps (pseudopolyps). Barium enema: loss of haustrations, mucosal irregularity, ulcerations.

CROHN'S DISEASE

■ PATHOLOGY

Any part of GI tract, usually terminal ileum and/or colon; transmural inflammation, bowel wall thickening, linear ulcerations, and submucosal thickening leading to cobblestone pattern; discontinuous (skip areas); histologic features include transmural inflammation, granulomas (often absent), fissures, fistulas.

■ CLINICAL MANIFESTATIONS

Fever, abdominal pain, diarrhea (often without blood), fatigue, weight loss, growth retardation in children; acute ileitis mimicking appendicitis; anorectal fissures, fistulas, abscesses. Clinical course falls into three broad patterns: (1) inflammatory, (2) stricturing, and (3) fistulizing.

■ COMPLICATIONS

Intestinal obstruction (edema vs. fibrosis); rarely toxic megacolon or perforation; intestinal fistulas to bowel, bladder, vagina, skin, soft tissue, often with abscess formation; bile salt malabsorption leading to cholesterol gallstones and/or oxalate kidney stones; intestinal malignancy; amyloidosis.

■ DIAGNOSIS

Sigmoidoscopy/colonoscopy, barium enema, upper GI and small-bowel series: nodularity, rigidity, ulcers that may be deep or longitudinal, cobblestoning, skip areas, strictures, fistulas. CT may show thickened, matted bowel loops or an abscess.

DIFFERENTIAL DIAGNOSIS (TABLE 151-2)

■ INFECTIOUS ENTEROCOLITIS

Shigella, *Salmonella*, *Campylobacter*, *Yersinia* (acute ileitis), *Plesiomonas shigelloides*, *Aeromonas hydrophila*, *Escherichia coli* serotype O157:H7, *Gonorrhea*, *Lymphogranuloma venereum*, *Clostridium difficile* (pseudomembranous colitis), tuberculosis, amebiasis, cytomegalovirus, AIDS.

■ OTHERS

Ischemic bowel disease, appendicitis, diverticulitis, radiation enterocolitis, bile salt-induced diarrhea (ileal resection), drug-induced colitis (e.g., NSAIDs), bleeding colonic lesion (e.g., neoplasm), irritable bowel syndrome (no bleeding), microscopic (lymphocytic) or collagenous colitis (chronic watery diarrhea)—normal colonoscopy, but biopsies show superficial colonic epithelial inflammation and, in collagenous colitis, a thick subepithelial layer of collagen; response to aminosalicylates and glucocorticoids variable.

EXTRINTESTINAL MANIFESTATIONS OF UC AND CD

1. *Joint*: peripheral arthritis—parallels activity of bowel disease; ankylosing spondylitis and sacroiliitis (associated with HLA-B27)—activity independent of bowel disease
2. *Skin*: erythema nodosum, aphthous ulcers, pyoderma gangrenosum, cutaneous CD
3. *Eye*: conjunctivitis, episcleritis, iritis, uveitis

TABLE 151-2 Diseases That Mimic IBD

Infectious etiologies		
Bacterial	Mycobacterial	Viral
<i>Salmonella</i>	Tuberculosis	Cytomegalovirus
<i>Shigella</i>	<i>Mycobacterium avium</i>	Herpes simplex
Toxicogenic	Parasitic	HIV
<i>Escherichia coli</i>	Amebiasis	Fungal
<i>Campylobacter</i>	<i>Isospora</i>	Histoplasmosis
<i>Yersinia</i>	<i>Trichuris trichiura</i>	<i>Candida</i>
<i>Clostridium difficile</i>	Hookworm	<i>Aspergillus</i>
Gonorrhea	<i>Strongyloides</i>	
<i>Chlamydia trachomatis</i>		
Noninfectious etiologies		
Inflammatory	Neoplastic	Drugs and Chemicals
Appendicitis	Lymphoma	NSAIDs
Diverticulitis	Metastatic	Phosphosoda
Diversion colitis	Carcinoma	Cathartic colon
Collagenous/ lymphocytic colitis	Carcinoma of the ileum	Gold
Ischemic colitis	Carcinoid	Oral contraceptives
Radiation colitis/ enteritis	Familial polyposis	Cocaine
Solitary rectal ulcer syndrome		Ipilimumab
Eosinophilic gastroenteritis		Mycophenolate mofetil
Neutropenic colitis		
Behçet's syndrome		
Graft-versus-host disease		

Abbreviations: IBD, inflammatory bowel disease; NSAIDs, nonsteroidal anti-inflammatory drugs.

- Liver:* fatty liver, "pericholangitis" (intrahepatic sclerosing cholangitis), primary sclerosing cholangitis, cholangiocarcinoma, chronic hepatitis
- Others:* autoimmune hemolytic anemia, phlebitis, pulmonary embolus (hypercoagulable state), kidney stones, metabolic bone disease

TREATMENT

Inflammatory Bowel Diseases (Fig. 151-1)

SUPPORTIVE

Antidiarrheal agents (diphenoxylate and atropine, loperamide) in mild disease; IV hydration and blood transfusions in severe disease; parenteral nutrition or defined enteral formulas—effective as primary therapy in CD, although high relapse rate when oral feeding is resumed; should not replace drug therapy; important role in preoperative preparation of malnourished pt; emotional support.

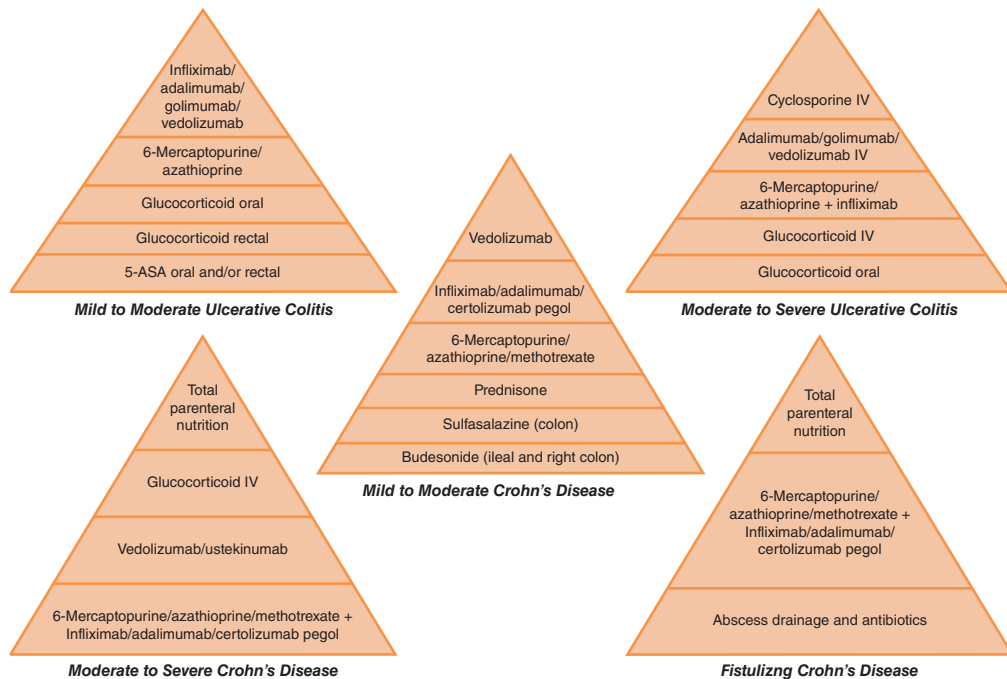


FIGURE 151-1 Medical management of IBD. 5-ASA, 5-aminosalicylic acid. CD, Crohn's disease; UC, ulcerative colitis.

SULFASALAZINE AND AMINOSALICYLATES

Active component of sulfasalazine is 5-aminosalicylic acid (5-ASA) linked to sulfapyridine carrier; useful in colonic disease of mild to moderate severity (3–6 g PO qd); maintenance of remission (2–4 g PO qd). Toxicity (generally due to sulfapyridine component): dose related—nausea, headache, rarely hemolytic anemia—may resolve when drug dose is lowered; idiosyncratic—fever, rash, neutropenia, pancreatitis, hepatitis, etc.; miscellaneous—oligospermia. Newer aminosalicylates are as effective as sulfasalazine but with fewer side effects. Enemas containing 4 g of 5-ASA (mesalamine) may be used in distal UC, one nightly retained qhs until remission, then q2hs or q3hs. Suppositories containing 500 mg of 5-ASA may be used in proctitis.

GLUCOCORTICOIDS

Useful in severe disease and ileal or ileocolonic CD. Prednisone, 40–60 mg PO qd, then taper; IV hydrocortisone, 100 mg tid or equivalent, in hospitalized pts; IV adrenocorticotropic hormone drip (120 U qd) may be preferable in first attacks of UC. Nightly hydrocortisone retention enemas in proctosigmoiditis. Numerous side effects make long-term use problematic.

IMMUNOSUPPRESSIVE AGENTS

Azathioprine, 6-mercaptopurine—50 mg PO qd up to 2.0 or 1.5 mg/kg qd, respectively. Useful as steroid-sparing agents and in intractable or fistulous CD (may require 2- to 6-month trial before efficacy seen). Toxicity—immunosuppression, pancreatitis, ?carcinogenicity. Avoid in pregnancy.

METRONIDAZOLE

Appears effective in colonic CD (500 mg PO bid) and refractory perineal CD (10–20 mg/kg PO qd). Toxicity—peripheral neuropathy, metallic taste, ?carcinogenicity. Avoid in pregnancy. Other antibiotics (e.g., ciprofloxacin 500 mg PO bid) may be of value in terminal ileal and perianal CD, and broad-spectrum IV antibiotics are indicated for fulminant colitis and abscesses.

OTHERS

Cyclosporine (potential value in a dose of 4 [mg/kg]/d IV for 7–14 days in severe UC and possibly intractable Crohn's fistulas); experimental—tacrolimus, methotrexate, chloroquine, fish oil, nicotine, others. Infliximab (monoclonal antibody to tumor necrosis factor [TNF]) 5 mg/kg IV induces responses in 65% (complete in 33%) of CD pts refractory to 5-ASA, glucocorticoids, and 6-mercaptopurine. In UC, 27–49% of pts respond.

Adalimumab is a humanized version of the anti-TNF antibody that is less likely to elicit neutralizing antibodies in the pt. Pegylated versions of anti-TNF antibody may be used once monthly.

Natalizumab is an anti-integrin antibody with activity against CD, but some pts develop progressive multifocal leukoencephalopathy. Vedolizumab is specific for $\alpha 4\beta 7$ integrin and is more gut selective in its effects.

SURGERY

UC: Colectomy (curative) for intractability, toxic megacolon (if no improvement with aggressive medical therapy in 24–48 h), cancer, dysplasia. Ileal pouch—anal anastomosis is operation of choice in UC, but contraindicated in CD and in elderly. CD: Resection for fixed obstruction (or stricturoplasty), abscesses, persistent symptomatic fistulas, intractability.

152 Colonic and Anorectal Diseases



IRRITABLE BOWEL SYNDROME (IBS)

Characterized by altered bowel habits, abdominal pain, and absence of detectable organic pathology. Most common GI disease in clinical practice. Three types of clinical presentations: (1) spastic colon (chronic abdominal pain and constipation), (2) alternating constipation and diarrhea, or (3) chronic, painless diarrhea.

■ PATHOPHYSIOLOGY

Visceral hyperalgesia to mechanoreceptor stimuli is common. Reported abnormalities include altered colonic motility at rest and in response to stress, cholinergic drugs, cholecystokinin; altered small-intestinal motility; enhanced visceral sensation (lower pain threshold in response to gut distention); and abnormal extrinsic innervation of the gut. Pts presenting with IBS to a physician have an increased frequency of psychological disturbances—depression, hysteria, obsessive-compulsive disorder. Specific food intolerances and malabsorption of bile acids by the terminal ileum may account for a few cases.

■ CLINICAL MANIFESTATIONS

Onset often before age 30; females:males = 2:1. Abdominal pain and irregular bowel habits. Additional symptoms often include abdominal distention, relief of abdominal pain with bowel movement, increased frequency of stools with pain, loose stools with pain, mucus in stools, and sense of incomplete evacuation. Associated findings include pasty stools, ribbon or pencil-thin stools, heartburn, bloating, back pain, weakness, faintness, palpitations, and urinary frequency.

■ DIAGNOSIS

IBS is a diagnosis of exclusion. Rome criteria for diagnosis are shown in [Table 152-1](#). Consider sigmoidoscopy and barium radiographs to exclude inflammatory bowel disease or malignancy; consider excluding giardiasis, intestinal lactase deficiency, and hyperthyroidism.

TREATMENT

Irritable Bowel Syndrome ([Table 152-2](#))

Reassurance and supportive physician-pt relationship, avoidance of stress or precipitating factors, dietary bulk (fiber, psyllium extract, e.g., Metamucil one tsp daily or bid); for diarrhea, trials of loperamide (2-mg tabs PO q A.M. then 1 PO after each loose stool to a maximum of 8/d, then titrate), diphenoxylate

TABLE 152-1 Rome IV Diagnostic Criteria for Irritable Bowel Syndrome^a

Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with ≥ 2 of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

^aCriteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

TABLE 152-2 Possible Drugs for a Dominant Symptom in IBS

SYMPTOM	DRUG	DOSE
Diarrhea	Loperamide	2–4 mg when necessary/ maximum 12 g/d
	Cholestyramine resin	4 g with meals
	Alosetron ^a	0.5–1 mg bid (for severe IBS, women)
Constipation	Psyllium husk	3–4 g bid with meals, then adjust
	Methylcellulose	2 g bid with meals, then adjust
	Calcium polycarbophil	1 g qd to qid
	Lactulose syrup	10–20 g bid
	70% sorbitol	15 mL bid
	Polyethylene glycol 3350	17 g in 250 mL water qd
	Lubiprostone (Amitiza)	24 mg bid
	Magnesium hydroxide	30–60 mL qd
	Linaclotide	290 µg qd
Abdominal pain	Smooth-muscle relaxant	qd to qid ac
	Tricyclic antidepressants	Start 25–50 mg hs, then adjust
	Selective serotonin reuptake inhibitors	Begin small dose, increase as needed
Gas and bloating	Low FODMAP diet	
	Probiotics	qd
	Rifaximin	550 mg bid

^aAvailable only in the United States.

Abbreviations: FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

Source: Adapted from Longstreth GF et al: Functional bowel disorders. *Gastroenterology* 130:1480, 2006.

(Lomotil) (up to 2-mg tabs PO qid), or cholestyramine (up to 1-g packet mixed in water PO qid); for pain, anticholinergics (e.g., dicyclomine HCl 10–40 mg PO qid) or hyoscyamine as Levsin 1–2 PO q4h prn. Amitriptyline 25–50 mg PO qhs or other antidepressants in low doses may relieve pain. Selective serotonin reuptake inhibitors such as paroxetine are being evaluated in constipation-dominant pts, and serotonin receptor antagonists such as alosetron are being evaluated in diarrhea-dominant pts. Altering gut flora with probiotics (*Bifidobacterium infantis* 35624) or oral nonabsorbable antibiotics (rifaximin) is being evaluated with some promising early results. Psychotherapy, hypnotherapy of possible benefit in severe refractory cases. Some pts respond to dietary changes to eliminate or severely reduce fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) (see Table 152-3).

DIVERTICULAR DISEASE

Herniations or saclike protrusions of the mucosa through the muscularis at points of nutrient artery penetration; possibly due to increased intraluminal pressure, low-fiber diet; most common in sigmoid colon.

■ CLINICAL PRESENTATION

1. *Asymptomatic* (detected by barium enema or colonoscopy).
2. *Pain:* recurrent left lower quadrant pain relieved by defecation; alternating constipation and diarrhea. Diagnosis by barium enema.

TABLE 152-3 Some Common Food Sources of FODMAPs

FOOD TYPE	FREE FRUCTOSE	LACTOSE	FRUCTANS	GALACTO-OLIGOSACCHARIDES	POLYOLS
Fruits	Apple, cherry, mango, pear, watermelon		Peach, persimmon, watermelon		Apple, apricot, pear, avocado, blackberries, cherry, nectarine, plum, prune
Vegetables	Asparagus, artichokes, sugar snap peas		Artichokes, beetroot, Brussels sprout, chicory, fennel, garlic, leek, onion, peas		Cauliflower, mushroom, snow peas
Grains and cereals			Wheat, rye, barley		
Nuts and seeds			Pistachios		
Milk and milk products		Milk, yogurt, ice cream, custard, soft cheeses			
Legumes			Legumes, lentils, chickpeas	Legumes, chickpeas, lentils	
Other	Honey, high-fructose corn syrup		Chicory drinks		
Food additives			Inulin, FOS		Sorbitol, mannitol, maltitol, xylitol, isomalt

Abbreviations: FODMAPs, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; FOS, fructo-oligosaccharides.

Source: Adapted from Gibson PR et al: Food choice as a key management strategy for functional gastrointestinal symptoms. *Am J Gastroenterol* 107:657, 2012.

3. *Diverticulitis*: pain, fever, altered bowel habits, tender colon, leukocytosis. Best confirmed and staged by CT after opacification of bowel. (In pts who recover with medical therapy, perform elective barium enema or colonoscopy in 4–6 weeks to exclude cancer.) Complications: pericolic abscess, perforation, fistula (to bladder, vagina, skin, soft tissue), liver abscess, stricture. Frequently require surgery or, for abscesses, percutaneous drainage.
4. *Hemorrhage*: usually in absence of diverticulitis, often from ascending colon and self-limited. If persistent, manage with mesenteric arteriography and intra-arterial infusion of vasopressin, or surgery (**Chap. 43**).

TREATMENT

Diverticular Disease

PAIN

High-fiber diet, psyllium extract (e.g., Metamucil 1 tsp PO qd or bid), anticholinergics (e.g., dicyclomine HCl 10–40 mg PO qid).

DIVERTICULITIS

NPO, IV fluids, antibiotics for 7–10 d (e.g., trimethoprim/sulfamethoxazole or ciprofloxacin and metronidazole; add ampicillin to cover enterococci in nonresponders); for ambulatory pts, ampicillin/clavulanate (clear liquid diet); surgical resection in refractory or frequently recurrent cases, young persons (age <50), immunosuppressed pts, or when there is inability to exclude cancer.

Pts who have had at least two documented episodes and those who respond slowly to medical therapy should be offered surgical options to achieve removal of the diseased colonic segment, controlling sepsis, eliminating obstructions or fistulas, and restoring intestinal continuity.

INTESTINAL PSEUDOObSTRUCTION

Recurrent attacks of nausea, vomiting, and abdominal pain and distention mimicking mechanical obstruction; may be complicated by steatorrhea due to bacterial overgrowth.

■ CAUSES

Primary: Familial visceral neuropathy, familial visceral myopathy, idiopathic.

Secondary: Scleroderma, amyloidosis, diabetes, celiac disease, parkinsonism, muscular dystrophy, drugs, electrolyte imbalance, postsurgical.

TREATMENT

Intestinal Pseudoobstruction

For acute attacks: intestinal decompression with long tube. Oral antibiotics for bacterial overgrowth (e.g., metronidazole 250 mg PO tid, tetracycline 500 mg PO qid, or ciprofloxacin 500 mg bid 1 week out of each month, usually in an alternating rotation of at least two antibiotics). Avoid surgery. In refractory cases, consider long-term parenteral hyperalimentation.

VASCULAR DISORDERS (SMALL AND LARGE INTESTINE)

■ MECHANISMS OF MESENTERIC ISCHEMIA

(1) Occlusive: embolus (atrial fibrillation, valvular heart disease); arterial thrombus (atherosclerosis); venous thrombosis (trauma, neoplasm, infection, cirrhosis,

oral contraceptives, antithrombin-III deficiency, protein S or C deficiency, lupus anticoagulant, factor V Leiden mutation, idiopathic); vasculitis (systemic lupus erythematosus, polyarteritis, rheumatoid arthritis, Henoch-Schönlein purpura); (2) nonocclusive: hypotension, heart failure, arrhythmia, digitalis (vasoconstrictor).

■ ACUTE MESENTERIC ISCHEMIA

Periumbilical pain out of proportion to tenderness; nausea, vomiting, distention, GI bleeding, altered bowel habits. Abdominal x-ray shows bowel distention, air-fluid levels, thumbprinting (submucosal edema), but may be normal early in course. Peritoneal signs indicate infarcted bowel requiring surgical resection. Early celiac and mesenteric arteriography is recommended in all cases following hemodynamic resuscitation (avoid vasopressors, digitalis). Intra-arterial vasodilators (e.g., papaverine) can be administered to reverse vasoconstriction. Laparotomy indicated to restore intestinal blood flow obstructed by embolus or thrombosis or to resect necrotic bowel. Postoperative anticoagulation indicated in mesenteric venous thrombosis, controversial in arterial occlusion.

■ CHRONIC MESENTERIC INSUFFICIENCY

"Abdominal angina": dull, crampy periumbilical pain 15–30 min after a meal and lasting for several hours; weight loss; occasionally diarrhea. Evaluate with mesenteric arteriography for possible bypass graft surgery.

■ ISCHEMIC COLITIS

Usually due to nonocclusive disease in pts with atherosclerosis. Severe lower abdominal pain, rectal bleeding, hypotension. Abdominal x-ray shows colonic dilation, thumbprinting. Sigmoidoscopy shows submucosal hemorrhage, friability, ulcerations; rectum often spared. Conservative management (NPO, IV fluids); surgical resection for infarction or posts ischemic stricture.

■ COLONIC ANGIODYSPLASIA

In persons aged >60, vascular ectasias, usually in right colon, account for up to 40% of cases of chronic or recurrent lower GI bleeding. May be associated with aortic stenosis. Diagnosis is by arteriography (clusters of small vessels, early and prolonged opacification of draining vein) or colonoscopy (flat, bright red, fern-like lesions). For bleeding, treat by colonoscopic electro- or laser coagulation, band ligation, arteriographic embolization, or, if necessary, right hemicolectomy (Chap. 43).

ANORECTAL DISEASES

■ HEMORRHOIDS

Due to increased hydrostatic pressure in hemorrhoidal venous plexus (associated with straining at stool, pregnancy). May be external, internal, thrombosed, acute (prolapsed or strangulated), or bleeding. Treat pain with bulk laxative and stool softeners (psyllium extract, dioctyl sodium sulfosuccinate 100–200 mg/d), sitz baths one to four per day, witch hazel compresses, analgesics as needed. Bleeding may require rubber band ligation or injection sclerotherapy. Operative hemorrhoidectomy in severe or refractory cases.

■ ANAL FISSURES

Medical therapy as for hemorrhoids. Relaxation of the anal canal with nitroglycerin ointment (0.2%) applied tid or botulinum toxin type A up to 20 U injected into the internal sphincter on each side of the fissure. Internal anal sphincterotomy in refractory cases.

■ PRURITUS ANI

Often of unclear cause; may be due to poor hygiene, fungal or parasitic infection. Treat with thorough cleansing after bowel movement, topical glucocorticoid, and antifungal agent if indicated.

■ ANAL CONDYLOMAS (GENITAL WARTS)

Wartlike papillomas due to sexually transmitted papillomavirus. Treat with cautious application of liquid nitrogen or podophyllotoxin or with intralesional interferon α . Tend to recur. May be prevented by vaccination with human papilloma virus (HPV) vaccine.

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**Cholelithiasis, Cholecystitis,
and Cholangitis****CHOLELITHIASIS**

There are two major types of gallstones: cholesterol and pigment stones. Cholesterol gallstones contain >50% cholesterol monohydrate. Pigment stones have <20% cholesterol and are composed primarily of calcium bilirubinate. In Western industrialized countries, >90% are cholesterol stones.

■ EPIDEMIOLOGY

In the United States, the prevalence of gallstones is 7.9% in men and 16.6% in women. Predisposing factors include demographic/genetics, obesity, weight loss, female sex hormones, age, gallbladder hypomotility, pregnancy, ileal disease, chronic hemolysis, and cirrhosis.

■ SYMPTOMS AND SIGNS

Many gallstones are “silent,” i.e., present in asymptomatic pts. Symptoms occur when stones trigger inflammation or cause obstruction of the cystic or common bile ducts (CBDs). Major symptoms: (1) biliary colic—a severe steady ache in the RUQ or epigastrium that begins suddenly; often occurs 30–90 min after meals, lasts for several hours, and occasionally radiates to the right scapula or back; (2) nausea, vomiting. Physical examination may be normal or show epigastric or RUQ tenderness.

■ LABORATORY

Occasionally, mild and transient elevations in bilirubin (<85 $\mu\text{mol/L}$ [<5 mg/dL]) accompany biliary colic.

■ IMAGING

Only 10–15% of cholesterol gallstones are radiopaque. Ultrasonography is best diagnostic test. The oral cholecystogram has been largely replaced by ultrasound, but may be used to assess the patency of the cystic duct and gallbladder emptying function (Table 153-1).

■ DIFFERENTIAL DIAGNOSIS

Includes peptic ulcer disease (PUD), gastroesophageal reflux, irritable bowel syndrome, and hepatitis.

■ COMPLICATIONS

Cholecystitis, pancreatitis, cholangitis.

TABLE 153-1 Diagnostic Evaluation of the Bile Ducts

DIAGNOSTIC ADVANTAGES	DIAGNOSTIC LIMITATIONS	CONTRAINDICATIONS	COMPLICATIONS	COMMENT
Hepatobiliary ultrasound				
Rapid Simultaneous scanning of GB, liver, bile ducts, pancreas Accurate identification of dilated bile ducts Not limited by jaundice, pregnancy Guidance for fine-needle biopsy	Bowel gas Massive obesity Ascites Barium Partial bile duct obstruction Poor visualization of distal CBD	None	None	Initial procedure of choice in investigating possible biliary tract obstruction
Computed tomography				
Simultaneous scanning of GB, liver, bile ducts, pancreas Accurate identification of dilated bile ducts, masses Not limited by jaundice, gas, obesity, ascites High-resolution image Guidance for fine-needle biopsy	Extreme cachexia Movement artifact Ileus Partial bile duct obstruction	Pregnancy	Reaction to iodinated contrast, if used	Indicated for evaluation of hepatic or pancreatic masses Procedure of choice in investigating possible biliary obstruction if diagnostic limitations prevent HBUS

(Continued)

TABLE 153-1 Diagnostic Evaluation of the Bile Ducts (Continued)

DIAGNOSTIC ADVANTAGES	DIAGNOSTIC LIMITATIONS	CONTRAINDICATIONS	COMPLICATIONS	COMMENT
Magnetic resonance cholangiopancreatography				
Useful modality for visualizing pancreatic and biliary ducts Has excellent sensitivity for bile duct dilatation, biliary stricture, and intraductal abnormalities Can identify pancreatic duct dilatation or stricture, pancreatic duct stenosis, and pancreas divisum	Cannot offer therapeutic intervention High cost	Claustrophobia Certain metals (iron)	None	
Endoscopic retrograde cholangiopancreatography				
Simultaneous pancreatography Best visualization of distal biliary tract Bile or pancreatic cytology Endoscopic sphincterotomy and stone removal Biliary manometry	Gastroduodenal obstruction Roux-en-Ybiliary-entericanastomosis	Pregnancy Acute pancreatitis Severe cardiopulmonary disease	Pancreatitis Cholangitis, sepsis Infected pancreatic pseudocyst Perforation (rare) Hypoxemia, aspiration	Cholangiogram of choice in: Absence of dilated ducts Pancreatic, ampullary or gastroduodenal disease Prior biliary surgery Endoscopic sphincterotomy treatment possibility

Percutaneous transhepatic cholangiogram

Extremely successful when bile ducts dilated	Nondilated or sclerosed ducts	Pregnancy	Bleeding	Indicated when ERCP is contraindicated or failed
Best visualization of proximal biliary tract		Uncorrectable coagulopathy	Hemobilia	
Bile cytology/culture		Massive ascites	Bile peritonitis	
Percutaneous transhepatic drainage		Hepatic abscess	Bacteremia, sepsis	
Endoscopic ultrasound				
Most sensitive method to detect ampullary stones				Excellent for detecting choledocholithiasis

Abbreviations: CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; GB, gallbladder; HBUS, hepatobiliary ultrasound.

TREATMENT**Cholelithiasis**

In asymptomatic pts, risk of developing complications requiring surgery is small. Elective cholecystectomy should be reserved for: (1) symptomatic pts (i.e., biliary colic despite low-fat diet); (2) persons with previous complications of cholelithiasis (see below); and (3) presence of an underlying condition predisposing to an increased risk of complications (calcified or porcelain gallbladder). Pts with gallstones >3 cm or with an anomalous gallbladder containing stones should also be considered for surgery. Laparoscopic cholecystectomy is minimally invasive and is the procedure of choice for most pts undergoing elective cholecystectomy. Oral dissolution agents (ursodeoxycholic acid) partially or completely dissolve small radiolucent stones in 50% of selected pts within 6–24 months. Because of the frequency of stone recurrence and the effectiveness of laparoscopic surgery, the role of oral dissolution therapy has been largely confined to pts who are not candidates for elective cholecystectomy.

ACUTE CHOLECYSTITIS

Acute inflammation of the gallbladder is usually caused by cystic duct obstruction by an impacted stone. Inflammatory response is evoked by (1) mechanical inflammation from increased intraluminal pressure; (2) chemical inflammation from release of lysolecithin; (3) bacterial inflammation, which plays a role in 50–85% of pts with acute cholecystitis.

■ ETIOLOGY

Approximately 90% calculous; 5–10% acalculous. Acalculous cholecystitis is associated with higher complication rate and acute illness (i.e., burns, trauma, major surgery), fasting, hyperalimentation leading to gallbladder stasis, vasculitis, carcinoma of gallbladder or CBD, some gallbladder infections (*Leptospira*, *Streptococcus*, *Salmonella*, or *Vibrio cholerae*), but in >50% of cases an underlying explanation is not found.

■ SYMPTOMS AND SIGNS

(1) Biliary colic (RUQ or epigastric pain) that progressively worsens; (2) nausea, vomiting, anorexia; and (3) fever. Examination typically reveals RUQ tenderness; palpable RUQ mass found in 20% of pts. *Murphy's sign* is present when deep inspiration or cough during palpation of the RUQ produces increased pain or inspiratory arrest.

■ LABORATORY

Mild leukocytosis; serum bilirubin, alkaline phosphatase, and aspartate aminotransferase (AST) may be mildly elevated.

■ IMAGING

Ultrasonography is useful for demonstrating gallstones and signs of gallbladder inflammation. Radionuclide scans (HIDA, DIDA, DISIDA, etc.) may identify cystic duct obstruction.

■ DIFFERENTIAL DIAGNOSIS

Includes acute pancreatitis, appendicitis, pyelonephritis, PUD, hepatitis, and hepatic abscess.

■ COMPLICATIONS

Empyema, hydrops, gangrene, perforation, fistula formation, gallstone ileus, porcelain gallbladder.

TREATMENT**Acute Cholecystitis**

No oral intake, nasogastric suction, IV fluids and electrolytes, analgesia (meperidine or NSAIDs), and antibiotics guided by the most common gram-negative organisms and anaerobes (piperacillin+tazobactam, ceftriaxone+metronidazole, levofloxacin+metronidazole); anaerobic coverage should be added if gangrenous or emphysematous cholecystitis is suspected; imipenem/meropenem covers the spectrum of bacteria causing ascending cholangitis but should be reserved for the most life-threatening infections when other antibiotics have failed. Optimal timing of surgery depends on pt stabilization and pts with acute uncomplicated cholecystitis should undergo laparoscopic cholecystectomy ideally within 48–72 hours of diagnosis. Urgent cholecystectomy is appropriate in most pts with a suspected or confirmed complication. Delayed surgery is reserved for pts with high risk of emergent surgery and where the diagnosis is in doubt.

CHRONIC CHOLECYSTITIS**■ ETIOLOGY**

Chronic inflammation of the gallbladder; almost always associated with gallstones. Results from repeated acute/subacute cholecystitis or prolonged mechanical irritation of gallbladder wall.

■ SYMPTOMS AND SIGNS

May be asymptomatic for years, may progress to symptomatic gallbladder disease or to acute cholecystitis, or present with complications.

■ LABORATORY

Tests are usually normal.

■ IMAGING

Ultrasonography preferred; usually shows gallstones within a contracted gallbladder (Table 153-1).

■ DIFFERENTIAL DIAGNOSIS

PUD, esophagitis, irritable bowel syndrome.

TREATMENT**Chronic Cholecystitis**

Surgery indicated if pt is symptomatic.

CHOLEDOCHOLITHIASIS/CHOLANGITIS**■ ETIOLOGY**

In pts with cholelithiasis, passage of gallstones into CBD occurs in 10–15%; increases with age. At cholecystectomy, undetected stones are left behind in 1–5% of pts.

■ SYMPTOMS AND SIGNS

Choledocholithiasis may present as an incidental finding, biliary colic, obstructive jaundice, cholangitis, or pancreatitis. Cholangitis usually presents as fever, RUQ pain, and jaundice (*Charcot's triad*).

■ LABORATORY

Elevations in serum bilirubin, alkaline phosphatase, and aminotransferases. Leukocytosis usually accompanies cholangitis; blood cultures are frequently positive. Biochemical evidence of pancreatic inflammation is seen in >30% of cases.

■ IMAGING

Diagnosis usually made by cholangiography either preoperatively by endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), or intraoperatively at the time of cholecystectomy. Ultrasonography may reveal dilated bile ducts but has poor visualization of the distal CBD (Table 153-1).

■ DIFFERENTIAL DIAGNOSIS

Acute cholecystitis, renal colic, perforated viscus, pancreatitis.

■ COMPLICATIONS

Cholangitis, obstructive jaundice, gallstone-induced pancreatitis, and secondary biliary cirrhosis.

TREATMENT**Choledocholithiasis/Cholangitis**

Laparoscopic cholecystectomy and ERCP have decreased the need for choledocholithotomy and T-tube drainage of the bile ducts. When CBD stones are suspected prior to laparoscopic cholecystectomy, preoperative ERCP with endoscopic papillotomy and stone extraction is the preferred approach. CBD stones should be suspected in gallstone pts with (1) history of jaundice or pancreatitis, (2) abnormal LFT, and (3) ultrasound evidence of a dilated CBD or stones in the duct. Cholangitis treated like acute cholecystitis; no oral intake, hydration, analgesia, and antibiotics are the mainstays; stones should be removed surgically or endoscopically.

PRIMARY SCLEROSING CHOLANGITIS (PSC)

PSC is a sclerosing, inflammatory, and obliterative process involving the biliary tree.

■ ETIOLOGY

Associations: inflammatory bowel disease (90% of cases of PSC—especially ulcerative colitis), autoimmune pancreatitis, AIDS, multifocal fibrosclerosis syndromes.

■ SYMPTOMS AND SIGNS

Pruritus, RUQ pain, jaundice, fever, weight loss, and malaise. Approximately 44% may be asymptomatic at diagnosis. May progress to cirrhosis with portal hypertension.

■ LABORATORY

Evidence of cholestasis (elevated bilirubin and alkaline phosphatase) common.

■ RADIOLOGY/ENDOSCOPY

Transhepatic or endoscopic cholangiograms reveal stenosis and dilation of the intra- and extrahepatic bile ducts.

■ DIFFERENTIAL DIAGNOSIS

Cholangiocarcinoma, Caroli disease (cystic dilation of bile ducts), *Fasciola hepatica* infection, echinococcosis, and ascariasis. IgG4-associated cholangitis.

TREATMENT**Primary Sclerosing Cholangitis**

No satisfactory therapy. Cholangitis should be treated as outlined earlier. Cholestyramine may control pruritus. Supplemental vitamin D and calcium may retard bone loss. Glucocorticoids, methotrexate, and cyclosporine have not been shown to be effective. Ursodeoxycholic acid improves liver tests but has not been shown to affect survival. Surgical relief of biliary obstruction may be appropriate but has a high complication rate. Liver transplantation should be considered in pts with end-stage cirrhosis. Median survival: 9–12 years after diagnosis, with age, bilirubin level, histologic stage, and splenomegaly being predictors of survival.

154 Pancreatitis

**ACUTE PANCREATITIS**

Any severe acute pain in the abdomen or back should suggest the possibility of acute pancreatitis. The diagnosis is established by two of the following three criteria: (1) typical abdominal pain in the epigastrium that may radiate to the back, (2) threefold or greater elevation in serum lipase and/or amylase, and (3) confirmatory findings of acute pancreatitis on cross-sectional abdominal imaging. Pathologically, acute pancreatitis varies from *interstitial pancreatitis*, which is usually a mild and self-limited disorder, to *necrotizing pancreatitis*, in which the degree of necrosis may correlate with the severity of the attack and its systemic manifestations.

■ ETIOLOGY

Most common causes in the United States are cholelithiasis and alcohol. Others are listed in [Table 154-1](#).

■ CLINICAL FEATURES

Can vary from mild abdominal pain to shock. *Common symptoms:* (1) steady, boring pain in the epigastric and periumbilical region may radiate to the back, chest, flanks, and lower abdomen; (2) nausea, vomiting, abdominal distention.

Physical examination: (1) low-grade fever, tachycardia, hypotension; (2) erythematous skin nodules due to subcutaneous fat necrosis; (3) basilar rales, pleural effusion (often on the left); (4) abdominal tenderness and rigidity, diminished bowel sounds, palpable upper abdominal mass; (5) Cullen's sign: blue discoloration in the periumbilical area due to hemoperitoneum; (6) Turner's sign: blue-red-purple or green-brown discoloration of the flanks due to tissue catabolism of hemoglobin.

■ LABORATORY

1. Serum amylase and lipase values threefold or more above normal almost always secure the diagnosis if gut perforation, ischemia, and infarction are excluded. Serum lipase is the preferred test. There is no correlation between

TABLE 154-1 Causes of Acute Pancreatitis**Common Causes**

Gallstones (including microlithiasis)
 Alcohol (acute and chronic alcoholism)
 Hypertriglyceridemia
 Endoscopic retrograde cholangiopancreatography (ERCP), especially after biliary manometry
 Drugs (azathioprine, 6-mercaptopurine, sulfonamides, estrogens, tetracycline, valproic acid, anti-HIV medications, 5-aminosalicylic acid [5-ASA])
 Trauma (especially blunt abdominal trauma)
 Postoperative (abdominal and nonabdominal operations)

Uncommon Causes

Vascular causes and vasculitis (ischemic-hypoperfusion states after cardiac surgery)
 Connective tissue disorders and thrombotic thrombocytopenic purpura (TTP)
 Cancer of the pancreas
 Hypercalcemia
 Periapillary diverticulum
 Pancreas divisum
 Hereditary pancreatitis
 Cystic fibrosis
 Renal failure
 Infections (mumps, coxsackievirus, cytomegalovirus, echovirus, parasites)
 Autoimmune (e.g., type 1 and type 2)

Causes to Consider in Pts with Recurrent Bouts of Acute Pancreatitis without an Obvious Etiology

Occult disease of the biliary tree or pancreatic ducts, especially microlithiasis, biliary sludge
 Drugs
 Alcohol abuse
 Metabolic: Hypertriglyceridemia, hypercalcemia
 Anatomic: Pancreas divisum
 Pancreatic cancer
 Intraductal papillary mucinous neoplasm (IPMN)
 Hereditary pancreatitis
 Cystic fibrosis
 Autoimmune
 Idiopathic

the severity of pancreatitis and the degree of serum lipase and amylase elevations. After 3–7 days, amylase values tend to return toward normal; however, pancreatic lipase levels may remain elevated for 7–14 days.

2. *Other tests:* *Hypocalcemia* occurs in ~25% of pts. *Leukocytosis* (15,000–20,000/ μ L) occurs frequently. *Hemoconcentration* may be the harbinger of more severe disease (i.e., pancreatic necrosis), azotemia is a significant risk factor for mortality. *Hypertriglyceridemia* occurs in 5–10% of cases and can cause a spuriously normal serum amylase level. *Hyperglycemia* is common. *Serum bilirubin*, *alkaline phosphatase*, and *aspartate aminotransferase* can be transiently elevated. *Hypoalbuminemia* and marked elevations of *serum lactic dehydrogenase* (LDH) are associated with an increased mortality rate. *Hypoxemia* is present in 5–10% of pts and may herald the onset of ARDS.

■ IMAGING

1. *Ultrasound* often fails to visualize the pancreas because of overlying intestinal gas but may detect gallstones, pseudocysts, mass lesions, or edema or enlargement of the pancreas.
2. *CT* can confirm the clinical impression of acute pancreatitis. It can also be helpful in evaluating the complications of acute pancreatitis.

■ DIFFERENTIAL DIAGNOSIS

Intestinal perforation (especially peptic ulcer), cholecystitis, acute intestinal obstruction, mesenteric vascular occlusion, renal colic, inferior myocardial infarction, aortic dissection, connective tissue disorders, pneumonia, and diabetic ketoacidosis.

■ SEVERITY AND COMPLICATIONS

Risk factors and markers of severity are listed in [Table 154-2](#).

In the modified Marshall scoring system 3 organ systems are assessed to define organ failure: respiratory, cardiovascular, and renal. The median prevalence of

TABLE 154-2 Severe Acute Pancreatitis

Risk Factors for Severity

- Age >60 years
- Obesity, BMI >30
- Comorbid disease (Charlson Comorbidity Index)

Markers of Severity at Admission or within 24 h

- SIRS—defined by presence of 2 or more criteria:
 - Core temperature <36°C or >38°C
 - Heart rate >90 beats/min
 - Respirations >20/min or PCO₂ <32 mmHg
 - White blood cell count >12,000/μL, <4000/μL, or 10% bands
- APACHE II
- Hemoconcentration (hematocrit >44%)
- Admission BUN (>22 mg/dL)
- BISAP Score
 - (B) BUN >25 mg/dL
 - (I) Impaired mental status
 - (S) SIRS: ≥2 of 4 present
 - (A) Age >60 years
 - (P) Pleural effusion
- Organ failure (Modified Marshall Score)
- Cardiovascular: systolic BP <90 mmHg, heart rate >130 beats/min
- Pulmonary: PaO₂ <60 mmHg
- Renal: serum creatinine >2.0 mg %

Markers of Severity during Hospitalization

- Persistent organ failure
- Pancreatic necrosis

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; BISAP, Bedside Index of Severity in Acute Pancreatitis; BP, blood pressure; BUN, blood urea nitrogen; SIRS, systemic inflammatory response syndrome.

organ failure is 54% in necrotizing pancreatitis. With single-organ system failure, the mortality is 3–10% but increases to 47% with multisystem organ failure.

Three *severity classifications* have been defined:

- *Mild acute pancreatitis*—without local complications or organ failure.
- *Moderately severe acute pancreatitis*—transient organ failure (resolves in <48 h) or local or systemic complications in the absence of persistent organ failure.
- *Severe acute pancreatitis*—persistent organ failure (>48 h). CT or MRI should be obtained to assess for necrosis or other local complications.

Systemic complications

Shock, GI bleeding, common duct obstruction, ileus, splenic infarction or rupture, disseminated intravascular coagulation, subcutaneous fat necrosis, acute respiratory distress syndrome, pleural effusion, acute renal failure, sudden blindness.

Local complications

1. Sterile or infected *pancreatic necrosis*. Percutaneous aspiration of necrosis with Gram stain and culture should be considered if there are ongoing signs of possible pancreatic infection such as sustained leukocytosis, fever, or organ failure. Repeated fine-needle aspiration and Gram stain with culture of pancreatic necrosis may be done every 5–7 days in the presence of persistent fever. Repeated CT or MRI imaging should also be considered with any change in clinical course to monitor for complications. *Sterile necrosis* is most often managed conservatively unless complications arise. Once a diagnosis of *infected necrosis* is established and an organism identified, targeted antibiotics should be instituted. Pancreatic debridement (necrosectomy) should be considered for definitive management of *infected necrosis*, but clinical decisions are generally influenced by response to antibiotic treatment and overall clinical condition. A step-up approach (percutaneous or endoscopic transgastric drainage followed, if necessary, by open necrosectomy) has been successfully reported by some pancreatic centers.
2. *Pancreatic pseudocysts*. The incidence of pseudocyst is low, most acute collections of fluid resolve over time, <10% of pts have persistent fluid collections after 6 weeks that would meet the definition of a pseudocyst. Only symptomatic collections should be drained with surgery or endoscopy or by percutaneous route.
3. Other complications: Pancreatic ascites, pancreatic duct disruption, walled-off necrosis, pancreatic fluid collections, involvement of contiguous organs by necrotizing pancreatitis, thrombosis of blood vessels, pancreatic enteric fistula, bowel infarction, obstructive jaundice.

TREATMENT

Acute Pancreatitis

Most (85–90%) cases are self-limited and subside over a period of 3–7 days. Following diagnosis, the most important treatment is safe, aggressive IV fluid resuscitation. Severity should be assessed to determine if ICU care is required. Other conventional measures: no oral alimentation and analgesics for abdominal pain. A low-fat solid diet can be given with mild acute pancreatitis after the abdominal pain has resolved. Precipitating factors (alcohol, medications) must be eliminated.

CHRONIC PANCREATITIS

Chronic pancreatitis is a disease process characterized by irreversible damage to the pancreas.

■ ETIOLOGY

Alcoholism is the most frequent cause of clinically apparent chronic pancreatitis; in 25% of adults, etiology is unknown. Other causes are listed in [Table 154-3](#).

■ SYMPTOMS AND SIGNS

Pain is cardinal symptom. Weight loss, steatorrhea, and other signs and symptoms of malabsorption common. Physical examination often unremarkable.

TABLE 154-3 Chronic Pancreatitis and Pancreatic Exocrine Insufficiency: TIGAR-O Classification System

Toxic-Metabolic

Alcoholic
Tobacco smoking
Hypercalcemia
Hyperlipidemia
Chronic renal failure
Medications—phenacetin abuse
Toxins—organotin compounds (e.g., dibutyltin dichloride, DBTC)

Idiopathic

Early onset
Late onset
Tropical

Genetic

Cationic trypsinogen (*PRSS1*)
Cystic fibrosis transmembrane conductance regulator gene (*CFTR*)
Calcium-sensing receptor (*CASR*)
Chymotrypsin C gene (*CTRC*)
Pancreatic secretory trypsin inhibitor gene (*SPINK1*)

Autoimmune

Type 1 autoimmune chronic pancreatitis
IgG4 systemic
Type 2 autoimmune chronic pancreatitis

Recurrent and Severe Acute Pancreatitis

Postnecrotic (severe acute pancreatitis)
Recurrent acute pancreatitis
Vascular diseases/ischemia
Radiation induced

Obstructive

Pancreas divisum
Duct obstruction (e.g., tumor)
Preampullary duodenal wall cysts
Posttraumatic pancreatic duct scars

Abbreviations: DBTC, dibutyltin dichloride; TIGAR-O, toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, obstructive.

LABORATORY

No specific laboratory test for chronic pancreatitis. Serum amylase and lipase levels are often normal. Serum bilirubin and alkaline phosphatase may be elevated. The fecal elastase-1 and small-bowel biopsy are useful in the evaluation of pts with suspected pancreatic steatorrhea. Many pts have impaired glucose tolerance. Secretin stimulation test is a relatively sensitive test for pancreatic exocrine deficiency and becomes abnormal when $\geq 60\%$ of the pancreatic exocrine function has been lost.

IMAGING

CT scan is the imaging modality of choice followed by MRI, endoscopic ultrasound, and pancreas function testing. Diffuse calcifications noted on plain film of the abdomen usually indicate significant damage to the pancreas and are pathognomic for chronic pancreatitis.

DIFFERENTIAL DIAGNOSIS

Important to distinguish from pancreatic carcinoma; may require radiographically guided biopsy.

TREATMENT**Chronic Pancreatitis**

Aimed at controlling malabsorption and pain. Pancreatic enzyme replacement has been the cornerstone of therapy as it usually controls diarrhea and restores absorption of fat to an acceptable level and allows weight gain. Because pancreatic enzymes are inactivated by acid, proton pump inhibitors may improve their efficacy (but should not be given with enteric-coated preparations). The management of pain in pts with chronic pancreatitis is problematic. Recent meta-analyses have shown no consistent benefit of enzyme therapy at reducing pain in chronic pancreatitis. A recent prospective study reported that pregabalin can improve pain in chronic pancreatitis and lower pain medication requirement. Surgery with ductal decompression may control pain if there is a large-duct disease. Subtotal pancreatectomy may also control pain but at the cost of exocrine insufficiency and diabetes.

COMPLICATIONS

Chronic abdominal pain, gastroparesis, malabsorption/maldigestion, impaired glucose tolerance. Nondiabetic retinopathy due to vitamin A and/or zinc deficiency. GI bleeding, icterus, effusions, subcutaneous fat necrosis, and metabolic bone disease. Increased risk for pancreatic carcinoma.

155 Acute Hepatitis

**VIRAL HEPATITIS**

Acute viral hepatitis is a systemic infection predominantly affecting the liver. Clinically characterized by malaise, nausea, vomiting, diarrhea, and low-grade fever followed by dark urine, jaundice, and tender hepatomegaly; may be subclinical and detected on the basis of elevated

aspartate and alanine aminotransferase (AST and ALT) levels. Hepatitis B may be associated with immune-complex phenomena, including arthritis, serum sickness-like illness, glomerulonephritis, and a polyarteritis nodosa-like vasculitis. Hepatitis-like illnesses may be caused not only by hepatotropic viruses (A, B, C, D, E) but also by other viruses (Epstein-Barr, CMV, coxsackievirus, etc.), alcohol, drugs, hypotension and ischemia, and biliary tract disease ([Table 155-1](#)).

■ HEPATITIS A (HAV)

27-nm picornavirus (hepatovirus) with single-stranded RNA genome.

Clinical Course (See [Fig. 155-1](#))

Outcome

Recovery within 6–12 months, usually with no clinical sequelae; a small proportion will have one or two apparent clinical and serologic relapses; in some cases, pronounced cholestasis suggesting biliary obstruction may occur; rare fatalities (fulminant hepatitis), no chronic carrier state.

Diagnosis

IgM anti-HAV in acute or early convalescent serum sample.

Epidemiology

Fecal-oral transmission; endemic in underdeveloped countries; food-borne and waterborne epidemics; outbreaks in day-care centers, residential institutions.

Prevention

After exposure: immune globulin 0.02 mL/kg IM within 2 weeks to household, sexual, and institutional contacts (not casual contacts at work). *Before exposure:* inactivated HAV vaccine 1 mL IM (unit dose depends on formulation); half dose to children; repeat at 6–12 months; target travelers, military recruits, animal handlers, day-care personnel, laboratory workers, and pts with chronic liver disease (especially hepatitis C).

■ HEPATITIS B (HBV)

42-nm hepadnavirus with outer surface coat (HBsAg), inner nucleocapsid core (HBcAg), DNA polymerase, and partially double-stranded DNA genome of 3200 nucleotides. Circulating form of HBcAg is HBeAg, a marker of viral replication and infectivity. Multiple serotypes and genetic heterogeneity.

Clinical Course (See [Fig. 155-2](#))

Outcome

Recovery >90%, fulminant hepatitis (<1%), chronic hepatitis or carrier state (only 1–2% of immunocompetent adults; higher in neonates, elderly, immunocompromised), cirrhosis, and hepatocellular carcinoma (especially following chronic infection beginning in infancy or early childhood) ([Chap. 157](#)). Reactivation of HBV has been observed with immunosuppression, particularly with rituximab.

Diagnosis

HBsAg in serum (acute or chronic infection); IgM anti-HBc (early anti-HBc indicative of acute or recent infection). Most sensitive test is detection of HBV DNA in serum; not generally required for routine diagnosis.

Epidemiology

Percutaneous (needle stick), sexual, or perinatal transmission. Endemic in sub-Saharan Africa and Southeast Asia, where up to 20% of population acquire infection, usually early in life.

Prevention

After exposure in unvaccinated persons: hepatitis B immune globulin (HBIG) 0.06 mL/kg IM immediately after needle stick to within 14 days of sexual exposure

TABLE 155-1 Clinical and Epidemiologic Features of Viral Hepatitis

FEATURE	HAV	HBV	HCV	HDV	HEV
Incubation (days)	15–45, mean 30	30–180, mean 60–90	15–160, mean 50	30–180, mean 60–90	14–60, mean 40
Onset	Acute	Insidious or acute	Insidious or acute	Insidious or acute	Acute
Age preference	Children, young adults	Young adults (sexual and percutaneous), babies, toddlers	Any age, but more common in adults	Any age (similar to HBV)	Epidemic cases: young adults (20–40 years); sporadic cases: older adults (>60)
Transmission					
Fecal-oral	+++	–	–	–	+++
Percutaneous	Unusual	+++	+++	+++	–
Perinatal	–	+++	± ^a	+	–
Sexual	±	++	± ^a	++	–
Clinical					
Severity	Mild	Occasionally severe	Moderate	Occasionally severe	Mild
Fulminant	0.1%	0.1–1%	0.1%	5–20% ^b	1–2% ^e
Progression to chronicity	None	Occasional (1–10%) (90% of neonates)	Common (85%)	Common ^d	None ^f
Carrier	None	0.1–30% ^c	1.5–3.2%	Variable ^g	None
Cancer	None	+ (neonatal infection)	+	±	None
Prognosis	Excellent	Worse with age, debility	Moderate	Acute, good Chronic, poor	Good

Prophylaxis	Ig, inactivated vaccine	HBIG, recombinant vaccine	None	HBV vaccine (none for HBV carriers)	Vaccine
Therapy	None	Interferon Lamivudine Adefovir Pegylated interferon ^h Entecavir ^h Telbivudine Tenofovir ^h	Pegylated interferon ribavirin telaprevir, ⁱ boceprevir, ⁱ simeprevir, sofosbuvir, ledipasvir, paritaprevir/ ritonavir ombitasvir, dasabuvir daclatasvir, velpatasvir, grazoprevir, elbasvir	Pegylated interferon ±	None ^j

^aPrimarily with HIV co-infection and high-level viremia in index case; more likely in persons with multiple sex partners or sexually transmitted diseases; risk ~5%.

^bUp to 5% in acute HBV/HDV co-infection; up to 20% in HDV superinfection of chronic HBV infection.

^cVaries considerably throughout the world and in subpopulations within countries; see text.

^dIn acute HBV/HDV co-infection, the frequency of chronicity is the same as that for HBV; in HDV superinfection, chronicity is invariable.

^e10–20% in pregnant women.

^fExcept as observed in immunosuppressed liver allograft recipients or other immunosuppressed hosts.

^gCommon in Mediterranean countries; rare in North America and western Europe.

^hFirst-line agents.

ⁱNo longer recommended.

^jAnecdotal reports and retrospective studies suggest that pegylated interferon and/or ribavirin are effective in treating chronic hepatitis E, observed in immunocompromised persons; ribavirin monotherapy has been used successfully in acute, severe hepatitis E.

Abbreviation: HBIG, hepatitis B immunoglobulin. See text for other abbreviations.

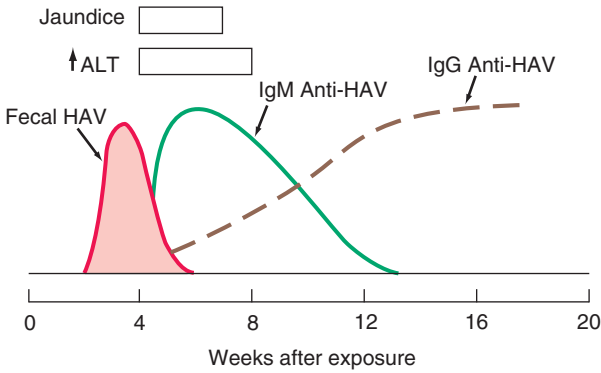


FIGURE 155-1 Scheme of typical clinical and laboratory features of HAV. ALT, alanine aminotransferase.

in combination with vaccine series. For perinatal exposure (HbsAg+ mother) HBIG 0.5 mL in the thigh immediately after birth with the vaccine series started within the first 12 h of life. *Before exposure:* recombinant hepatitis B vaccine IM (dose depends on formulation as well as adult or pediatric and hemodialysis); at 0, 1, and 6 months; deltoid, not gluteal injection. Has been targeted to high-risk groups (e.g., health workers, persons with multiple sexual partners, IV drug users, hemodialysis pts, hemophiliacs, household and sexual contacts of HBsAg carriers, persons traveling in endemic areas, unvaccinated children <18). Universal vaccination of all children is now recommended in the United States.

■ HEPATITIS C (HCV)

Caused by flavi-like virus in the genus Hepacivirus with RNA genome of 9600 nucleotides; genetic heterogeneity. Incubation period 7–8 weeks.

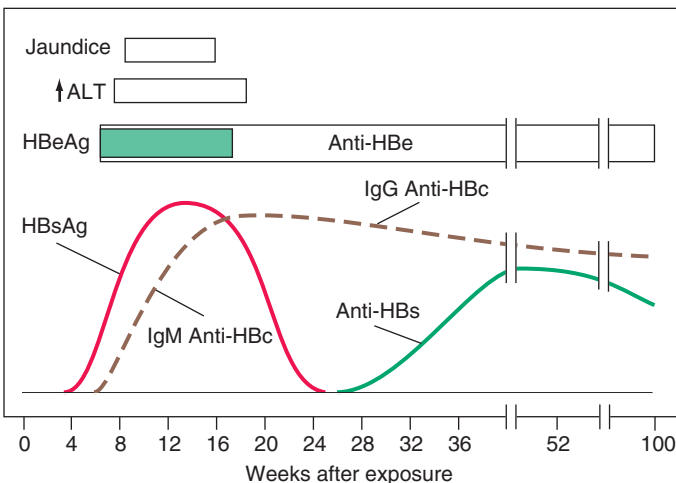


FIGURE 155-2 Scheme of typical clinical and laboratory features of HBV. ALT, alanine aminotransferase.

Clinical Course

Often clinically mild and marked by fluctuating elevations of serum aminotransferase levels; >50% likelihood of chronicity, leading to cirrhosis in >20%.

Diagnosis

Anti-HCV in serum. Current third-generation immunoassay incorporates proteins from the core, NS3, and NS5 regions. The most sensitive indicator of HCV infection is HCV RNA (Fig. 155-3).

Epidemiology

HCV accounts for >90% of transfusion-associated hepatitis cases. IV drug use accounts >50% of reported cases of hepatitis C. Little evidence for frequent sexual or perinatal transmission.

Prevention

Exclusion of paid blood donors, testing of donated blood for anti-HCV. Anti-HCV detected by enzyme immunoassay in blood donors with normal ALT is often falsely positive (30%); result should be confirmed by HCV RNA in serum.

HEPATITIS D (HDV, DELTA AGENT)

Defective 37-nm RNA virus that requires HBV for its replication; either co-infects with HBV or superinfects a chronic HBV carrier. Enhances severity of HBV infection (acceleration of chronic hepatitis to cirrhosis, occasionally fulminant acute hepatitis).

Diagnosis

Anti-HDV in serum (acute hepatitis D—often in low titer, is transient; chronic hepatitis D—in higher titer, is sustained).

Epidemiology

Endemic among HBV carriers in Mediterranean Basin, where it is spread predominantly by nonpercutaneous means. In nonendemic areas (e.g., northern Europe, United States) HDV is spread percutaneously among HBSAg+ IV drug users or by transfusion in hemophiliacs.

Prevention

Hepatitis B vaccine (noncarriers only).

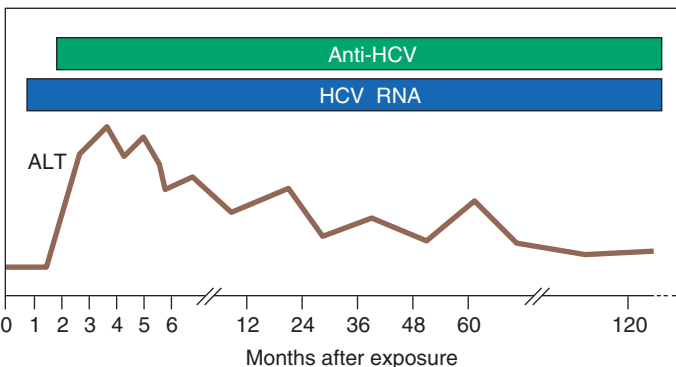


FIGURE 155-3 Scheme of typical laboratory features during acute hepatitis C progressing to chronicity. HCV RNA is the first detectable event, preceding alanine aminotransferase (ALT) elevation and the appearance of anti-HCV.

■ HEPATITIS E (HEV)

Caused by 29- to 32-nm agent resembling caliciviruses but considered within its own genus, Hepevirus. Enterically transmitted and responsible for waterborne epidemics of hepatitis in India, parts of Asia and Africa, and Central America. Self-limited illness with high (10–20%) mortality rate in pregnant women.

TREATMENT**Viral Hepatitis**

Activity as tolerated, high-calorie diet (often tolerated best in morning), IV hydration for severe vomiting, cholestyramine up to 4 g PO four times daily for severe pruritus, avoid hepatically metabolized drugs; no role for glucocorticoids. Liver transplantation for fulminant hepatic failure. In rare instances of severe acute HBV, treatment with a nucleoside analogue has been used successfully. Most authorities would recommend antiviral therapy for severe acute HBV (**Chap. 156**). For acute HCV, delay in treatment initiation for up to 6 months with counseling and monitoring of HCV RNA levels are recommended. Health workers who sustain HCV-contaminated needle sticks and injection-drug users are the two main settings where acute HCV can be identified and are candidates for treatment (**Chap. 156**).

TOXIC AND DRUG-INDUCED HEPATITIS**■ DOSE-DEPENDENT (DIRECT HEPATOTOXINS)**

Onset is within 48 h, predictable, necrosis around terminal hepatic venule—e.g., carbon tetrachloride, benzene derivatives, mushroom poisoning, acetaminophen, or microvesicular steatosis (e.g., tetracyclines, valproic acid).

■ IDIOSYNCRATIC

Variable dose and time of onset; small number of exposed persons affected; may be associated with fever, rash, arthralgias, eosinophilia. In many cases, mechanism may actually involve toxic metabolite, possibly determined on genetic basis—e.g., isoniazid, halothane, phenytoin, methyl dopa, carbamazepine, diclofenac, oxacillin, sulfonamides.

TREATMENT**Toxic and Drug-Induced Hepatitis**

Supportive as for viral hepatitis; withdraw suspected agent, and include use of gastric lavage and oral administration of charcoal or cholestyramine. Liver transplantation if necessary. In acetaminophen overdose, more specific therapy is available in the form of sulfhydryl compounds (e.g., *N*-acetylcysteine). These agents appear to act by providing a reservoir of sulfhydryl groups to bind the toxic metabolites or by stimulating synthesis of hepatic glutathione. Therapy should be begun within 8 h of ingestion but may be effective even if given as late as 24–36 h after overdose.

FULMINANT HEPATITIS

Massive hepatic necrosis with impaired consciousness occurring within 8 weeks of the onset of illness.

■ CAUSES

Infections (viral, including HAV, HBV, HCV [rarely], HDV, HEV; bacterial, rickettsial, parasitic), drugs and toxins, ischemia (shock), Budd-Chiari syndrome, idiopathic chronic active hepatitis, acute Wilson's disease, microvesicular fat syndromes (Reye's syndrome, acute fatty liver of pregnancy).

■ CLINICAL MANIFESTATIONS

Pts usually present with signs and symptoms of encephalopathy that may evolve to deep coma. The combination of rapidly shrinking liver size, rapidly rising bilirubin level, and marked prolongation of the PT, even as aminotransferase levels fall, together with clinical signs of confusion, disorientation, somnolence, ascites, and edema, indicates that the pt has hepatic failure with encephalopathy. Cerebral edema is common; brainstem compression, gastrointestinal bleeding, sepsis, respiratory failure, cardiovascular collapse, and renal failure are terminal events. The mortality rate is exceedingly high (>80% in pts with deep coma).

TREATMENT

Fulminant Hepatitis

The goal of therapy is to support the pt by maintenance of fluid balance, support of circulation and respiration, control of bleeding, correction of hypoglycemia, and treatment of other complications of the comatose state in anticipation of liver regeneration and repair. Protein intake should be restricted, and oral lactulose or neomycin administered. Meticulous intensive care that includes prophylactic antibiotic coverage is the one factor that does appear to improve survival. Liver transplantation should be considered.

156 Chronic Hepatitis



A group of disorders of varying causes and severity in which hepatic inflammation and necrosis continue for at least 6 months.

OVERVIEW

■ ETIOLOGY

Hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV, delta agent), drugs (methyl dopa, nitrofurantoin, isoniazid, dantrolene), autoimmune hepatitis, Wilson's disease, hemochromatosis, α_1 -antitrypsin deficiency.

■ HISTOLOGIC CLASSIFICATION

Chronic hepatitis can be classified based on its cause, *grade*, and *stage*. The grade is a histologic assessment of necrosis and inflammatory activity and is based on examination of the liver biopsy. The stage of chronic hepatitis reflects the level of disease progression and is based on the degree of fibrosis (see [Table 334-2](#), p. 2376, HPIM-20).

■ PRESENTATION

Wide clinical spectrum ranging from asymptomatic serum aminotransferase elevations to apparently acute, even fulminant, hepatitis. Common symptoms

include fatigue, malaise, anorexia, low-grade fever; jaundice is frequent in severe disease. Some pts may present with complications of cirrhosis: ascites, variceal bleeding, encephalopathy, coagulopathy, and hypersplenism. In chronic HBV or HCV and autoimmune hepatitis, extrahepatic features may predominate.

CHRONIC HEPATITIS B

Follows ~1% of cases of acute hepatitis B in immunocompetent hosts; more frequent in immunocompromised hosts. Spectrum of disease: asymptomatic antigenemia, chronic hepatitis, cirrhosis, hepatocellular cancer; early phase often associated with continued symptoms of hepatitis, elevated aminotransferase levels, presence in serum of HBeAg and HBV DNA, and presence in liver of replicative form of HBV; later phase in some pts may be associated with clinical and biochemical improvement, disappearance of HBeAg and HBV DNA and appearance of anti-HBeAg in serum, and integration of HBV DNA into host hepatocyte genome. In Mediterranean and European countries as well as in Asia, a frequent variant is characterized by readily detectable HBV DNA, but without HBeAg (anti-HBeAg-reactive). Most of these cases are due to a mutation in the pre-C region of the HBV genome that prevents HBeAg synthesis (may appear during course of chronic wild-type HBV infection as a result of immune pressure and may also account for some cases of fulminant hepatitis B). Chronic hepatitis B ultimately leads to cirrhosis in 25–40% of cases (particularly in pts with HDV superinfection or the pre-C mutation) and hepatocellular carcinoma in many of these pts (particularly when chronic infection is acquired early in life).

■ EXTRAHEPATIC MANIFESTATIONS (IMMUNE COMPLEX-MEDIATED)

Rash, urticaria, arthritis, polyarteritis nodosa-like vasculitis, polyneuropathy, glomerulonephritis.

TREATMENT

Chronic Hepatitis B

There are currently multiple approved drugs for the treatment of chronic HBV: interferon α (IFN- α), pegylated interferon (PEG IFN), lamivudine, adefovir dipivoxil, entecavir, telbivudine, tenofovir, and tenofovir alafenamide (see [Table 156-1](#)). Use of IFN- α has been supplanted by PEG-IFN. [Table 156-2](#) summarizes recommendations for treatment of chronic HBV.

CHRONIC HEPATITIS C

Follows 50–70% of cases of transfusion-associated and sporadic hepatitis C. Clinically mild, often waxing and waning aminotransferase elevations; mild chronic hepatitis on liver biopsy. Extrahepatic manifestations include cryoglobulinemia, porphyria cutanea tarda, membranoproliferative glomerulonephritis, and lymphocytic sialadenitis. Diagnosis confirmed by detecting anti-HCV in serum. May lead to cirrhosis in 20–25% of cases after 20 years.

TREATMENT

Chronic Hepatitis C

Therapy for chronic HCV is currently stratified based on HCV genotype and the presence of treatment naïve or treatment experienced disease in addition to pt-specific factors (see [Table 334-6](#), p. 2391-2, HPIM-20). Therapeutic options for

TABLE 156-1 Comparison of Pegylated Interferon (PEG IFN), Lamivudine, Adefovir, Entecavir, Telbivudine, and Tenofovir Therapy for Chronic Hepatitis B^a

FEATURE	PEG IFN ^b	LAMIVUDINE	ADEFOVIR	ENTECAVIR	TELBIVUDINE	TENOFOVIR
Route of administration	Subcutaneous injection	Oral	Oral	Oral	Oral	Oral
Duration of therapy ^c	48–52 weeks	≥52 weeks	≥48 weeks	≥48 weeks	≥52 weeks	≥48 weeks
Tolerability	Poorly tolerated	Well tolerated	Well tolerated; creatinine monitoring recommended	Well tolerated	Well tolerated	Well tolerated; creatinine monitoring recommended
HBeAg seroconversion						
1 yr Rx	18–20%	16–21%	12%	21%	22%	21%
>1 yr Rx	NA	up to 50% @ 5 yrs	43% @ 3 yrs ^d	31% @ 2 yrs 44% @ 6 yrs	30% @ 2 yrs	40% @ 5 yrs
Log ₁₀ HBV DNA reduction (mean copies/mL)						
HBeAg-reactive	4.5	5.5	median 3.5–5	6.9	6.4	6.2
HBeAg-negative	4.1	4.4–4.7	median 3.5–3.9	5.0	5.2	4.6
HBV DNA PCR negative (<300–400 copies/mL; <1000 copies/mL for adefovir) at end of yr 1						
HBeAg-reactive	10–25%	36–44%	13–21%	67% (91% @ 4 yrs)	60%	76%
HBeAg-negative	63%	60–73%	48–77%	90%	88%	93%

(Continued)

TABLE 156-1 Comparison of Pegylated Interferon (PEG IFN), Lamivudine, Adefovir, Entecavir, Telbivudine, and Tenofovir Therapy for Chronic Hepatitis B^a (Continued)

FEATURE	PEG IFN ^b	LAMIVUDINE	ADEFOVIR	ENTECAVIR	TELBIVUDINE	TENOFOVIR
ALT normalization at end of yr 1						
HBeAg-reactive	39%	41–75%	48–61%	68%	77%	68%
HBeAg-negative	34–38%	62–79%	48–77%	78%	74%	76%
HBsAg loss yr 1	3–4%	≤1%	0%	2%	<1%	3%
>yr 1	12% 5 yr after 1 yr of Rx	No data	5% at yr 5	6% at yr 6	No data	8% at yr 5
Histologic improvement (≥2 point reduction in HAI) at yr 1						
HBeAg-reactive	38% 6 months after	49–62%	53–68%	72%	65%	74%
HBeAg-negative	48% 6 months after	61–66%	64%	70%	67%	72%
Viral resistance	None	15–30% @ 1 yr 70% @ 5 yrs	None @ 1 yr 29% @ 5 yrs	≤1% @ 1 yr ^e 1.2% @ 6 yrs ^e	Up to 5% @ yr 1 Up to 22% @ yr 2	0% @ yr 1 0% through yr 8

Pregnancy category	C	C ^f	C	C	B	B
Cost (US\$) for 1 yr	~\$18,000	~\$2500	~\$6500	~\$8700 ^g	~\$6000	~\$6000

^aGenerally, these comparisons are based on data on each drug tested individually versus placebo in registration clinical trials; because, with rare exception, these comparisons are not based on head-to-head testing of these drugs, relative advantages and disadvantages should be interpreted cautiously.

^bAlthough standard interferon α administered daily or three times a week is approved as therapy for chronic hepatitis B, it has been supplanted by PEG IFN, which is administered once a week and is more effective. Standard interferon has no advantages over PEG IFN.

^cDuration of therapy in clinical efficacy trials; use in clinical practice may vary.

^dBecause of a computer-generated randomization error that resulted in misallocation of drug versus placebo during the second year of clinical trial treatment, the frequency of HBeAg seroconversion beyond the first year is an estimate (Kaplan-Meier analysis) based on the small subset in whom adefovir was administered correctly.

^e7% during a year of therapy (43% at year 4) in lamivudine-resistant pts.

^fDespite its Class C designation, lamivudine has an extensive pregnancy safety record in women with HIV/AIDS.

^gApproximately \$17,400 for lamivudine-refractory pts.

Abbreviations: ALT, alanine aminotransferase; HAI, histologic activity index; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, not applicable; PEG IFN, pegylated interferon; PCR, polymerase chain reaction; Rx, therapy; yr, year.

TABLE 156-2 Recommendations for Treatment of Chronic Hepatitis B^a

HBeAg STATUS	CLINICAL	HBV DNA (IU/mL)	ALT	RECOMMENDATION
HBeAg-reactive	^b	$>2 \times 10^4$	$\leq 2 \times \text{ULN}^{\text{c,d}}$	No treatment; monitor. In pts >40 , with family history of hepatocellular carcinoma, and/or ALT persistently at the high end of the twofold range, liver biopsy may help in decision to treat
	Chronic hepatitis	$>2 \times 10^{4\text{d}}$	$>2 \times \text{ULN}^{\text{d}}$	Treat ^e
	Cirrhosis compensated	$>2 \times 10^3$	$< \text{or} > \text{ULN}$	Treat ^e with oral agents, not PEG IFN
	Cirrhosis decompensated	$<2 \times 10^3$	$>\text{ULN}$	Consider treatment ^f
		Detectable	$< \text{or} > \text{ULN}$	Treat ^e with oral agents ^g , not PEG IFN; refer for liver transplantation
	Undetectable	$< \text{or} > \text{ULN}$	Observe; refer for liver transplantation	
HBeAg-negative	^b	$\leq 2 \times 10^3$	$\leq \text{ULN}$	Inactive carrier; treatment not necessary
	Chronic hepatitis	$>10^3$	1 to $>2 \times \text{ULN}^{\text{d}}$	Consider liver biopsy; treat ^h if biopsy shows moderate to severe inflammation or fibrosis
	Chronic hepatitis	$>10^4$	$>2 \times \text{ULN}^{\text{d}}$	Treat ^{h,i}
	Cirrhosis compensated	$>2 \times 10^3$	$< \text{or} > \text{ULN}$	Treat ^e with oral agents, not PEG IFN
		$<2 \times 10^3$	$>\text{ULN}$	Consider treatment ^f
	Cirrhosis decompensated	Detectable	$< \text{or} > \text{ULN}$	Treat ^h with oral agents ^g , not PEG IFN; refer for liver transplantation
	Undetectable	$< \text{or} > \text{ULN}$	Observe; refer for liver transplantation	

^aBased on practice guidelines of the American Association for the Study of Liver Diseases (AASLD). Except as indicated in footnotes, these guidelines are similar to those issued by the European Association for the Study of the Liver (EASL).

^bLiver disease tends to be mild or inactive clinically; most such pts do not undergo liver biopsy.

^cThis pattern is common during early decades of life in Asian pts infected at birth.

^dAccording to the EASL guidelines, treat if HBV DNA is $>2 \times 10^3$ IU/mL and ALT $>$ ULN.

^eOne of the potent oral drugs with a high barrier to resistance (entecavir or tenofovir) or PEG IFN can be used as first-line therapy (see text). These oral agents, but not PEG IFN, should be used for interferon-refractory/intolerant and immunocompromised pts. PEG IFN is administered weekly by subcutaneous injection for a year; the oral agents are administered daily for at least a year and continued indefinitely or until at least 6 months after HBeAg seroconversion.

^fAccording to EASL guidelines, pts with compensated cirrhosis and detectable HBV DNA at any level, even with normal ALT, are candidates for therapy. Most authorities would treat indefinitely, even in HBeAg-positive disease after HBeAg seroconversion.

^gBecause the emergence of resistance can lead to loss of antiviral benefit and further deterioration in decompensated cirrhosis, a low-resistance regimen is recommended—entecavir or tenofovir monotherapy or combination therapy with the more resistance-prone lamivudine (or telbivudine) plus adefovir. Therapy should be instituted urgently.

^hBecause HBeAg seroconversion is not an option, the goal of therapy is to suppress HBV DNA and maintain a normal ALT. PEG IFN is administered by subcutaneous injection weekly for a year; caution is warranted in relying on a 6-month posttreatment interval to define a sustained response, because the majority of such responses are lost thereafter. Oral agents, entecavir or tenofovir, are administered daily, usually indefinitely or until, as very rarely occurs, virologic and biochemical responses are accompanied by HBsAg seroconversion.

ⁱFor older pts and those with advanced fibrosis, consider lowering the HBV DNA threshold to $>2 \times 10^3$ IU/mL.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PEG IFN, pegylated interferon; ULN, upper limit of normal.

chronic HCV have evolved rapidly such that current recommendations as established by leading expert panels should be reviewed prior to deciding on the most appropriate treatment regimen (www.hcvguidelines.org).

HEPATITIS A

Although hepatitis A rarely causes fulminant hepatic failure, it may do so more frequently in pts with chronic liver disease—especially those with chronic hepatitis B or C. The hepatitis A vaccine is immunogenic and well tolerated in pts with chronic hepatitis. Thus, pts with chronic liver disease, especially those with chronic hepatitis B or C, should be vaccinated against hepatitis A.

AUTOIMMUNE HEPATITIS

■ CLASSIFICATION

Type I: classic autoimmune hepatitis, anti-smooth-muscle and/or antinuclear antibodies (ANA). *Type II:* associated with anti-liver/kidney microsomal (anti-LKM) antibodies, which are directed against cytochrome P450 2D6 (seen primarily in southern Europe). *Type III* pts lack ANA and anti-LKM, have antibodies reactive with hepatocyte cytokeratins; clinically similar to type I. Criteria have been suggested by an international group for establishing a diagnosis of autoimmune hepatitis.

■ CLINICAL MANIFESTATIONS

Classic autoimmune hepatitis (type I): 80% women, third to fifth decades. Abrupt onset (acute hepatitis) in a third. Insidious onset in two-thirds; progressive jaundice, anorexia, hepatomegaly, abdominal pain, epistaxis, fever, fatigue, amenorrhea. Leads to cirrhosis; >50% 5-year mortality if untreated.

■ EXTRAHEPATIC MANIFESTATIONS

Rash, arthralgias, keratoconjunctivitis sicca, thyroiditis, hemolytic anemia, nephritis.

■ SEROLOGIC ABNORMALITIES

Hypergammaglobulinemia, positive rheumatoid factor, smooth-muscle antibody (40–80%), ANA (20–50%), antimitochondrial antibody (10–20%), false-positive anti-HCV enzyme immunoassay but usually not HCV RNA, atypical p-ANCA. Type II: anti-LKM antibody.

TREATMENT

Autoimmune Hepatitis

A treatment response occurs in 80% of pts, but may not prevent progression to cirrhosis. Foundation is prednisone or prednisolone 20–60 mg/d PO tapered to 10–20 mg/d over several weeks; often azathioprine 50 mg/d PO is also administered to permit lower glucocorticoid doses and avoid associated side effects. Symptoms may improve rapidly, but biochemical improvement may take weeks or months and subsequent histologic improvement (to lesion of mild chronic hepatitis or normal biopsy) up to 6–24 months. Therapy should be continued for 12–18 months. Relapse occurs in at least 50% of cases. The majority of pts require maintenance therapy with low-dose glucocorticoids or azathioprine 2 (mg/kg)/d. Other immunosuppressive agents have been used for medically refractory cases.

157

Cirrhosis and Alcoholic Liver Disease

**CIRRHOSIS**

Cirrhosis is defined histopathologically and has a variety of causes, clinical features, and complications. In cirrhosis, there is the development of liver fibrosis to the point that there is architectural distortion with the formation of regenerative nodules, which results in decreased liver function.

■ **CAUSES (SEE TABLE 157-1)**

■ **CLINICAL MANIFESTATIONS**

May be absent, with cirrhosis being incidentally found at surgery.

Symptoms

Anorexia, nausea, vomiting, diarrhea, vague RUQ pain, fatigue, weakness, fever, jaundice, amenorrhea, impotence, infertility.

Signs

Spider angiomas, palmar erythema, jaundice, scleral icterus, parotid and lacrimal gland enlargement, clubbing, Dupuytren's contracture, gynecomastia, testicular atrophy, hepatosplenomegaly, ascites, gastrointestinal bleeding (e.g., varices), hepatic encephalopathy.

Laboratory Findings

Anemia (microcytic due to blood loss, macrocytic due to folate deficiency; hemolytic called *Zieve's syndrome*), pancytopenia (hypersplenism), prolonged PT, rarely overt DIC; hyponatremia, hypokalemic alkalosis, glucose disturbances, hypoalbuminemia.

■ **DIAGNOSTIC STUDIES**

Depends on clinical setting. Serum: HBsAg, anti-HBc, anti-HBs, anti-HCV, anti-HDV, Fe, total iron-binding capacity, ferritin, antimitochondrial antibody (AMA), smooth-muscle antibody (SMA), anti-liver/kidney microsomal (anti-LKM) antibody, ANA, ceruloplasmin, α_1 -antitrypsin (and phenotyping); abdominal ultrasound with Doppler study, CT or MRI (may show cirrhotic liver, splenomegaly, collaterals, venous thrombosis). Definitive diagnosis often depends on liver biopsy (percutaneous, transjugular, or open).

TABLE 157-1 Causes of Cirrhosis

Alcoholism	Cardiac cirrhosis
Chronic viral hepatitis	Inherited metabolic liver disease
Hepatitis B	Hemochromatosis
Hepatitis C	Wilson's disease
Autoimmune hepatitis	α_1 -Antitrypsin deficiency
Nonalcoholic steatohepatitis	Cystic fibrosis
Biliary cirrhosis	Cryptogenic cirrhosis
Primary biliary cholangitis	
Primary sclerosing cholangitis	
Autoimmune cholangiopathy	

TABLE 157-2 Complications of Cirrhosis

Portal hypertension	Coagulopathy
Gastroesophageal varices	Factor deficiency
Portal hypertensive gastropathy	Fibrinolysis
Splenomegaly, hypersplenism	Thrombocytopenia
Ascites	Bone disease
Spontaneous bacterial peritonitis	Osteopenia
Hepatorenal syndrome	Osteoporosis
Type 1	Osteomalacia
Type 2	Hematologic abnormalities
Hepatic encephalopathy	Anemia
Hepatopulmonary syndrome	Hemolysis
Portopulmonary hypertension	Thrombocytopenia
Malnutrition	Neutropenia

■ COMPLICATIONS (SEE TABLE 157-2 AND CHAPS. 44, 45, AND 158)

The Child-Pugh scoring system has been used to predict the severity of cirrhosis and the risk of complications (Table 157-3).

■ ALCOHOLIC LIVER DISEASE

Excessive alcohol use can cause fatty liver, alcoholic hepatitis, cirrhosis. Alcoholic cirrhosis accounts for about 40% of the deaths due to cirrhosis. History of excessive alcohol use often denied. Severe forms (hepatitis, cirrhosis) associated with ingestion of 160 g/d for 10–20 years; women more susceptible than men and develop advanced liver disease with less alcohol intake. Hepatitis B and C may be cofactors in the development of liver disease. Malnutrition may contribute to development of cirrhosis.

TABLE 157-3 Child-Pugh Classification of Cirrhosis

FACTOR	POINTS TOWARD TOTAL SCORE			
	UNITS	1	2	3
Serum bilirubin	μmol/L	<34	34–51	>51
	mg/dL	<2.0	2.0–3.0	>3.0
Serum albumin	g/L	>35	30–35	<30
	g/dL	>3.5	3.0–3.5	<3.0
Prothrombin time	seconds prolonged	<4	4–6	>6
	INR ^a	<1.7	1.7–2.3	>2.3
Ascites		None	Easily controlled	Poorly controlled
Hepatic encephalopathy		None	Minimal	Advanced

^aInternational normalized ratio.

Note: The Child-Pugh score is calculated by adding the scores for the five factors and can range from 5 to 15. The resulting Child-Pugh class can be A (a score of 5–6), B (7–9), or C (≥10). Decompensation indicates cirrhosis, with a Child-Pugh score of ≥7 (class B). This level has been the accepted criterion for listing a pt for liver transplantation.

■ FATTY LIVER

Often presents as asymptomatic hepatomegaly and mild elevations in biochemical liver tests. Reverses on withdrawal of ethanol; does not lead to cirrhosis.

■ ALCOHOLIC HEPATITIS

Clinical presentation ranges from asymptomatic to severe liver failure with jaundice, ascites, GI bleeding, and encephalopathy. Typically anorexia, nausea, vomiting, fever, jaundice, tender hepatomegaly. Occasional cholestatic picture mimicking biliary obstruction. Aspartate aminotransferase (AST) usually <400 U/L and more than twofold higher than alanine aminotransferase (ALT). Bilirubin and WBC may be elevated. Diagnosis defined by liver biopsy findings: hepatocyte swelling, alcoholic hyaline (Mallory-Denk bodies), infiltration of PMNs, necrosis of hepatocytes, pericentral venular fibrosis.

■ OTHER METABOLIC CONSEQUENCES OF ALCOHOLISM

Increased NADH/NAD ratio leads to lactic acidemia, ketoacidosis, hyperuricemia, hypoglycemia, hypomagnesemia, hypophosphatemia. Also mitochondrial dysfunction, induction of microsomal enzymes resulting in altered drug metabolism, lipid peroxidation leading to membrane damage, hypermetabolic state; many features of alcoholic hepatitis are attributable to toxic effects of acetaldehyde and cytokines (interleukins 1 and 6, and TNF, released because of impaired detoxification of endotoxin).

■ ADVERSE PROGNOSTIC FACTORS

Critically ill pts with alcoholic hepatitis have 30-day mortality rates $>50\%$. Severe alcoholic hepatitis characterized by PT $>5 \times$ above control, bilirubin >137 $\mu\text{mol/L}$ (>8 mg/dL), hypoalbuminemia, azotemia. A discriminant function can be calculated as $4.6 \times (\text{pt's PT in seconds}) / (\text{control PT in seconds}) + \text{serum bilirubin (mg/dL)}$. Values ≥ 32 are associated with poor prognosis. A Model for End-Stage Liver Disease (MELD) score > 21 is also associated with significant mortality in alcoholic hepatitis. Ascites, variceal hemorrhage, encephalopathy, hepatorenal syndrome predict a poor prognosis.

TREATMENT**Alcoholic Liver Disease**

Abstinence is essential; 8500- to 12,500-kJ (2000- to 3000-kcal) diet with 1 g/kg protein (less if encephalopathy). Daily multivitamin, thiamine 100 mg, folic acid 1 mg. Correct potassium, magnesium, and phosphate deficiencies. Transfusions of packed red cells, plasma as necessary. Monitor glucose (hypoglycemia in severe liver disease). Pts with severe alcoholic hepatitis defined as a discriminant function >32 or MELD >20 should be given prednisone 40 mg/d or prednisolone 32 mg/d PO for 4 weeks followed by a taper. In one trial pentoxifylline demonstrated improved survival, primarily due to a decrease in hepatorenal syndrome but subsequent trials failed to find increased benefit with use of this agent. Liver transplantation may be an option in carefully selected pts with end-stage cirrhosis.

PRIMARY BILIARY CIRRHOSIS (PBC)

PBC is a progressive nonsuppurative destructive intrahepatic cholangitis. Strong female predominance, median age of 50 years. Presents as asymptomatic elevation in alkaline phosphatase (better prognosis) or with pruritus, progressive jaundice, consequences of impaired bile excretion, and ultimately cirrhosis and liver failure.

TABLE 157-4 Indications for Liver Transplantation

CHILDREN	ADULTS
Biliary atresia	Primary biliary cirrhosis
Neonatal hepatitis	Secondary biliary cirrhosis
Congenital hepatic fibrosis	Primary sclerosing cholangitis
Alagille's syndrome ^a	Autoimmune hepatitis
Byler's disease ^b	Caroli's disease ^c
α_1 -Antitrypsin deficiency	Cryptogenic cirrhosis
Inherited disorders of metabolism	Chronic hepatitis with cirrhosis
Wilson's disease	Hepatic vein thrombosis
Tyrosinemia	Fulminant hepatitis
Glycogen storage diseases	Alcoholic cirrhosis
Lysosomal storage diseases	Chronic viral hepatitis
Protoporphyrin	Primary hepatocellular malignancies
Crigler-Najjar disease type I	Hepatic adenomas
Familial hypercholesterolemia	Nonalcoholic steatohepatitis
Primary hyperoxaluria type I	Familial amyloid polyneuropathy
Hemophilia	

^aArteriohepatic dysplasia, with paucity of bile ducts, and congenital malformations, including pulmonary stenosis.

^bIntrahepatic cholestasis, progressive liver failure, and mental and growth retardation.

^cMultiple cystic dilatations of the intrahepatic biliary tree.

■ CLINICAL MANIFESTATIONS

Pruritus, fatigue, jaundice, xanthelasma, xanthomata, osteoporosis, steatorrhea, skin pigmentation, hepatosplenomegaly, portal hypertension; elevations in serum alkaline phosphatase, bilirubin, cholesterol, and IgM levels.

■ ASSOCIATED DISEASES

Sjögren's syndrome, collagen vascular diseases, thyroiditis, glomerulonephritis, pernicious anemia, renal tubular acidosis.

■ DIAGNOSIS

AMA in 90% (directed against enzymes of the pyruvate dehydrogenase complex and other 2-oxo-acid dehydrogenase mitochondrial enzymes). Liver biopsy most important in AMA-negative PBC. Biopsies identify four stages: stage 1—destruction of interlobular bile ducts, granulomas; stage 2—ductular proliferation; stage 3—fibrosis; stage 4—cirrhosis.

■ PROGNOSIS

Correlates with age, serum bilirubin, serum albumin, prothrombin time, edema.

TREATMENT

Primary Biliary Cirrhosis

Ursodeoxycholic acid 13–15 mg/kg per day has been shown to improve the biochemical and histologic features of disease. Response is greatest when given early. Cholestyramine with meals for pruritus; in refractory cases consider rifampin, naltrexone, plasmapheresis. Calcium, vitamin D, and bisphosphonates are given for osteoporosis. Liver transplantation for end-stage disease.

TABLE 157-5 Contraindications to Liver Transplantation

ABSOLUTE	RELATIVE
Uncontrolled extrahepatobiliary infection	Age >70
Active, untreated sepsis	Prior extensive hepatobiliary surgery
Uncorrectable, life-limiting congenital anomalies	Portal vein thrombosis
Active substance or alcohol abuse	Renal failure not attributable to liver disease
Advanced cardiopulmonary disease	Previous extrahepatic malignancy (not including nonmelanoma skin cancer)
Extrahepatobiliary malignancy (not including nonmelanoma malignancy skin cancer)	Severe obesity
Metastatic malignancy to the liver	Severe malnutrition/wasting
Cholangiocarcinoma	Medical noncompliance
AIDS	HIV seropositivity with failure to control HIV viremia or CD4 <100/ μ L
Life-threatening systemic diseases	Intrahepatic sepsis Severe hypoxemia secondary to right-to-left intrapulmonary shunts (PO_2 <50 mmHg) Severe pulmonary hypertension (mean pulmonary artery pressure >35 mmHg) Uncontrolled psychiatric disorder

LIVER TRANSPLANTATION

Consider in the absence of contraindications for chronic, irreversible, progressive liver disease or fulminant hepatic failure when no alternative therapy is available (Table 157-4).

■ CONTRAINDICATIONS (SEE TABLE 157-5)

■ SELECTION OF DONOR

Matched for ABO blood group compatibility and liver size (reduced-size grafts may be used, esp. in children). Should be negative for HIV, HBV, and HCV. Living-donor transplant has gained increased popularity with transplantation of the right hepatic lobe from a healthy adult donor to an adult. Living-donor transplant of the left lobe accounts for one-third of all liver transplants in children.

■ IMMUNOSUPPRESSION

Various combinations of tacrolimus or cyclosporine and glucocorticoids, sirolimus, everolimus, mycophenolate mofetil, or OKT3 (monoclonal antithymocyte globulin).

■ MEDICAL COMPLICATIONS AFTER TRANSPLANTATION

Liver graft dysfunction (primary nonfunction, acute or chronic rejection, ischemia, hepatic artery thrombosis, biliary obstruction or leak, recurrence of primary disease); infections (bacterial, viral, fungal, opportunistic); renal dysfunction; neuropsychiatric disorders, cardiovascular instability, pulmonary compromise.

■ SUCCESS RATE

Currently, 5-year survival rates exceed 60%; less for certain conditions (e.g., chronic hepatitis B, hepatocellular carcinoma).

158 Portal Hypertension



Portal hypertension is defined as elevation of the hepatic venous pressure gradient to >5 mmHg, which occurs as a consequence of cirrhosis ([Chap. 157](#)). It is caused by increased intrahepatic resistance to the passage of blood flow through the liver due to cirrhosis together with increased splanchnic blood flow due to vasodilatation within the splanchnic vascular bed.

■ CLASSIFICATION (SEE [TABLE 158-1](#))

■ CONSEQUENCES

The primary complications of portal hypertension are gastroesophageal varices with hemorrhage, ascites ([Chap. 45](#)), hypersplenism, hepatic encephalopathy, spontaneous bacterial peritonitis ([Chap. 45](#)), hepatorenal syndrome ([Chap. 45](#)), hepatocellular carcinoma ([Chap. 72](#)).

ESOPHAGOGASTRIC VARICES

About one-third of pts with cirrhosis have varices, and one-third of pts with varices will develop bleeding. Bleeding is a life-threatening complication; risk of bleeding correlates with variceal size and location, the degree of portal hypertension (portal venous pressure >12 mmHg), and the severity of cirrhosis, e.g., Child-Pugh classification (see [Table 157-3](#)).

TABLE 158-1 Classification of Portal Hypertension

Prehepatic

- Portal vein thrombosis
- Splenic vein thrombosis
- Massive splenomegaly (Banti's syndrome)

Hepatic

Presinusoidal

- Schistosomiasis
- Congenital hepatic fibrosis

Sinusoidal

- Cirrhosis—many causes
- Alcoholic hepatitis

Postsinusoidal

- Hepatic sinusoidal obstruction (venoocclusive syndrome)

Posthepatic

- Budd-Chiari syndrome
- Inferior vena caval webs
- Cardiac causes
 - Restrictive cardiomyopathy
 - Constrictive pericarditis
 - Severe congestive heart failure

■ DIAGNOSIS

Esophagogastrosocopy: procedure of choice for evaluation of upper GI hemorrhage in pts with known or suspected portal hypertension. *Celiac* and *mesenteric arteriography* are alternatives when massive bleeding prevents endoscopy and to evaluate portal vein patency (portal vein may also be studied by ultrasound with Doppler and MRI).

TREATMENT

Esophagogastric Varices

See **Chap. 43** for general measures to treat GI bleeding.

CONTROL OF ACUTE BLEEDING

Choice of approach depends on clinical setting and availability.

1. Endoscopic intervention is employed as first-line treatment to control bleeding acutely. Endoscopic variceal ligation (EVL) is used to control acute bleeding in >90% of cases. EVL is less successful when varices extend into proximal stomach. Some endoscopists will use variceal injection (sclerotherapy) as initial therapy, particularly when bleeding is vigorous.
2. *Vasoconstricting agents*: somatostatin or octreotide (50–100 µg/h by continuous infusion).
3. Balloon tamponade (Sengstaken-Blakemore- or Minnesota tube). Can be used when endoscopic therapy is not immediately available or in pts who need stabilization prior to endoscopic therapy. Complications—obstruction of pharynx, asphyxiation, aspiration, esophageal ulceration. Generally reserved for massive bleeding, failure of vasopressin and/or endoscopic therapy.
4. Transjugular intrahepatic portosystemic shunt (TIPS)—portacaval shunt placed by interventional radiologic technique, reserved for failure of other approaches; risk of hepatic encephalopathy (20–30%), shunt stenosis or occlusion, infection.

PREVENTION OF RECURRENT BLEEDING

1. EVL should be repeated until obliteration of all varices is accomplished.
2. Propranolol or nadolol—nonselective beta blockers that act as portal venous antihypertensives; may decrease the risk of variceal hemorrhage and mortality due to hemorrhage.
3. TIPS—regarded as useful “bridge” to liver transplantation in pt who has failed pharmacologic therapy and is awaiting a donor liver.
4. Portosystemic shunt surgery used less commonly with the advent of TIPS; could be considered for pts with good hepatic synthetic function.

PREVENTION OF INITIAL BLEED

For pts at high risk of variceal bleeding, consider prophylaxis with EVL and/or nonselective beta blockers.

HEPATIC ENCEPHALOPATHY

An alteration in mental status and cognitive function occurring in the presence of liver failure; may be acute and reversible or chronic and progressive.

■ CLINICAL FEATURES

Confusion, slurred speech, change in personality that can include being violent and hard to manage, being sleepy and difficult to arouse, asterixis (flapping tremor). Can progress to coma; initially responsive to noxious stimuli, later unresponsive.

■ PATHOPHYSIOLOGY

Gut-derived neurotoxins that are not removed by the liver because of vascular shunting and decreased hepatic mass reach the brain and cause the symptoms of hepatic encephalopathy. Ammonia levels are typically elevated in encephalopathy, but the correlation between the severity of liver disease and height of ammonia levels is often poor. Other compounds that may contribute include false neurotransmitters and mercaptans.

■ PRECIPITANTS

GI bleeding, azotemia, constipation, high-protein meal, hypokalemic alkalosis, CNS depressant drugs (e.g., benzodiazepines and barbiturates), hypoxia, hypercarbia, sepsis.

TREATMENT**Hepatic Encephalopathy**

Remove precipitants; correct electrolyte imbalances. Lactulose (nonabsorbable disaccharide) results in colonic acidification and diarrhea and is the mainstay of treatment; goal is to produce 2–3 soft stools per day. Poorly absorbed antibiotics are often used in pts who do not tolerate lactulose, with alternating administration of neomycin and metronidazole being used to reduce the individual side effects of each. Rifaximin has recently also been used; zinc supplementation is sometimes helpful. Liver transplantation when otherwise indicated.

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Diseases of Immediate-Type
Hypersensitivity

■ DEFINITION

These diseases result from IgE-dependent release of mediators from sensitized basophils and mast cells upon contact with an offending antigen (allergen). Associated disorders include anaphylaxis (Chap. 28), allergic rhinitis, urticaria, asthma, and eczematous (atopic) dermatitis.

■ PATHOPHYSIOLOGY

IgE binds to the surface of mast cells and basophils through a high-affinity receptor. Cross-linking of this IgE by antigen causes cellular activation with subsequent release of preformed and newly synthesized mediators (Fig. 159-1). These mediators have been implicated in many pathophysiologic events associated with immediate-type hypersensitivity, such as vasodilation, increased vasopermeability, smooth-muscle contraction, and chemotaxis of neutrophils and other inflammatory cells. The clinical manifestations of each allergic reaction depend largely on the anatomic site(s) and time course of mediator release.

URTIARIA AND ANGIOEDEMA

■ DEFINITION

May occur together or separately. *Urticaria* involves only the superficial dermis and presents as pruritic, circumscribed wheals with raised serpiginous borders and blanched centers. *Angioedema* involves deeper layers of skin and may include subcutaneous tissue; it is marked by dramatic swelling with more pain than pruritus. Recurrent episodes of urticaria and/or angioedema of <6 weeks duration are considered acute, whereas attacks persisting beyond this period are chronic.

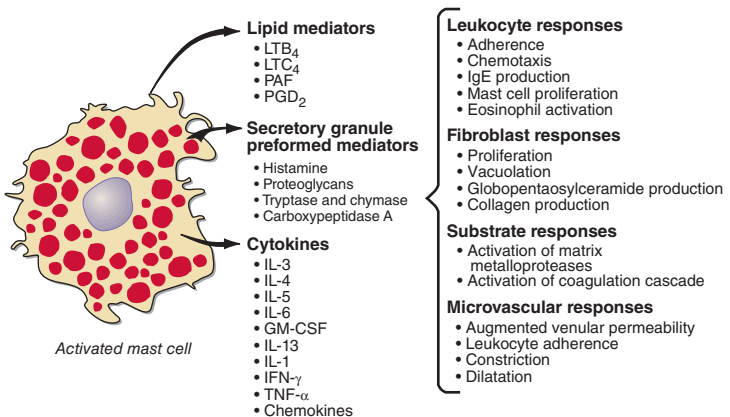


FIGURE 159-1 Bioactive mediators of three categories generated by IgE-dependent activation of murine mast cells can elicit common but sequential target cell effects leading to acute and sustained inflammatory responses. GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LT, leukotriene; PAF, platelet-activating factor; PGD₂, prostaglandin D₂; TNF, tumor necrosis factor.

■ CLASSIFICATION, ETIOLOGY, AND PATHOPHYSIOLOGY

The classification of urticaria-angioedema focuses on mechanisms that elicit clinical disease and can be useful for differential diagnosis (Table 159-1). Acute urticaria is most often the result of exposure to a food, environmental or drug allergen or viral infection. Chronic urticaria is often idiopathic with additional etiologies including physical stimuli. Up to 45% of pts with chronic urticaria have an autoimmune cause including autoantibodies to IgE or to the α chain of Fc ϵ RI. *Hereditary angioedema* (HAE) is a fully penetrant, autosomal dominant disease due to a mutation in the SERPING1 gene leading to a deficiency of C1 inhibitor (C1INH) (type 1—85% of pts) or to a dysfunctional protein (type 2).

■ DIAGNOSIS

History, with special attention to possible offending exposures and/or ingestion as well as the duration of lesions. Urticarial eruptions appear in crops of 12- to 36-h duration, with old lesions fading as new ones appear. In physical urticarias, individual lesions usually last <2 h. Lesions that last >36 h, result in scarring, and are painful rather than pruritic warrant skin biopsy for urticarial vasculitis. The most common sites for angioedema are periorbital and perioral; upper respiratory tract angioedema may be life-threatening. HAE is suggested by family history, lack of pruritus or urticarial lesions, GI involvement with attacks of colic, and episodes of laryngeal edema.

- Skin testing to food and/or inhalant antigens
- Direct reproduction of the lesion in physical urticaria
- Laboratory examination: CBC with differential (eosinophilia), TSH, erythrocyte sedimentation rate (ESR) are recommended. C1INH and complement

TABLE 159-1 Classification of Urticaria and/or Angioedema

ACUTE	CHRONIC
Drug reactions	Idiopathic—a subset with autoimmune component
NSAIDs, IV contrast, angiotensin-converting enzyme (ACE) inhibitors, etc.	Collagen vascular disease—urticarial vasculitis
Foods	Physical stimuli
Inhalation or contact with environmental allergens	Dermatographism
Transfusion reactions	Cholinergic urticaria
Insects	Vibration, cold, pressure, water (aquagenic)
Infections—viral, bacterial, parasitic	Sun (solar)
	Mastocytosis/urticaria pigmentosa
	Hereditary
	Hereditary angioedema (HAE)
	Familial cold urticaria
	C3b inhibitor deficiency
	Muckle-Wells syndrome
	Schnitzler syndrome
	Hypereosinophilic syndrome
	Gleich syndrome

levels if HAE is suggested. Expanded testing should be guided by history: assay for serum allergen-specific IgE, mast cell studies, cryoglobulins, hepatitis testing, autoantibody screen.

- Skin biopsy may be necessary.

■ DIFFERENTIAL DIAGNOSIS

Atopic dermatitis, contact sensitivity, cutaneous mastocytosis (urticaria pigmentosa), systemic mastocytosis.

■ PREVENTION

Identification and avoidance of offending agent(s), if possible.

TREATMENT

Urticaria and Angioedema

- H₁ antihistamines: e.g., chlorpheniramine, diphenhydramine; or the low or nonsedating agents, e.g., loratadine, desloratadine, fexofenadine, cetirizine, levocetirizine.
- H₂ antihistamines: e.g., ranitidine, famotidine, cimetidine.
- Older agents with antihistamine properties: doxepin, cyproheptadine, hydroxyzine when H₁ agents are inadequate.
- CysLT₁ receptor antagonists can be add-on therapy: e.g., montelukast 10 mg daily or zafirlukast 20 mg bid.
- Monoclonal anti-IgE antibodies (Omalizumab): for chronic urticaria that has failed long-acting H₁ antihistamines QID and a CysLT₁ receptor antagonist.
- Topical glucocorticoids are of no value in the management of urticaria and/or angioedema.
- Systemic glucocorticoids should not be used in the treatment of idiopathic, allergen-induced, or physical urticaria because of their long-term toxicity. Can be considered with urticarial vasculitis, idiopathic angioedema with or without urticaria, or unresponsive debilitating chronic urticaria.
- Infusion of isolated or recombinant C1INH protein is approved for prophylaxis of and acute attacks of HAE; a bradykinin 2 receptor antagonist (Icatibant) or a kallikrein inhibitor (Ecallantide) may be used for acute HAE.

ALLERGIC RHINITIS

■ DEFINITION

Characterized by sneezing; rhinorrhea; obstruction of the nasal passages; conjunctival, nasal, and pharyngeal itching; and lacrimation, all occurring in a temporal relationship to allergen exposure. Prevalence in North America is 10–20% with a peak prevalence >30% occurring in the fifth decade. Commonly seasonal due to triggering by airborne pollens; can be perennial in response to allergens present throughout the year such as house dust mites and animal danders.

■ PATHOPHYSIOLOGY

Deposition of pollens and other allergens on nasal mucosa of sensitized individuals results in IgE-dependent triggering of mast cells with subsequent release of mediators that cause development of mucosal hyperemia, swelling, and fluid transudation.

■ DIAGNOSIS

Accurate history of symptoms correlated with time of seasonal pollination of plants in a given locale; special attention must be paid to other potentially sensitizing antigens.

- Physical examination: nasal mucosa may be boggy or erythematous; nasal polyps may be present; conjunctivae may be inflamed or edematous; manifestations of other allergic conditions (e.g., asthma, eczema) may be present.
- Skin tests to inhalant and/or food antigens.
- Nasal smear may reveal large numbers of eosinophils.
- Total and specific serum IgE (as assessed by immunoassay) may be elevated.

■ DIFFERENTIAL DIAGNOSIS

Vasomotor rhinitis, upper respiratory infection (URI), irritant exposure, pregnancy with nasal mucosal edema, rhinitis medicamentosa, nonallergic rhinitis with eosinophilia, rhinitis due to α -adrenergic agents.

■ PREVENTION

Identification and avoidance of offending antigen(s).

TREATMENT**Allergic Rhinitis**

- Older antihistamines (e.g., chlorpheniramine, diphenhydramine) are effective but cause sedation and psychomotor impairment including reduced hand-eye coordination and impaired automobile driving skills. Newer antihistamines (e.g., fexofenadine, loratadine, desloratadine, cetirizine, levocetirizine, olopatadine, bilastine, and azelastine) are equally effective but are less sedating and more H₁ specific.
- Oral sympathomimetics, e.g., pseudoephedrine; may aggravate hypertension; combination antihistamine/decongestant preparations may balance side effects.
- Topical vasoconstrictors—should be used sparingly due to rebound congestion and chronic rhinitis associated with prolonged use.
- Topical nasal glucocorticoids—all achieve up to 70% overall symptom relief.
- Topical nasal cromolyn sodium, one to two sprays in each nostril qid.
- Other topical agents, e.g., azelastine, ipratropium
- Montelukast is approved for seasonal and perennial rhinitis.
- Hyposensitization therapy, if more conservative therapy is unsuccessful.

SYSTEMIC MASTOCYTOSIS**■ DEFINITION**

A systemic disorder defined by a clonal expansion of mast cells that in most instances is indolent and nonmalignant. Generally involves bone marrow, skin, gastrointestinal (GI) mucosa, liver, and spleen. Classified as cutaneous mastocytosis with variants, five systemic forms (indolent, smoldering, associated with concomitant hematologic non-mast cell lineage disease, aggressive, mast cell leukemia), and rare mast cell sarcoma.

TABLE 159-2 Diagnostic Criteria for Systemic Mastocytosis^a**Major:**

Multifocal dense infiltrates of mast cells (>15 mast cells per aggregate) in bone marrow or other extracutaneous tissues

Minor:

Abnormal mast cell morphology (spindle shape, bi- or multi-lobed or eccentric nucleus, hypogranulated cytoplasm)

Aberrant mast cell surface phenotype with expression of CD25 (IL-2 receptor alpha chain) and/or CD2

Detection of codon 816 mutation in peripheral blood cells, bone marrow cells, or an extracutaneous lesional tissue

Total serum tryptase >20 ng/mL

^aDiagnosis requires either the major criterion and one minor criterion or three minor criteria.

■ PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

The clinical manifestations of systemic mastocytosis are due to tissue occupancy by the mast cell mass, the tissue response to that mass (fibrosis), and the release of bioactive substances acting both locally (urticaria pigmentosa, crampy abdominal pain, gastritis, peptic ulcer) and at distal sites (headache, pruritus, flushing, vascular collapse). Clinical manifestations may be aggravated by alcohol, temperature changes, stress, narcotics, and NSAIDs.

■ DIAGNOSIS

Although the diagnosis of mastocytosis may be suspected on the basis of clinical and laboratory findings, it can be established only by tissue biopsy (usually bone marrow biopsy). The diagnostic criteria for systemic mastocytosis are shown in [Table 159-2](#). Serum tryptase level is elevated in >50%. Other studies are directed by organ-specific presentations. Other flushing disorders (e.g., carcinoid syndrome, pheochromocytoma) should be excluded.

TREATMENT**Systemic Mastocytosis**

- H₁ and H₂ antihistamines.
- Proton pump inhibitors for gastric hypersecretion.
- Oral cromolyn sodium for diarrhea and abdominal pain.
- Aspirin for severe flushing to block PGD₂.
- Systemic glucocorticoids may help malabsorption, but have frequent complications.
- Mast cell cytoreductive therapy with midostaurin, IFN- α , or cladribine is generally reserved for advanced, nonindolent variants.
- Chemotherapy for frank leukemias.
- Stem cell transplantation can be effective in a small subset of pts with advanced mastocytosis.

160

Primary Immune Deficiency Diseases

**DEFINITION**

Primary immunodeficiencies are genetic diseases that can involve all possible aspects of immune responses, from innate through adaptive, as well as cell differentiation, effector function, and immune regulation (Table 160-1). The consequences of primary immunodeficiencies vary widely as a function of the molecules that are defective and include vulnerability to infection by pathogenic and opportunistic infection, immunopathologic responses such as allergy, lymphoproliferations, and autoimmunity, and increased risk of cancers. The locations and sites of infection and the causal microorganisms often aid the physician in diagnosis.

DIAGNOSIS (SEE TABLE 160-2)**CLASSIFICATION (TABLE 160-1)****■ DEFICIENCIES OF THE INNATE IMMUNE SYSTEM**

Account for ~10% of all primary immunodeficiencies (Table 160-1).

■ DEFICIENCIES OF THE ADAPTIVE IMMUNE SYSTEM**T-Lymphocyte Deficiency Syndromes****SEVERE COMBINED IMMUNODEFICIENCY (SCID)**

Group of rare primary immunodeficiencies characterized by a profound block in T-cell development as a consequence of an intrinsic deficiency. Clinical consequences occur within 3–6 months following birth. The most frequent clinical manifestations are recurrent oral candidiasis, failure to thrive, protracted diarrhea, *Pneumocystis jirovecii* infections. Five distinct causative mechanisms have been identified:

- *Cytokine signaling deficiency*: Most frequent SCID accounting for 40–50% of cases with the absence of T and NK cells. These pts have a deficiency in the gamma chain receptor shared by several cytokine receptors (interleukins 2, 4, 7, 9, 15, 21). The same phenotype seen in X-linked SCID can be inherited as an autosomal recessive disease due to mutations in the JAK3 protein kinase gene.
- *Purine metabolism deficiency*: About 20% of SCID pts are deficient in adenosine deaminase (ADA) due to mutations in the ADA gene.
- *Defective rearrangements of T- and B-cell receptors*: Account for ~20–30% of SCID cases. Main deficiencies involve recombinase activating genes (RAG-1, RAG-2) DNA-dependent protein kinase, DNA ligase 4, and Cernunnos deficiencies.
- *Defective (pre-) T-cell receptor signaling in the thymus*: Rare deficiencies in CD3 subunits associated with the (pre) TCR and CD45.
- *Reticular dysgenesis*: Extremely rare. Results from adenylate kinase 2 deficiency.

TREATMENT**Severe Combined Immunodeficiency**

Curative treatment relies on hematopoietic stem cell transplant (HSCT).

TABLE 160-1 Classification of Primary Immune Deficiency Diseases**Deficiencies of the innate immune system**

- Phagocytic cells:
 - Impaired production: severe congenital neutropenia (SCN)
 - Asplenia
 - Impaired adhesion: leukocyte adhesion deficiency (LAD)
 - Impaired killing: chronic granulomatous disease (CGD)
- Innate immunity receptors and signal transduction:
 - Defects in Toll-like receptor signaling
 - Mendelian susceptibility to mycobacterial disease
- Complement deficiencies:
 - Classical, alternative, and lectin pathways
 - Lytic phase

Deficiencies of the adaptive immune system

- | | |
|--|---|
| <ul style="list-style-type: none"> • T lymphocytes: <ul style="list-style-type: none"> – Impaired development – Impaired survival, migration, function | Severe combined immune deficiencies (SCIDs)
DiGeorge's syndrome
Combined immunodeficiencies
Hyper-IgE syndrome (autosomal dominant)
DOCK8 deficiency
CD40 ligand deficiency
Wiskott-Aldrich syndrome
Ataxia-telangiectasia and other DNA repair deficiencies |
| <ul style="list-style-type: none"> • B lymphocytes: <ul style="list-style-type: none"> – Impaired development – Impaired function | XL and AR agammaglobulinemia
Hyper-IgM syndrome
Common variable immunodeficiency (CVID)
IgA deficiency |

Regulatory defects

- | | |
|---|--|
| <ul style="list-style-type: none"> • Innate immunity | Autoinflammatory syndromes (outside the scope of this chapter)
Severe colitis
Hemophagocytic lymphohistiocytosis (HLH) |
| <ul style="list-style-type: none"> • Adaptive immunity | Autoimmune lymphoproliferation syndrome (ALPS)
Autoimmunity and inflammatory diseases (IPEX, APECED) |

Abbreviations: APECED, autoimmune polyendocrinopathy candidiasis ectodermal dysplasia; AR, autosomal recessive; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; XL, X-linked.

TABLE 160-2 Tests Most Frequently Used to Diagnose a Primary Immune Deficiency (PID)

TEST	INFORMATION	PID DISEASE
<ul style="list-style-type: none"> Blood cell counts and cell morphology 	Neutrophil counts ^a Lymphocyte counts ^a Eosinophilia Howell-Jolly bodies	↓ Severe congenital neutropenia, ↑↑ LAD T cell ID WAS, hyper-IgE syndrome Asplenia
<ul style="list-style-type: none"> Chest x-ray 	Thymic shadow Costochondral junctions	SCID, DiGeorge's syndrome Adenosine deaminase deficiency
<ul style="list-style-type: none"> Bone x-ray 	Metaphyseal ends	Cartilage hair hypoplasia
<ul style="list-style-type: none"> Immunoglobulin serum levels 	IgG, IgA, IgM IgE	B cell ID Hyper-IgE syndrome, WAS, T cell ID
<ul style="list-style-type: none"> Lymphocyte phenotype 	T, B lymphocyte counts	T cell ID, agammaglobulinemia
<ul style="list-style-type: none"> Dihydrorhodamine fluorescence (DHR) assay Nitroblue tetrazolium (NBT) assay 	Reactive oxygen species production by PMNs	Chronic granulomatous disease
<ul style="list-style-type: none"> CH50, AP50 	Classic and alternative complement pathways	Complement deficiencies
<ul style="list-style-type: none"> Ultrasonography of the abdomen 	Spleen size	Asplenia

^aNormal counts vary with age. For example, the lymphocyte count is between 3000 and 9000/μL of blood below the age of 3 months and between 1500 and 2500/μL in adults.

Abbreviations: ID, immunodeficiency; LAD, leukocyte adhesion deficiency; PMNs, polymorphonuclear leukocytes; SCID, severe combined immunodeficiency; WAS, Wiskott-Aldrich syndrome.

Other T Cell–Related Primary Immunodeficiencies

- *DiGeorge syndrome*: Maldevelopment of the thymus
- *Hyper-IgE syndrome*
- *CD40 ligand deficiency*
- *Wiskott-Aldrich syndrome*
- *Ataxia-telangiectasia and other DNA repair deficiencies*

TREATMENT

Other T Cell–Related Primary Immunodeficiencies

Treatment is complex and largely investigational. HSCT plays a role in some diseases. Live vaccines and blood transfusions containing viable T cells should be strictly avoided. Prophylaxis for *P. jirovecii* pneumonia should be considered in selected pts with severe T-cell deficiency.

B-Lymphocyte Deficiency Syndromes

Deficiencies that affect B cells are the most common primary immunodeficiencies and account for ~60–70% of all cases. Defective antibody production predisposes

to invasive pyogenic bacterial infections as well as recurrent sinus and pulmonary infections. Complete lack of antibody production (agammaglobulinemia) predisposes to disseminated enteroviral infections causing meningoencephalitis, hepatitis, and a dermatomyositis-like disease. Diagnosis relies on the determination of serum Ig level.

- *Agammaglobulinemia*: Due to an X-linked mutation in the Bruton's tyrosine kinase (Btk) gene in 85% of cases.
- *Hyper IgM*: In most pts this syndrome results from an X-linked defect in the gene encoding CD40 ligand. Pts exhibit normal or increased serum IgM with low or absent IgG and IgA.
- *Common variable immunodeficiency (CVID)*: Heterogeneous group of syndromes characterized by low serum levels of one or more Ig isotypes. Prevalence estimated to be 1 in 20,000. Besides infections, pts may develop lymphoproliferation, granulomatous lesions, colitis, antibody-mediated autoimmune diseases, and lymphomas.
- *Isolated IgA deficiency*: Most common immunodeficiency; affects 1 in 600 people. The majority of affected individuals do not have increased infections; antibodies against IgA may lead to anaphylaxis during transfusion of blood or plasma; may progress to CVID.
- *Selective antibody deficiency to polysaccharide antigens*.

TREATMENT

B Cell/Immunoglobulin Deficiency Syndromes

Immunoglobulin replacement should be guided by the occurrence of infections in pts who are deficient in IgG.

- Can be performed by IV or subcutaneous routes. IV immunoglobulin is repeated every 3–4 weeks, with a residual target level of 800 mg/mL. Subcutaneous injections are typically performed once a week, although the frequency can be adjusted on a case-by-case basis; a trough level of 800 mg/dL is desirable.

REGULATORY DEFECTS

Rare but increasingly described primary immunodeficiencies that cause homeostatic dysregulation of the immune system either alone or in association with increased vulnerability to infection (Table 160-1).

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Systemic Lupus Erythematosus



DEFINITION AND PATHOGENESIS

Disease of unknown etiology in which tissues and cells undergo damage mediated by tissue-binding autoantibodies and immune complexes. Genetic, environmental, and sex hormonal factors are likely of pathogenic importance. T- and B-cell hyperactivity, production of autoantibodies with specificity for nuclear antigenic determinants, and abnormalities of T-cell function occur.

■ CLINICAL MANIFESTATIONS

Approximately 90% of pts are women, usually of child-bearing age; highest prevalence is in African-American and Afro-Caribbean women. Course of disease is often characterized by periods of exacerbation and relative quiescence. May involve virtually any organ system and have a wide range of disease severity. Common features include:

- *Constitutional*: fatigue, fever, malaise, weight loss
- *Cutaneous*: rashes (especially malar “butterfly” rash), photosensitivity, vasculitis, alopecia, oral ulcers
- *Arthritis*: inflammatory, symmetric, nonerosive
- *Hematologic*: anemia (may be hemolytic), neutropenia, thrombocytopenia, lymphadenopathy, splenomegaly, venous or arterial thrombosis
- *Cardiopulmonary*: pleuritis, pericarditis, myocarditis, endocarditis. Pts are also at increased risk of myocardial infarction usually due to accelerated atherosclerosis.
- *Nephritis*: classification is primarily histologic (Table 349-2, p. 2518, in HPIM-20).
- *GI*: peritonitis, vasculitis
- *Neurologic*: organic brain syndromes, seizures, psychosis, cerebritis

Drug-Induced Lupus

A clinical and immunologic picture similar to spontaneous SLE may be induced by drugs; in particular: procainamide, hydralazine, isoniazid, chlorpromazine, methyldopa, minocycline, TNF inhibitors. Features are predominantly constitutional, joint, and pleuropericardial; CNS and renal disease are rare. All pts have ANAs; antihistone antibodies may be present, but antibodies to dsDNA and hypocomplementemia are uncommon. Most pts improve following withdrawal of offending drug.

■ EVALUATION

- History and physical examination
- ANA present in >98% of pts, but a (+) ANA is not specific for SLE. Laboratory assessment should include: CBC, ESR, ANA and ANA subtypes (antibodies to dsDNA, ssDNA, Sm, anti-Ro/SS-A, anti-La/SS-B, histone), complement levels (C3, C4, CH50), serum immunoglobulins, VDRL, PT, PTT, anticardiolipin antibody, lupus anticoagulant, urinalysis.
- Appropriate radiographic studies
- ECG
- Consideration of renal biopsy if evidence of glomerulonephritis

■ DIAGNOSIS

Classification criteria used to confirm SLE in studies can provide a basis in individual pts for estimating the probability that a disease is SLE. Four or more published criteria carry a 93% specificity and 92% sensitivity for SLE (Table 349-3, p. 2518, in HPIM-20).

TREATMENT

Systemic Lupus Erythematosus

Choice of therapy is based on type and severity of disease manifestations. Goals are to control acute, severe flares and to develop maintenance strategies, whereby symptoms are suppressed to an acceptable level. Treatment choices depend on (1) whether disease is life threatening or likely to cause organ damage; (2) whether manifestations are reversible; and (3) the best approach to prevent complications of disease and treatment (Fig. 349-2, p. 2519, and Table 349-5, p. 2521, in HPIM-20). As SLE

predominantly affects young women, teratogenic potential and need for effective contraception must be considered with each prescribed medication.

CONSERVATIVE THERAPIES FOR NON-LIFE-THREATENING DISEASE

- *Sun protection*: as UV exposure may exacerbate cutaneous and/or systemic SLE, sunscreen use is strongly recommended.
- *NSAIDs*: Must consider renal, GI, and cardiovascular complications.
- *Antimalarials (hydroxychloroquine)*: may improve constitutional, cutaneous, articular manifestations. Ophthalmologic evaluation required before and during treatment to rule out ocular toxicity.
- *Methotrexate*: can be considered for dermatitis, arthritis.
- *Belimumab*: B-lymphocyte stimulator (BLyS)-specific inhibitor. Should not be used in severe SLE such as nephritis or CNS disease and limited to pts with mild to moderate active disease.
- *Baricitinib*: oral inhibitor of JAK1 and JAK2 (small molecule inhibitor). In a randomized trial, found to be effective for arthritis and rash in SLE.

TREATMENTS FOR LIFE-THREATENING SLE

- *Systemic glucocorticoids*.
- *Cytotoxic/immunosuppressive agents*: added to glucocorticoids to treat serious SLE.
 1. *Cyclophosphamide*: can be given as intermittent IV or daily oral. Two IV regimens have been studied—high-dose cyclophosphamide 500–1000 mg/M² IV × 6 months used for severe nephritis or other life-threatening SLE. European studies have found low-dose cyclophosphamide 500 mg every 2 weeks for 6 doses to be effective, but it remains unclear whether these data apply to U.S. populations. Both regimens are followed by maintenance with mycophenolate or azathioprine.
 2. *Mycophenolate (mycophenolate mofetil, mycophenolate sodium)*: A higher proportion of African-American pts appears to respond to mycophenolate mofetil compared with cyclophosphamide. As there is teratogenic potential, effective contraception must be discussed in women with child-bearing potential and men whose female partner can become pregnant.
 3. *Azathioprine*: may be effective but is slower in inducing therapeutic response.
 4. *Rituximab*: anti-CD20 B cell depleting monoclonal antibody. The role of rituximab in SLE is controversial. Use generally limited to those with severe disease that has not responded to standard approaches.

162 Rheumatoid Arthritis



■ DEFINITION AND PATHOGENESIS

A chronic multisystem disease of unknown etiology characterized by persistent inflammatory synovitis, usually involving peripheral joints symmetrically. Although cartilaginous destruction, bony erosions, and joint deformity are hallmarks, the course of RA can be quite variable. An association with HLA-DR4 has

been noted; both genetic and environmental factors may play a role in initiating disease. The propagation of RA is an immunologically mediated event in which joint injury occurs from synovial hyperplasia; lymphocytic infiltration of synovium; and local production of cytokines and chemokines by activated lymphocytes, macrophages, and fibroblasts.

■ CLINICAL MANIFESTATIONS

RA occurs in 0.5–1.0% of the population; more common in females than in males with a 2–3:1 ratio; incidence increases between 25 and 55 year of age, plateaus until age 75 then decreases.

Articular Manifestations

Typically, a symmetric polyarthritis of peripheral joints with pain, tenderness, and swelling of affected joints; morning stiffness is common; proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints frequently involved; joint deformities may develop after persistent inflammation.

Extra-articular Manifestations

Cutaneous: rheumatoid nodules, vasculitis

Pulmonary: nodules, interstitial disease, bronchiolitis obliterans–organizing pneumonia (BOOP), pleural disease, Caplan’s syndrome [RA associated with pneumoconiosis]

Ocular: keratoconjunctivitis sicca (KCS), episcleritis, scleritis

Hematologic: anemia, Felty’s syndrome (splenomegaly and neutropenia)

Cardiac: pericarditis, myocarditis

Neurologic: myelopathies secondary to cervical spine disease, entrapment, vasculitis

Associated Conditions

Cardiovascular disease: most common cause of death in RA

Osteoporosis: more common in RA than general population

Hypoandrogenism: decreased testosterone, LH, DHEA

Lymphoma: 2–4-fold increase risk in RA pts

■ EVALUATION

- History and physical examination with careful examination of all joints
- Rheumatoid factor (RF) is present in 75–80% of pts; its presence correlates with severe disease, nodules, extra-articular features.
- Antibodies to cyclic citrullinated protein (anti-CCP) have similar sensitivity but higher specificity than RF; may be most useful in early RA; presence most common in pts with aggressive disease with a tendency for developing bone erosions.
- Other laboratory data: CBC, ESR
- Synovial fluid analysis: useful to rule out crystalline disease, infection
- Radiographs: juxta-articular osteopenia, joint space narrowing, marginal erosions. CXR should be obtained.

■ DIAGNOSIS

Not difficult in pts with typical established disease. May be confusing early. Classification criteria were updated in 2010 (Table 351-1, p. 2535, HPIM-20).

■ DIFFERENTIAL DIAGNOSIS

Gout, SLE, psoriatic arthritis, infectious arthritis, osteoarthritis, spondyloarthritis, sarcoid, polymyalgia rheumatica.

TREATMENT**Rheumatoid Arthritis**

Goals: lessen pain, reduce inflammation, improve/maintain function, prevent long-term joint damage, control of systemic involvement. Increasing trend to treat RA more aggressively earlier in disease course (Table 351-2, p. 2537, HPIM-20). All RA therapies have individual toxicities, with many requiring pretreatment screening and monitoring.

- Pt education on disease, joint protection.
- Physical and occupational therapy: strengthen periarticular muscles, consider assistive devices.
- Aspirin or NSAIDs.
- Intra-articular glucocorticoids.
- Systemic glucocorticoids.
- Disease-modifying antirheumatic drugs (DMARDs): e.g., methotrexate, hydroxychloroquine, sulfasalazine, leflunomide.
- TNF-inhibitors (etanercept, infliximab, adalimumab, golimumab, certolizumab): effective at controlling RA in many pts and can slow the rate of progression of radiographic joint damage and decrease disability; carry potential for serious infection and individual toxicities. There are FDA-approved biosimilar products for etanercept, infliximab, adalimumab.
- Abatacept (CTLA4-Ig): inhibits T-cell activation, can be given with or without methotrexate.
- Rituximab: a chimeric antibody directed to CD20 that depletes mature B cells.
- IL-6 receptor antagonists (tocilizumab, sarilumab): affects the acute phase response due to impact on IL-6.
- Small-molecule inhibitors: oral JAK inhibitors; tofacitinib primarily inhibits JAK1 and JAK3, baricitinib primarily inhibits JAK1 and JAK2.
- Anakinra: an IL-1 receptor antagonist approved, but rarely used, for RA due to only modest clinical efficacy.
- Surgery: may be considered for severe functional impairment due to deformity.

163 The Spondyloarthritis

**DEFINITION**

The *spondyloarthritis* (SpA) are a family of diseases that include ankylosing spondylitis (AS), reactive arthritis (ReA), psoriatic arthritis (PsA), enteropathic arthritis, juvenile-onset SpA, and undifferentiated SpA. More recently, these disorders have been broadly classified as predominantly axial SpA, affecting the spine, pelvis, and thoracic cage, or predominantly peripheral SpA, affecting the extremities. Classification criteria based on these main clinical features have been developed that aid in early identification (Tables 163-1 and 163-2).

TABLE 163-1 ASAS Criteria for Classification of Axial Spondyloarthritis (To Be Applied for Pts with Back Pain ≥ 3 Months and Age of Onset < 45 Years)^a

SACROILIITIS ON IMAGING PLUS ≥ 1 SPA FEATURE	OR	HLA-B27 PLUS ≥ 2 OTHER SPA FEATURES
Sacroiliitis on imaging <ul style="list-style-type: none"> Active (acute) inflammation on MRI highly suggestive of SpA-associated sacroiliitis^b and/or <ul style="list-style-type: none"> Definite radiographic sacroiliitis according to modified New York criteria^c 		SpA features <ul style="list-style-type: none"> Inflammatory back pain^d Arthritis^e Enthesitis (heel)^f Anterior uveitis^g Dactylitis^e Psoriasis^e Crohn's disease or ulcerative colitis^e Good response to NSAIDs^h Family history of SpAⁱ HLA-B27 Elevated CRP^j

^aSensitivity 83%, specificity 84%. The imaging arm (sacroiliitis) alone has a sensitivity of 66% and a specificity of 97%.

^bBone marrow edema and/or osteitis on short tau inversion recovery (STIR) or gadolinium-enhanced T1 image.

^cBilateral grade ≥ 2 or unilateral grade 3 or 4.

^dSee text for criteria.

^ePast or present, diagnosed by a physician.

^fPast or present pain or tenderness on examination at calcaneus insertion of Achilles tendon or plantar fascia.

^gPast or present, confirmed by an ophthalmologist.

^hSubstantial relief of back pain at 24–48 h after a full dose of NSAID.

ⁱFirst- or second-degree relatives with ankylosing spondylitis (AS), psoriasis, uveitis, reactive arthritis (ReA), or inflammatory bowel disease (IBD).

^jAfter exclusion of other causes of elevated CRP

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CRP, C-reactive protein; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; SpA, spondyloarthritis.

Source: Rudwaleit M et al: The development of assessment of spondyloarthritis international society classification criteria for axial spondyloarthritis (part II). *Ann Rheum Dis* 68:777, 2009. Adapted by permission from BMJ Publishing Group Limited.

ANKYLOSING SPONDYLITIS

■ DEFINITION

AS is a chronic and progressive inflammatory disease of the axial skeleton with sacroiliitis (usually bilateral) as its hallmark. Peripheral joints and extra-articular structures may also be affected. Most frequently presents in second or third decade more commonly in men; strong association with histocompatibility antigen HLA-B27.

■ CLINICAL MANIFESTATIONS

- Back pain and stiffness:** not relieved by lying down, often present at night forcing pt to leave bed, worse in the morning, improves with activity, insidious onset, duration > 3 months (often called symptoms of “inflammatory” back pain).
- Extra-axial arthritis:** hip and shoulders 25–35%, other peripheral joint involvement up to 30%, usually asymmetric.
- Chest pain:** from involvement of thoracic skeleton and muscular insertions.

TABLE 163-2 ASAS Criteria for Peripheral Spondyloarthritis^a**Arthritis^b Or Enthesitis Or Dactylitis****PLUS EITHER**

One or more of the following SpA features:

- Psoriasis
- Crohn's disease or ulcerative colitis
- Preceding infection
- Uveitis
- HLA-B27
- Sacroiliitis on imaging (radiographs or MRI)

OR two or more of the following SpA features:

- Arthritis
- Enthesitis
- Dactylitis
- Inflammatory back pain ever
- Family history for SpA

^aSensitivity 78%, specificity 82%.

^bPeripheral arthritis, usually predominantly lower limb and/or asymmetric. The various SpA features are as defined in Table 163-1. Preceding infection refers to preceding gastrointestinal or urogenital infection.

Source: Rudawaleit M et al: The assessment of spondyloarthritis international society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 70:25, 2011. Adapted by permission from BMJ Publishing Group Limited.

- *Extra/juxta-articular pain:* due to "enthesitis": inflammation at insertion of tendons and ligaments into bone; frequently affects greater trochanter, iliac crests, ischial tuberosities, tibial tubercles, heels.
- *Extra-articular findings*—include acute anterior uveitis in up to 40% of pts, aortitis, aortic insufficiency, GI inflammation, cardiac conduction defects, amyloidosis, bilateral upper lobe pulmonary fibrosis.
- *Constitutional symptoms:* fever, fatigue, weight loss may occur.
- *Neurologic complications:* related to spinal fracture/dislocation (can occur with even minor trauma), atlantoaxial subluxation (can lead to spinal cord compression), cauda equina syndrome.

■ PHYSICAL EXAMINATION

- Tenderness over involved joints
- Diminished chest expansion
- Diminished flexion and extension of spine (Schober test measures lumbar spine flexion)

■ EVALUATION

- ESR and C-reactive protein often elevated.
- Mild anemia.
- Rheumatoid factor and ANA negative.
- HLA-B27 may be helpful in pts with inflammatory back symptoms but negative x-rays.
- Radiographs: early may be normal. Sacroiliac joints: usually symmetric; bony erosions with "pseudowidening" followed by fibrosis and ankylosis. Spine: squaring of vertebrae; syndesmophytes; ossification of annulus fibrosus and anterior longitudinal ligament causing "bamboo spine." Sites of enthesitis may ossify and be visible on x-ray. MRI is procedure of choice when plain

radiographs do not reveal sacroiliac abnormalities and can show early intra-articular inflammation, cartilage changes, and bone marrow edema.

■ DIAGNOSIS (TABLE 163-1)

Differential Diagnosis

Osteoarthritis/spondylosis, degenerative disk disease, muscular strain, fibromyalgia; metabolic, infectious, or malignant causes of back pain; diffuse idiopathic skeletal hyperostosis.

TREATMENT

Ankylosing Spondylitis

- Exercise program to maintain posture and mobility is important.
- NSAIDs first-line treatment, useful in most pts.
- TNF-modulatory agents (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol) have been found to improve disease activity and function and reduce bone marrow edema on MRI. Generally used in active disease with failure of at least two NSAIDs.
- Secukinumab, an IL-17A antagonist, has been found to reduce signs and symptoms of active disease.
- Sulfasalazine 2–3 g/d is of modest benefit, primarily for peripheral arthritis.
- No documented therapeutic role for systemic glucocorticoids.
- Intra-articular glucocorticoids for persistent enthesitis or peripheral synovitis.
- Uveitis managed with ocular or systemic glucocorticoids, other immunosuppressive agents, TNF-inhibitors.
- Surgery done rarely for severe hip arthritis, extreme flexion deformities, atlantoaxial subluxation.

REACTIVE ARTHRITIS

■ DEFINITION

ReA refers to acute nonpurulent arthritis complicating an infection elsewhere in the body. The term has been used primarily to refer to SpA following enteric or urogenital infections.

■ PATHOGENESIS

The bacteria identified as being definitive triggers of ReA include enteric organisms *Shigella*, *Salmonella*, *Yersinia*, *Campylobacter* species; and genitourinary infection with *Chlamydia trachomatis*; there is also evidence implicating *Clostridium difficile*, certain toxigenic *Escherichia coli*, and possibly other agents.

■ CLINICAL MANIFESTATIONS

Average age 18–40 years. The male:female ratio following enteric infection is 1:1; however, genitourinary-acquired ReA is predominantly seen in young males. In a majority of cases, history will elicit symptoms of genitourinary or enteric infection 1–4 weeks prior to onset of other features.

Constitutional: fatigue, malaise, fever, weight loss.

Arthritis: usually acute, asymmetric, oligoarticular, involving predominantly lower extremities; sacroiliitis may occur.

Enthesitis: inflammation at insertion of tendons and ligaments into bone; dactylitis or “sausage digit,” plantar fasciitis, and Achilles tendinitis are common.

Ocular features: conjunctivitis, usually minimal; uveitis, keratitis, and optic neuritis rarely present.

Urethritis: discharge intermittent and may be asymptomatic.

Other urogenital manifestations: prostatitis, cervicitis, salpingitis.

Mucocutaneous lesions: painless lesions on glans penis (circinate balanitis) and oral mucosa in approximately a third of pts; *keratoderma blennorrhagica*: cutaneous vesicles that become hyperkeratotic, most common on soles and palms.

Uncommon manifestations: pleuropericarditis, aortic regurgitation, neurologic manifestations, secondary amyloidosis.

ReA is associated with and may be the presenting sign and symptom of HIV.

■ EVALUATION

- Pursuit of triggering infection by culture, serology, or molecular methods as clinically suggested.
- Rheumatoid factor and ANA negative.
- Mild anemia, leukocytosis, elevated ESR may be seen.
- HLA-B27 association was initially overestimated with recent studies showing a prevalence <50%. May be helpful in atypical cases and may have prognostic significance.
- HIV screening should be performed in all pts.
- Synovial fluid analysis—often very inflammatory; negative for crystals or infection.
- Radiographs—erosions may be seen with new periosteal bone formation, ossification of entheses, sacroiliitis (often unilateral).

■ DIFFERENTIAL DIAGNOSIS

Includes septic arthritis (gram +/-), gonococcal arthritis, crystalline arthritis, PsA, Lyme disease.

TREATMENT

Reactive Arthritis

- Controlled trials have failed to demonstrate any benefit of antibiotics in reactive arthritis (ReA). Prompt antibiotic treatment of acute chlamydial urethritis may prevent subsequent ReA.
- NSAIDs benefit most pts if there are no contraindications.
- Intra-articular glucocorticoids.
- Sulfasalazine up to 3 g/d in divided doses may help some pts with persistent arthritis.
- Immunosuppressive agents, such as azathioprine (1–2 [mg/kg]/d) or methotrexate (7.5–15 mg/week), may be considered for debilitating disease refractory to other modalities; contraindicated in HIV disease.
- Anti-TNF agents can be considered in severe chronic cases.
- Uveitis may require aggressive treatment to prevent serious sequelae (see above for AS).

■ OUTCOME

Arthritis typically persists for 3–5 months; recurrence of the acute syndrome is common. Chronic joint symptoms persist in 15% with associated disability.

PSORIATIC ARTHRITIS

■ DEFINITION

PsA is a chronic inflammatory arthritis that affects up to 30% of persons with psoriasis. HLA-B27 is found in 50–70% with axial disease but <20% of pts with only peripheral involvement. Onset of psoriasis usually precedes development

of joint disease; approximately 15–20% of pts develop arthritis prior to onset of skin disease. Nail changes occur in most pts with PsA, dactylitis and enthesitis are common in PsA and help to distinguish it from other joint disorders.

■ PATTERNS OF JOINT INVOLVEMENT

There are five patterns of joint involvement in PsA, which can overlap:

- Asymmetric oligoarthritis: often involves distal interphalangeal/proximal interphalangeal (DIP/PIP) joints of hands and feet, knees, wrists, ankles.
- Symmetric polyarthritis (40%): resembles rheumatoid arthritis except rheumatoid factor is negative, absence of rheumatoid nodules.
- Predominantly DIP joint involvement (15%): high frequency of association with psoriatic nail changes.
- “Arthritis mutilans” (3–5%): aggressive, destructive form of arthritis with severe joint deformities and bony dissolution.
- Spondylitis and/or sacroiliitis: axial involvement is present in 20–40% of pts with psoriatic arthritis; may occur in absence of peripheral arthritis.

■ EVALUATION

- Negative tests for rheumatoid factor.
- Anemia, elevated ESR.
- HIV infection should be suspected in fulminant disease.
- Inflammatory synovial fluid and biopsy without specific findings.
- Radiographic features include erosion at joint margin, bony ankylosis, tuft resorption of terminal phalanges, “pencil-in-cup” deformity (bone proliferation at base of distal phalanx with tapering of proximal phalanx), axial skeleton with asymmetric sacroiliitis, asymmetric nonmarginal syndesmophytes.

■ DIAGNOSIS (TABLE 163-3)

TREATMENT

Psoriatic Arthritis

- Coordinated therapy is directed at the skin and joints.
- Pt education, physical and occupational therapy.
- TNF modulatory agents (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol) can improve joint disease and delay radiographic progression. Etanercept, infliximab, and certolizumab pegol can also be used for skin disease. Infliximab biosimilar can be used for skin and joint disease.
- Ustekinumab (anti-IL-12/23 p40 monoclonal antibody) has efficacy for both skin and joint disease.
- Apremilast (phosphodiesterase 4 inhibitor) benefit skin and joint involvement.
- Secukinumab and ixekizumab, (IL-17A antagonists), have been found to improve disease activity and can also be used for moderate to severe plaque psoriasis.
- Abatacept (CTLA4-Ig) has been used to reduce signs and symptoms of active PsA.
- Tofacitinib (Janus kinase inhibitor) used in adults with active PsA who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs).
- NSAIDs.

TABLE 163-3 The CASPAR (Classification Criteria for Psoriatic Arthritis) Criteria^a

To meet the CASPAR criteria, a pt must have inflammatory articular disease (joint, spine, or enthesal) with ≥ 3 points from any of the following five categories:

1. Evidence of current psoriasis,^{b,c} a personal history of psoriasis, or a family history of psoriasis^d
2. Typical psoriatic nail dystrophy^e observed on current physical examination
3. A negative test result for rheumatoid factor
4. Either current dactylitis^f or a history of dactylitis recorded by a rheumatologist
5. Radiographic evidence of juxtaarticular new bone formation^g in the hand or foot

^aSpecificity of 99% and sensitivity of 91%.

^bCurrent psoriasis is assigned 2 points; all other features are assigned 1 point.

^cPsoriatic skin or scalp disease present at the time of examination, as judged by a rheumatologist or dermatologist.

^dHistory of psoriasis in a first- or second-degree relative.

^eOnycholysis, pitting, or hyperkeratosis.

^fSwelling of an entire digit.

^gIII-defined ossification near joint margins, excluding osteophyte formation.

Source: From Taylor W et al: Classification criteria for psoriatic arthritis. *Arthritis Rheum*, 54:2665, 2006. Reprinted with permission from John Wiley & Sons, Inc.

- Intraarticular steroid injections—useful in some settings. Systemic glucocorticoids should rarely be used as may induce rebound flare of skin disease upon tapering.
- Sulfasalazine 2–3 g/d has clinical efficacy but does not halt joint erosion.
- Methotrexate 15 mg/week may not be disease modifying but it may have symptom-modifying effects and can improve skin scores.
- Leflunomide may be of benefit for skin and joint disease.

ENTEROPATHIC ARTHRITIS

Both peripheral and axial arthritis may be associated with the inflammatory bowel diseases (IBD) ulcerative colitis or Crohn's disease. The arthritis can occur after or before the onset of intestinal symptoms. Peripheral arthritis is episodic and asymmetric; it most frequently affects knee and ankle. Attacks usually subside within several weeks and characteristically resolve completely without residual joint damage. Enthesitis and dactylitis, can occur with manifestations of "sausage digit," Achilles tendinitis, and plantar fasciitis. Axial involvement can manifest as spondylitis and/or sacroiliitis (often symmetric). Laboratory findings are nonspecific; RF absent; HLA-B27 is positive in 70% with IBD and axial disease but <15% with IBD and peripheral arthritis; radiographs of peripheral joints usually normal; axial involvement is often indistinguishable from AS.

TREATMENT

Enteropathic Arthritis

Coordinated treatment directed at underlying IBD; anti-TNF agents have improved arthritis; NSAIDs may alleviate joint symptoms but can precipitate flares of IBD; sulfasalazine, azathioprine, methotrexate may benefit peripheral arthritis.

164 Other Connective Tissue Diseases



CONNECTIVE TISSUE DISEASE

■ DEFINITION

Heterogeneous disorders that share certain common features, including inflammation of skin, joints, and other structures rich in connective tissue; as well as altered patterns of immunoregulation, including production of autoantibodies and abnormalities of cell-mediated immunity. While distinct clinical entities can be defined, manifestations may vary considerably from one pt to the next, and overlap of clinical features between and among specific diseases can occur.

SYSTEMIC SCLEROSIS (SCLERODERMA, SSc)

■ DEFINITION AND PATHOGENESIS

SSc is a multisystem disorder characterized by thickening of the skin (scleroderma) and distinctive involvement of multiple internal organs (chiefly GI tract, lungs, heart, and kidney). Pathogenesis unclear; involves immunologic mechanisms leading to vascular endothelial damage and activation of fibroblasts.

■ CLINICAL MANIFESTATIONS

- *Cutaneous*: edema followed by fibrosis of the skin (chiefly extremities, face, trunk); telangiectasia; calcinosis; Raynaud's phenomenon
- *Arthralgias and/or arthritis*
- *GI*: esophageal hypomotility; intestinal hypofunction, gastric antral vascular ectasia (GAVE)
- *Pulmonary*: interstitial lung disease (ILD), pulmonary arterial hypertension, alveolitis
- *Cardiac*: pericarditis, cardiomyopathy, conduction abnormalities
- *Renal*: hypertension; renal crisis/failure

Two distinct subsets can be identified:

1. *Diffuse cutaneous SSc*: rapid development of symmetric skin thickening of proximal and distal extremity, face, and trunk. At high risk for development of visceral disease early in course.
2. *Limited cutaneous SSc*: often have long-standing Raynaud's phenomenon before other features appear; skin involvement limited to fingers (sclerodactyly), extremity distal to elbows, and face; generally associated with better prognosis but can be associated with pulmonary arterial hypertension; a subset of limited SSc has features of *CREST syndrome* (calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, telangiectasias).

■ EVALUATION

- History and physical examination with particular attention to blood pressure (heralding feature of renal disease).
- Laboratories: ESR, ANA (anticentromere pattern associated with limited SSc), specific antibodies may include anti-topoisomerase I (Scl-70), (UA). An increased range of autoantibodies correlating with specific clinical features have become recognized (Table 353-3, p. 2547, HPIM-20).
- Radiographs: CXR, barium swallow if indicated, hand x-rays may show distal tuft resorption and calcinosis.
- Additional studies: ECG, echo, PFT, consider skin biopsy.

TREATMENT**Systemic Sclerosis**

- Education regarding warm clothing, smoking cessation, anti-reflux measures.
- Calcium channel blockers (e.g., nifedipine) useful for Raynaud's phenomenon. Other agents with potential benefit include sildenafil, losartan, nitroglycerin paste, fluoxetine, bosentan, digital sympathectomy.
- ACE inhibitors: particularly important for controlling hypertension and limiting progression of renal disease.
- Antacids, H₂ antagonists, omeprazole, and metoclopramide may be useful for esophageal reflux.
- D-Penicillamine: controversial benefit to reduce skin thickening and prevent organ involvement; no advantages to using doses >125 mg every other day.
- Glucocorticoids: no efficacy in slowing progression of SSc; indicated for inflammatory myositis or pericarditis; high doses may be associated with development of renal crisis.
- Cyclophosphamide: improves lung function and survival in pts with alveolitis.
- Mycophenolate mofetil: found to be as effective as cyclophosphamide for SSc associated ILD.
- Epoprostenol or treprostinil (prostacyclin), bosentan (endothelin-1 receptor antagonist), sildenafil (phosphodiesterase type 5 inhibitor), riociguat (soluble guanylate cyclase stimulator), selexipag (selective IP prostacyclin receptor agonist): may improve cardiopulmonary hemodynamics in pts with pulmonary hypertension.

MIXED CONNECTIVE TISSUE DISEASE (MCTD)**■ DEFINITION**

Syndrome characterized by a combination of clinical features similar to those of SLE, SSc, polymyositis, and RA; unusually high titers of circulating antibodies to a nuclear ribonucleoprotein (RNP) are found. It is controversial whether MCTD is a truly distinct entity or a subset of SLE or SSc.

■ CLINICAL MANIFESTATIONS

Raynaud's phenomenon, polyarthritis, swollen hands or sclerodactyly, esophageal dysfunction, pulmonary fibrosis, inflammatory myopathy. Renal involvement occurs in about 25%. Laboratory abnormalities include high-titer ANAs, very high titers of antibody to RNP, positive RF in 50% of pts.

■ EVALUATION

Similar to that for SLE and SSc.

TREATMENT**Mixed Connective Tissue Disease**

Few published data. Treat based on manifestations with similar approach to that used if feature occurred in SLE/SSc/polymyositis/RA.

SJÖGREN'S SYNDROME

■ DEFINITION

An immunologic disorder characterized by progressive lymphocytic destruction of exocrine glands most frequently resulting in symptomatic eye and mouth dryness; can be associated with extraglandular manifestations; predominantly affects middle-age females; may be primary or secondary when it occurs in association with other autoimmune diseases. Lymphoma can occur in 6% with glandular MALT being most common.

■ CLINICAL MANIFESTATIONS

- *Constitutional*: fatigue
- *Sicca symptoms*: KCS and xerostomia
- *Dryness of other surfaces*: nose, vagina, trachea, skin
- *Extraglandular features*: arthralgia/arthritis, Raynaud's, lymphadenopathy, interstitial pneumonitis, vasculitis (usually cutaneous), nephritis, lymphoma

■ EVALUATION

- History and physical examination: with special attention to oral, ocular, lymphatic examination and presence of other autoimmune disorders.
- Presence of autoantibodies is a hallmark of disease (ANA, RF, anti-Ro/SS-A, anti-La/SS-B).
- Other laboratory tests: ESR; CBC; renal, liver, and thyroid function tests; serum protein electrophoresis (SPEP) (hypergammaglobulinemia or monoclonal gammopathy common); UA.
- Ocular studies: to diagnose and quantitate KCS; Schirmer's test, Rose Bengal staining.
- Oral examination: unstimulated salivary flow, dental examination.
- Labial salivary gland biopsy: demonstrates lymphocytic infiltration and destruction of glandular tissue.

■ DIAGNOSIS

International classification criteria based on clinical and laboratory features have been established (Table 354-5, p. 2562, HPIM-20).

TREATMENT

Sjögren's Syndrome

- Regular follow-up with dentist and ophthalmologist.
- Dry eyes: artificial tears, ophthalmic lubricating ointments, local stimulation with cyclosporine drops.
- Xerostomia: frequent sips of water, sugarless candy.
- Pilocarpine or cevimeline: may help sicca manifestations.
- Hydroxychloroquine: may help arthralgias.
- Glucocorticoids: not effective for sicca symptoms but may have role in treatment of extraglandular manifestations.

ANTIPHOSPHOLIPID SYNDROME (APS)

■ DEFINITION

Autoantibody-mediated acquired thrombophilia characterized by recurrent arterial or venous thromboses and/or pregnancy morbidity in the presence of autoantibodies against phospholipid (PL)-binding plasma proteins. Can occur alone (primary) or in association with another autoimmune disease (secondary).

■ CLINICAL MANIFESTATIONS

Consist of vascular thrombotic features and pregnancy morbidity (Table 350-2, p. 2527, HPIM-20). Catastrophic APS (CAPS) is rapidly progressive thromboembolic disease involving three or more organ systems that can be life-threatening.

■ EVALUATION

Laboratory examination of clotting parameters to include PTT, kaolin clotting time, dilute Russell viper venom test, antibodies directed against cardiolipin, β_2 glycoprotein, prothrombin. Antibodies should be measured on two occasions 12 weeks apart.

■ DIAGNOSIS

Suggested by the presence of at least one clinical and one laboratory feature.

TREATMENT

Antiphospholipid Syndrome

- After first thrombotic event, warfarin for life to achieve an international normalized ratio (INR) 2.5–3.5.
- Pregnancy morbidity prevented by heparin with aspirin 80 mg daily. IV immunoglobulins (IVIG) may also prevent pregnancy loss. Glucocorticoids are ineffective.
- For CAPS, consider anticoagulation, glucocorticoids, plasma exchange, and IVIG.

165 Vasculitis



■ DEFINITION AND PATHOGENESIS

A clinicopathologic process characterized by inflammation of and damage to blood vessels, compromise of vessel lumen, and resulting ischemia. Clinical manifestations depend on size and location of affected vessel. Most vasculitic syndromes appear to be mediated by immune mechanisms. May be primary or sole manifestation of a disease or secondary to another disease process. Unique vasculitic syndromes can differ greatly with regards to clinical features, disease severity, histology, and treatment.

■ PRIMARY VASCULITIS SYNDROMES

Granulomatosis with Polyangiitis (Wegener's)

Granulomatous vasculitis of upper and lower respiratory tracts together with glomerulonephritis; upper airway lesions affecting the nose and sinuses can cause purulent or bloody nasal discharge, mucosal ulceration, septal perforation, and cartilaginous destruction (saddlenose deformity). Lung involvement may be asymptomatic or cause cough, hemoptysis, dyspnea; eye involvement may occur; glomerulonephritis can be rapidly progressive and asymptomatic and can lead to renal failure.

Microscopic Polyangiitis

Small-vessel vasculitis that can affect the glomerulus and lungs; medium-sized vessels also may be affected.

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

Granulomatous vasculitis of multiple organ systems, particularly the lung; characterized by asthma, peripheral eosinophilia, eosinophilic tissue infiltration; glomerulonephritis can occur. Heart involvement is the leading cause of death.

Polyarteritis Nodosa

Medium-sized muscular arteries involved; frequently associated with arteriographic aneurysms; commonly affects renal arteries, liver, GI tract, peripheral nerves, skin, heart; can be associated with hepatitis B and C.

Giant Cell Arteritis

Inflammation of medium- and large-sized arteries; primarily involves branches of the carotid artery but systemic and large vessel involvement may occur; symptoms include headache, jaw/tongue claudication, scalp tenderness, fever, musculoskeletal symptoms (*polymyalgia rheumatica*); sudden blindness from involvement of optic vessels is a dreaded complication.

Takayasu Arteritis

Vasculitis of the large arteries with strong predilection for aortic arch and its branches; most common in young women; presents with inflammatory or ischemic symptoms in arms, legs, head, and neck, systemic inflammatory symptoms, aortic regurgitation.

IgA Vasculitis (Henoch-Schönlein)

Characterized by involvement of skin, GI tract, kidneys; more common in children.

Cryoglobulinemic Vasculitis

Majority of cases are associated with hepatitis C where an aberrant immune response leads to formation of cryoglobulin; characterized by cutaneous vasculitis, arthritis, peripheral neuropathy, and glomerulonephritis.

Idiopathic Cutaneous Vasculitis

Cutaneous vasculitis is defined broadly as inflammation of the blood vessels of the dermis; due to underlying disease in >70% of cases with 30% occurring idiopathically and isolated to the skin.

Miscellaneous Vasculitic Syndromes

- Kawasaki disease
- Primary central nervous system vasculitis
- Single organ vasculitis
- Behçet's disease
- Cogan's syndrome
- Polyangiitis overlap syndrome

■ SECONDARY VASCULITIS SYNDROMES

- Drug-induced vasculitis
- Serum sickness
- Vasculitis associated with infection, malignancy, rheumatic disease

■ EVALUATION (FIG. 165-1)

- Thorough history and physical examination: special reference to ischemic manifestations and systemic inflammatory signs/symptoms.
- Laboratories: important in assessing organ involvement: CBC with differential, ESR, renal function tests, UA. Should also be obtained to rule out other diseases: ANA, rheumatoid factor, anti-GBM, hepatitis B/C serologies, HIV.
- Antineutrophil cytoplasmic autoantibodies (ANCA): associated with granulomatosis with polyangiitis, microscopic polyangiitis, and some pts with

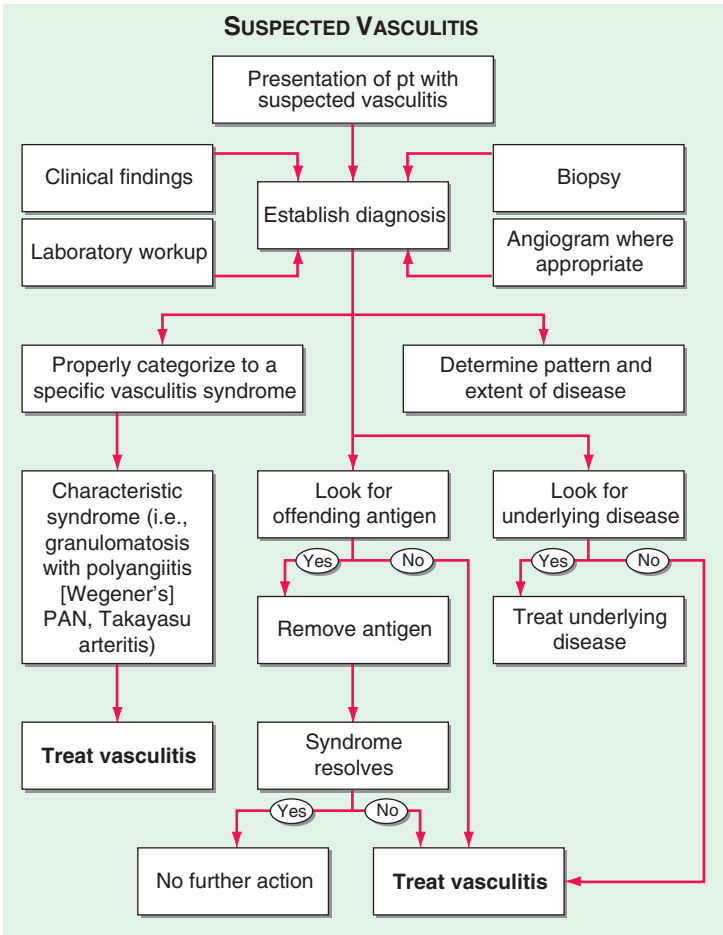


FIGURE 165-1 Algorithm for the approach to a pt with suspected diagnosis of vasculitis. PAN, polyarteritis nodosa.

eosinophilic granulomatosis with polyangiitis; presence of ANCA is adjunctive and should usually not be used in place of biopsy.

- Radiographs: CXR should be performed even in the absence of symptoms in small-vessel vasculitides.
- Diagnosis: can usually be made only by arteriogram or biopsy of affected organ(s).

■ DIFFERENTIAL DIAGNOSIS

Guided by organ manifestations. In many instances includes infections and neoplasms, which must be ruled out prior to beginning immunosuppressive therapy. Consideration must also be given for diseases that can mimic vasculitis (Table 165-1).

TABLE 165-1 Conditions That Can Mimic Vasculitis**Infectious Diseases**

Bacterial endocarditis
 Disseminated gonococcal infection
 Pulmonary histoplasmosis
 Coccidioidomycosis
 Syphilis
 Lyme disease
 Rocky Mountain spotted fever
 Whipple's disease

Coagulopathies/Thrombotic Microangiopathies

Antiphospholipid syndrome
 Thrombotic thrombocytopenic purpura

Neoplasms

Atrial myxoma
 Lymphoma
 Carcinomatosis

Drug Toxicity

Cocaine
 Levamisole
 Amphetamines
 Ergot alkaloids
 Methysergide
 Arsenic

Other

Sarcoidosis
 Atheroembolic disease
 Antiglomerular basement membrane disease (Goodpasture's syndrome)
 Amyloidosis
 Migraine
 Fibromuscular dysplasia
 Heritable disorders of connective tissue
 Segmental arterial mediolysis (SAM)
 Reversible cerebral vasoconstrictive syndrome

TREATMENT**Vasculitis**

Therapy is based on the specific vasculitic syndrome and the severity of its manifestations. Immunosuppressive therapy should be avoided in disease that rarely results in irreversible organ system dysfunction or that usually does not respond to such agents (e.g., isolated cutaneous vasculitis). Antiviral agents play an important role in treating vasculitis occurring with hepatitis B or C. Therapy that combines glucocorticoids with another immunosuppressive agent is particularly important in syndromes with life-threatening organ system involvement, especially active glomerulonephritis. Frequently used agents:

- Prednisone 1 (mg/kg)/d initially, then tapered.
- Cyclophosphamide 2 (mg/kg)/d, adjusted to avoid severe leukopenia. Morning administration with a large amount of fluid is important in minimizing bladder toxicity. IV cyclophosphamide (15 mg/kg every 2 weeks for three doses then every 3 weeks thereafter) can also induce remission but may be associated with a higher relapse rate. Treatment should be limited to 3–6 months followed by transition to maintenance therapy with methotrexate or azathioprine.
- Rituximab 375 (mg/m²)/week intravenously for 4 weeks. As effective as cyclophosphamide to induce remission of granulomatosis with polyangiitis or microscopic polyangiitis. Also used every 6 months for remission maintenance in these diseases.
- Methotrexate up to 25 mg/week may be used to induce remission in granulomatosis with polyangiitis or microscopic polyangiitis pts who do not have immediately life-threatening disease or cannot tolerate cyclophosphamide. It may also be used for maintaining remission after induction with cyclophosphamide. Cannot be used in renal insufficiency or chronic liver disease.
- Azathioprine 2 (mg/kg)/d. Less effective in treating active disease but useful in maintaining remission after induction with cyclophosphamide.
- Mycophenolate mofetil 1000 mg bid. Less effective than azathioprine to maintain remission but an option in pts who cannot take or who have relapsed with methotrexate and azathioprine.
- Tocilizumab 162 mg/week given subcutaneously. Decreased the rate of relapse in giant cell arteritis given in combination with glucocorticoids.
- Mepolizumab 300 mg subcutaneously once a month. Has been shown to be effective in non-life-threatening eosinophilic granulomatosis with polyangiitis.

166 Osteoarthritis



■ DEFINITION

Osteoarthritis (OA) is a disorder characterized by progressive joint failure in which all structures of the joint have undergone pathologic change. The pathologic sine qua non of OA is hyaline articular cartilage loss accompanied by increasing thickness and sclerosis of the subchondral bony plate, outgrowth of osteophytes at the joint margin, stretching of the articular capsule, and weakness of the muscles bridging the joint. There are numerous pathways that lead to OA, but the initial step is often joint injury in the setting of a failure of protective mechanisms.

■ EPIDEMIOLOGY

OA is the most common type of arthritis. The prevalence of OA correlates strikingly with age, and it is much more common in women than in men. Joint vulnerability and joint loading are the two major risk factors contributing to OA. These are influenced by factors that include age, female sex, race, genetic factors, nutritional factors, joint trauma, previous damage, malalignment, proprioceptive deficiencies, and obesity.

■ PATHOGENESIS

The earliest changes of OA may begin in cartilage. The two major components of cartilage are type 2 collagen, which provides tensile strength, and aggrecan, a proteoglycan. OA cartilage is characterized by gradual depletion of aggrecan, unfurling of the collagen matrix, and loss of type 2 collagen, which leads to increased vulnerability.

■ CLINICAL MANIFESTATIONS

OA can affect almost any joint but usually occurs in weight-bearing and frequently used joints such as the knee, hip, spine, and hands. The hand joints that are typically affected are the distal interphalangeal (DIP), proximal interphalangeal (PIP), or first carpometacarpal (thumb base); metacarpophalangeal joint involvement is rare.

Symptoms

- Use-related pain affecting one or a few joints (rest and nocturnal pain less common).
- Stiffness after rest or in morning may occur but is usually brief (<30 min).
- Loss of joint movement or functional limitation.
- Joint instability.
- Joint deformity.
- Joint crepitation (“crackling”).

Physical Examination

- Chronic monoarthritis or asymmetric oligo/polyarthritis.
- Firm enlargement of the joint margins, e.g., Heberden’s nodes (hand DIP) or Bouchard’s nodes (hand PIP).
- Mild synovitis with a cool effusion can occur but is uncommon.
- Crepitation—audible creaking or crackling of joint on passive or active movement.
- Deformity, e.g., OA of knee may involve medial, lateral, or patellofemoral compartments resulting in varus or valgus deformities.
- Restriction of movement, e.g., limitation of internal rotation of hip.
- Objective neurologic abnormalities may be seen with spine involvement (may affect intervertebral disks, apophyseal joints, and paraspinal ligaments).

■ EVALUATION

- Routine lab work usually normal.
- ESR usually normal but may be elevated in pts who have synovitis.
- Rheumatoid factor, ANA studies negative.
- Joint fluid is straw-colored with good viscosity; fluid WBCs <1000/ μL ; of value in ruling out crystal-induced arthritis, inflammatory arthritis, or infection.
- Radiographs may be normal at first but as disease progresses may show joint space narrowing, subchondral bone sclerosis, subchondral cysts, and osteophytes. Erosions are distinct from those of rheumatoid and psoriatic arthritis as they occur subchondrally along the central portion of the joint surface.

■ DIAGNOSIS

Usually established on the basis of pattern of joint involvement. Radiographic features, normal laboratory tests, and synovial fluid findings can be helpful if signs suggest an inflammatory arthritis.

Differential Diagnosis

Osteonecrosis, Charcot joint, rheumatoid arthritis, psoriatic arthritis, crystal-induced arthritides.

TREATMENT**Osteoarthritis**

- Treatment goal—alleviate pain and minimize loss of physical function.
- Nonpharmacotherapy strategies aimed at altering loading across the painful joint—include pt education, weight reduction, appropriate use of cane and other supports, isometric exercises to strengthen muscles around affected joints, bracing/orthotics to correct malalignment.
- Topical capsaicin cream may help relieve hand or knee pain.
- Acetaminophen—commonly used analgesic, caution regarding hepatic toxicity.
- NSAIDs, COX-2 inhibitors—GI, renal, cardiovascular toxicity, must weigh individual risks and benefits.
- Topical NSAIDs—fewer GI and systemic side effects; can cause skin irritation.
- Opioid analgesics—may be considered in rare selected pts whose symptoms are inadequately controlled with other measures and who cannot undergo surgery; habituation is a potential concern.
- Intraarticular glucocorticoids—may provide symptomatic relief but typically short-lived.
- Intraarticular hyaluronan—can be given for symptomatic knee and hip OA, but it is controversial whether it has efficacy beyond placebo.
- Glucosamine and chondroitin—large-scale trials have failed to show efficacy for pain relief; recent guidelines recommend against use.
- Systemic glucocorticoids have no place in the treatment of OA.
- Arthroscopic debridement and lavage—randomized trials have shown no greater effect on pain relief or disability compared to sham procedure or no treatment.
- Joint replacement surgery may be considered in pts with advanced OA who have intractable pain and loss of function in whom non-surgical management has failed.

167**Gout, Pseudogout, and Related Diseases****GOUT****DEFINITION**

Gout is a metabolic disease most often affecting middle-aged to elderly men and postmenopausal women. Hyperuricemia is the biologic hallmark of gout. When present, plasma and extracellular fluids become supersaturated with uric acid, which, under the right conditions, may crystallize and result in a spectrum of clinical manifestations that may occur singly or in combination.

PATHOGENESIS

Uric acid is the end product of purine nucleotide degradation; its production is closely linked to pathways of purine metabolism, with the intracellular

concentration of 5-phosphoribosyl-1-pyrophosphate (PRPP) being the major determinant of the rate of uric acid biosynthesis. Uric acid is excreted primarily by the kidney through mechanisms of glomerular filtration, tubular secretion, and reabsorption. Hyperuricemia may thus arise in a wide range of settings that cause overproduction or reduced excretion of uric acid or a combination of the two.

■ ACUTE GOUTY ARTHRITIS

Monosodium urate (MSU) crystals present in the joint are phagocytosed by leukocytes; release of inflammatory mediators and lysosomal enzymes leads to recruitment of additional phagocytes into the joint and to synovial inflammation.

■ CLINICAL MANIFESTATIONS

Acute arthritis: most frequent early clinical manifestation of gout. Usually initially affects one joint, but may be polyarticular in later episodes. The first metatarsophalangeal joint (*podagra*) is often involved. Acute gout frequently begins at night with dramatic pain, swelling, warmth, and tenderness. Attack will generally subside spontaneously after 3–10 days. Although some pts may have a single attack, most pts have recurrent episodes with intervals of varying length with no symptoms between attacks. Acute gout may be precipitated by dietary excess, trauma, surgery, excessive ethanol ingestion, diuretic medications, hypouricemic therapy, and serious medical illnesses such as myocardial infarction and stroke.

Chronic arthritis: a proportion of gout pts may have a chronic nonsymmetric synovitis; may rarely be the only manifestation. Can also present with periarticular *tophi* (aggregates of MSU crystals surrounded by a giant cell inflammatory reaction).

Extraarticular tophi: often occur in olecranon bursa, helix and anthelix of ears, ulnar surface of forearm, Achilles tendon.

Tenosynovitis

Urate nephropathy: deposition of MSU crystals in renal interstitium and pyramids. Can cause chronic renal insufficiency.

Acute uric acid nephropathy: reversible cause of acute renal failure due to precipitation of urate in the tubules; pts receiving cytotoxic treatment for neoplastic disease are at risk.

Uric acid nephrolithiasis: responsible for 10% of renal stones in the United States.

■ DIAGNOSIS

- Synovial fluid analysis: should be performed to confirm gout even when clinical appearance is strongly suggestive; joint aspiration and demonstration of both intracellular and extracellular needle-shaped negatively birefringent MSU crystals by polarizing microscopy. Gram stain and culture should be performed on all fluid to rule out infection. MSU crystals can also be demonstrated in chronically involved joints or tophaceous deposits.
- Serum uric acid: normal levels do not rule out gout.
- Urine uric acid: excretion of >800 mg/d on regular diet in the absence of drugs suggests overproduction.
- Screening for risk factors or sequelae: urinalysis; serum creatinine, liver function tests, glucose and lipids; complete blood counts.
- If overproduction is suspected, measurement of erythrocyte hypoxanthine guanine phosphoribosyl transferase (HGPRT) and PRPP levels may be indicated.
- Joint x-rays: may demonstrate cystic changes, erosions with sclerotic margins in advanced chronic arthritis.

- If renal stones suspected, consider abdominal flat plate (stones often radiolucent), ultrasound, IVP, or CT.
- Chemical analysis of renal stones.

Differential Diagnosis

Septic arthritis, reactive arthritis, calcium pyrophosphate dihydrate (CPPD) deposition disease, rheumatoid arthritis.

TREATMENT

Gout

ASYMPTOMATIC HYPERURICEMIA

As only ~5% of hyperuricemic pts develop gout, treatment of asymptomatic hyperuricemia is not indicated. Exceptions are pts about to receive cytotoxic therapy for neoplasms.

ACUTE GOUTY ARTHRITIS

Treatment is given for symptomatic relief only since attacks are self-limited and will resolve spontaneously. Toxicity of therapy must be considered in each pt.

- Analgesia
- NSAIDs: consider when not contraindicated.
- Colchicine: generally only effective within first 24 h of attack; overdose has potentially life-threatening side effects; use is contraindicated in pts with renal insufficiency, cytopenias, LFTs $>2 \times$ normal, sepsis. PO—0.6 mg every 8 h with tapering or 1.2 mg followed by 0.6 mg in 1 h with subsequent day dosing depending on response.
- Intraarticular glucocorticoids: septic arthritis must be ruled out prior to injection.
- Systemic glucocorticoids: brief taper may be considered in pts with a polyarticular gouty attack for whom other modalities are contraindicated and where articular or systemic infection has been ruled out.
- Anakinra, canakinumab (inhibitors of interleukin-1 β) have been studied, and can be used when other treatments have failed or were contraindicated.

URIC ACID-LOWERING AGENTS

Indications for initiating uric acid-lowering therapy include recurrent frequent acute gouty arthritis, polyarticular gouty arthritis, tophaceous gout, renal stones, prophylaxis during cytotoxic therapy. Should not start during an acute attack. Initiation of such therapy can precipitate an acute flare; in pts without contraindications consider concomitant PO colchicine 0.6 mg daily until uric acid <6.0 mg/dL, then discontinue.

1. *Xanthine oxidase inhibitors* (allopurinol, febuxostat): Decrease uric acid synthesis. Allopurinol must be dose-reduced in renal insufficiency. Both have side effects and drug interactions. Febuxostat has been associated with an increased risk of death (heart-related death and all-cause mortality) compared to allopurinol. The FDA recommends limiting use of febuxostat to pts not treated effectively or who have severe side effects with allopurinol.
2. *Uricosuric drugs* (probenecid, sulfapyrazone): Increases uric acid excretion by inhibiting its tubular reabsorption; ineffective in renal insufficiency; should not be used in these settings: age >60 , renal stones, tophi, increased urinary uric acid excretion, prophylaxis during cytotoxic therapy.

3. *Pegloticase*: Recombinant uricase that lowers uric acid by oxidizing urate to allantoin. Risk of severe infusion reactions. Should be used only in selected pts with chronic tophaceous gout refractory to conventional therapy.

CALCIUM PYROPHOSPHATE DIHYDRATE (CPPD) DEPOSITION DISEASE (PSEUDOGOUT)

■ DEFINITION AND PATHOGENESIS

CPPD disease is characterized by acute and chronic inflammatory joint disease, usually affecting older individuals. The knee and other large joints are most commonly affected. Calcium deposits in articular cartilage (*chondrocalcinosis*) may be seen radiographically; these are not always associated with symptoms.

CPPD is most often idiopathic but can be associated with other conditions (Table 167-1).

Crystals are thought not to form in synovial fluid but are probably shed from articular cartilage into joint space, where they are phagocytosed by neutrophils and incite an inflammatory response.

■ CLINICAL MANIFESTATIONS

- *Acute CPPD arthritis* (“*pseudogout*”): knee is most frequently involved, but polyarticular in two-thirds of cases; involved joint is erythematous, swollen, warm, and painful. Most pts have evidence of chondrocalcinosis.
- *Chronic arthropathy*: progressive degenerative changes in multiple joints; can resemble osteoarthritis (OA). Joint distribution may suggest CPPD with common sites including knee, wrist, metacarpophalangeal (MCP), hips, and shoulders.
- *Symmetric proliferative synovitis*: seen in familial forms with early onset; clinically similar to RA.
- *Intervertebral disk and ligament calcification*
- *Spinal stenosis*

■ DIAGNOSIS

- Synovial fluid analysis—demonstration of CPPD crystals that appear as short blunt rods, rhomboids, and cuboids with weak positive birefringence by polarizing microscopy.
- Radiographs may demonstrate chondrocalcinosis and degenerative changes (joint space narrowing, subchondral sclerosis/cysts).

TABLE 167-1 Conditions Associated with Calcium Pyrophosphate Crystal Deposition Disease

Aging
Disease-associated
Primary hyperparathyroidism
Hemochromatosis
Hypophosphatasia
Hypomagnesemia
Chronic gout
Postmeniscectomy
Gitelman's syndrome
Epiphyseal dysplasias

- Secondary causes of CPPD deposition disease should be considered in pts <50 years old.

Differential Diagnosis

OA, RA, gout, septic arthritis.

TREATMENT

Pseudogout

- NSAIDs—when not contraindicated.
- Intraarticular injection of glucocorticoids.
- Colchicine (variably effective).

CALCIUM APATITE DEPOSITION DISEASE

Apatite is the primary mineral of normal bone and teeth. Abnormal accumulation can occur in a wide range of clinical settings (Table 167-2). Apatite is an important factor in *Milwaukee shoulder*, a destructive arthropathy of the elderly that occurs in the shoulders and knees. Apatite crystals are small; clumps may stain purplish on Wright's stain and bright red with alizarin red S. Definitive identification requires electron microscopy or x-ray diffraction studies. Radiographic appearance resembles CPPD disease. *Treatment*: NSAIDs, repeated aspiration, and rest of affected joint.

CALCIUM OXALATE DEPOSITION DISEASE

CaOx crystals may be deposited in joints in primary oxalosis (rare) or secondary oxalosis (a complication of end-stage renal disease). Clinical syndrome similar to gout and CPPD disease. *Treatment*: marginally effective.

TABLE 167-2 Conditions Associated with Apatite Deposition Disease

Aging
Osteoarthritis
Hemorrhagic shoulder effusions in the elderly (Milwaukee shoulder)
Destructive arthropathy
Tendinitis, bursitis
Tumoral calcinosis (sporadic cases)
Disease-associated
Hyperparathyroidism
Milk-alkali syndrome
Renal failure/long-term dialysis
Connective tissue diseases (e.g., systemic sclerosis, dermatomyositis, SLE)
Heterotopic calcification after neurologic catastrophes (e.g., stroke, spinal cord injury)
Heredity
Bursitis, arthritis
Tumoral calcinosis
Fibrodysplasia ossificans progressiva

Abbreviation: SLE, systemic lupus erythematosus.

168 Other Musculoskeletal Disorders

RELAPSING POLYCHONDRITIS

An idiopathic disorder characterized by recurrent inflammation of cartilaginous structures. Cardinal manifestations include ear and nose involvement with floppy ear and saddlenose deformities, inflammation and collapse of tracheal and bronchial cartilaginous rings, and asymmetric episodic nondeforming polyarthritis. Other features can include scleritis, conjunctivitis, iritis, keratitis, aortic regurgitation, glomerulonephritis, and other features of systemic vasculitis. Onset is frequently abrupt, with the appearance of 1–2 sites of cartilaginous inflammation. Diagnosis is made clinically and may be confirmed by biopsy of affected cartilage.

TREATMENT

Relapsing Polychondritis

Glucocorticoids (prednisone 40–60 mg/d with subsequent taper) may suppress acute features and reduce the severity/frequency of recurrences. Cytotoxic and other immunosuppressive agents should be reserved for unresponsive disease or for pts who require high glucocorticoid doses. When airway obstruction is severe, tracheostomy may be required.

POLYMYALGIA RHEUMATICA (PMR)

Clinical syndrome characterized by aching and morning stiffness in the shoulder girdle, hip girdle, or neck for >1 month, elevated ESR, and rapid response to low-dose prednisone (10–20 mg qd). Rarely occurs before age 50; more common in women. PMR can occur in association with giant cell arteritis, which requires treatment with higher doses of prednisone. Evaluation should include a careful history to elicit symptoms suggestive of giant cell arteritis ([Chap. 165](#)); ESR; laboratory test results to rule out other processes usually include RF, ANA, CBC, CPK, serum protein electrophoresis; and renal, hepatic, and thyroid function tests.

TREATMENT

PMR

Pts rapidly improve on prednisone, 10–20 mg daily, but may require treatment over months to years.

NEUROPATHIC JOINT DISEASE

Also known as *Charcot's joint*, this is a severe destructive arthropathy that occurs in joints deprived of pain and position sense; may occur in diabetes mellitus, tabes dorsalis, syringomyelia, amyloidosis, spinal cord, or peripheral nerve injury. Distribution depends on the underlying joint disease. Joint effusions are usually noninflammatory but can be hemorrhagic. Radiographs can reveal either bone resorption or new bone formation with bone dislocation and fragmentation.

TREATMENT**Neuropathic Joint Disease**

Stabilization of joint; surgical fusion may improve function.

HYPERTROPHIC OSTEOARTHROPATHY

Syndrome consisting of periosteal new bone formation, digital clubbing, and arthritis. Most commonly seen in association with lung carcinoma but, also occurs with selected chronic lung or liver disease; congenital heart, lung, or liver disease in children; and idiopathic and familial forms. Symptoms include burning and aching pain most pronounced in distal extremities. Radiographs show periosteal thickening with new bone formation of distal ends of long bones.

TREATMENT**Hypertrophic Osteoarthropathy**

Identify and treat associated disorder; aspirin, NSAIDs, other analgesics, vagotomy, or percutaneous nerve block may help to relieve symptoms.

FIBROMYALGIA

A common disorder characterized by chronic widespread musculoskeletal pain, aching, stiffness, paresthesia, disturbed sleep, and easy fatigability along with multiple tender points. More common in women than in men. Diagnosis is made clinically; evaluation reveals soft tissue tender points but no objective joint abnormalities by examination, laboratory, or radiograph.

TREATMENT**Fibromyalgia**

Pregabalin, duloxetine, and milnacipran have shown benefit for fibromyalgia. Tricyclics for sleep disorder, local measures (heat, massage), physical conditioning, and cognitive-behavioral strategies to improve sleep hygiene.

OSTEONECROSIS (AVASCULAR NECROSIS)

Caused by death of cellular elements of bone, believed to be due to impairment in blood supply. Frequent associations include glucocorticoid treatment, connective tissue disease, trauma, sickle cell disease, embolization, alcohol use, and HIV disease. Commonly involved sites include femoral and humeral heads, femoral condyles, and proximal tibia. Hip disease is bilateral in >50% of cases. Clinical presentation is usually the abrupt onset of articular pain. Early changes are not visible on plain radiograph and are best seen by MRI; later stages demonstrate bone collapse ("crescent sign"), flattening of articular surface with joint space loss. Osteonecrosis of the jaw is a rare occurrence associated with cancer treatments (including radiation), infection, glucocorticoids, or bone antiresorptive therapies.

TREATMENT**Osteonecrosis**

Limited weight-bearing of unclear benefit; NSAIDs for symptoms. Surgical procedures to enhance blood flow may be considered in early-stage disease but are of controversial efficacy; joint replacement may be necessary in late-stage disease for pain unresponsive to other measures.

PERIARTICULAR DISORDERS**■ BURSITIS**

Inflammation of the thin-walled bursal sac surrounding tendons and muscles over bony prominences. The subacromial and greater trochanteric bursae are most commonly involved.

TREATMENT**Bursitis**

Prevention of aggravating conditions, rest, NSAIDs, and local glucocorticoid injections.

■ TENDINITIS

May involve virtually any tendon but frequently affects tendons of the rotator cuff around shoulder, especially the supraspinatus. Pain is dull and aching but becomes acute and sharp when tendon is squeezed below acromion.

TREATMENT**Tendinitis**

NSAIDs, glucocorticoid injection, and physical therapy may be beneficial. The rotator cuff tendons or biceps tendon may rupture acutely, frequently requiring surgical repair.

■ CALCIFIC TENDINITIS

Results from deposition of calcium salts (primarily hydroxyapatite) in tendon, usually supraspinatus. The resulting pain may be sudden and severe.

TREATMENT**Calcific Tendinitis**

Most are self-limited and respond to physical therapy, NSAIDs. Refractory disease treated with ultrasound-guided needle aspiration and lavage or surgery.

■ ADHESIVE CAPSULITIS ("FROZEN SHOULDER")

Results from conditions that enforce prolonged immobility of shoulder joint. Shoulder is painful and tender to palpation, and both active and passive range of motion is restricted.

TREATMENT**Adhesive Capsulitis**

Spontaneous improvement may occur; physical therapy is the foundation; NSAIDs, local injections of glucocorticoids may be helpful.

169 Sarcoidosis

**DEFINITION**

An inflammatory multisystem disease characterized by the presence of noncaseating granulomas of unknown etiology.

PATHOPHYSIOLOGY

The cause of sarcoidosis is unknown, and current evidence suggests that the triggering of an inflammatory response by an unidentified antigen in a genetically susceptible host is involved. The granuloma is the pathologic hallmark of sarcoidosis. The initial inflammatory response is an influx of CD4+ (helper) T cells and an accumulation of activated monocytes. This leads to an increased release of cytokines and the formation of a granuloma. The granuloma may resolve or lead to chronic disease, including fibrosis.

CLINICAL MANIFESTATIONS

Up to one-third of sarcoidosis pts are asymptomatic with 20–30% of pulmonary sarcoidosis being detected by CXR in asymptomatic individuals. Sarcoid manifests symptomatically in organs where it affects function or where it is readily observed. *Löfgren's syndrome* consists of hilar adenopathy, erythema nodosum, often with acute arthritis presenting in one or both ankles spreading to involve other joints.

Disease manifestations of sarcoid include:

- **Lung:** >90% of pts with sarcoidosis will have lung involvement. Features include hilar adenopathy, infiltrates, interstitial pneumonitis, and fibrosis; airways may be involved and cause obstruction to airflow; pulmonary hypertension from direct vascular involvement or lung fibrosis.
- **Lymph nodes:** intrathoracic nodes enlarged in 75–90% of pts. Extrathoracic lymph nodes affected in up to 20%.
- **Skin:** >33% will have skin involvement; lesions include erythema nodosum, maculopapular lesions, subcutaneous nodules, and *lupus pernio* (indurated blue-purple shiny lesions around nasal bridge, eyes, cheeks).
- **Eye:** uveitis 30% in the United States (higher in other countries); may progress to blindness.
- **Bone marrow and spleen**—lymphopenia, anemia 20%, splenomegaly 5–10%.
- **Liver:** involved on biopsy in >50%; 20–30% abnormal liver function studies.
- **Kidney:** parenchymal disease <5%, nephrolithiasis, acute renal failure due to hypercalcemia 1–2%.
- **Nervous system:** occurs in 5–10%; cranial/peripheral neuropathy, chronic meningitis, pituitary involvement, space-occupying lesions, seizures.
- **Heart:** disturbances of rhythm and/or contractility, pericarditis.

- *Musculoskeletal*: involvement of bone or muscle occurs in 10%, bone lesions consist of cysts in areas of expanded bone or lattice-like changes; joint involvement includes acute arthropathy often of the ankles and chronic mono- or oligoarthritis of knee, ankle, proximal interphalangeal (PIP) joints.
- *Constitutional symptoms*—fever, weight loss, anorexia, fatigue.
- *Other organ systems*—hypercalcemia 10%, endocrine/reproductive, exocrine glands, GI, upper respiratory tract.

EVALUATION

- History and physical examination.
- CBC, Ca²⁺, LFTs, ACE, tuberculosis screening.
- CXR and/or chest CT, ECG, PFTs.
- Biopsy of lung or other affected organ.
- Positron emission tomography (PET) has increasingly replaced gallium-67 scanning to identify areas of granulomatous disease. Both can be used to identify potential areas for biopsy.
- MRI can assess extrapulmonary sarcoidosis.

DIAGNOSIS

Made on the basis of clinical, radiographic, and histologic findings. Biopsy of lung or other affected organs is helpful in supporting the diagnosis and ruling out other diseases. Pulmonary involvement can be approached by bronchoscopy with transbronchial lung biopsy. Differential diagnosis includes neoplasms, infections including HIV, and other granulomatous processes.

TREATMENT

Sarcoidosis

As sarcoidosis may remit spontaneously, treatment is based largely on the level of symptoms and extent of organ involvement (Figs. 169-1 and 169-2). When systemic therapy is indicated, glucocorticoids are the mainstay of therapy.

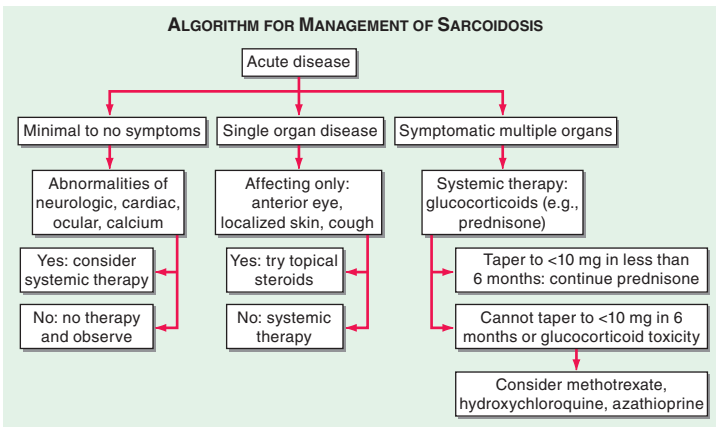


FIGURE 169-1 The management of acute sarcoidosis is based on level of symptoms and extent of organ involvement. In pts with mild symptoms, no therapy may be needed unless specified manifestations are noted.

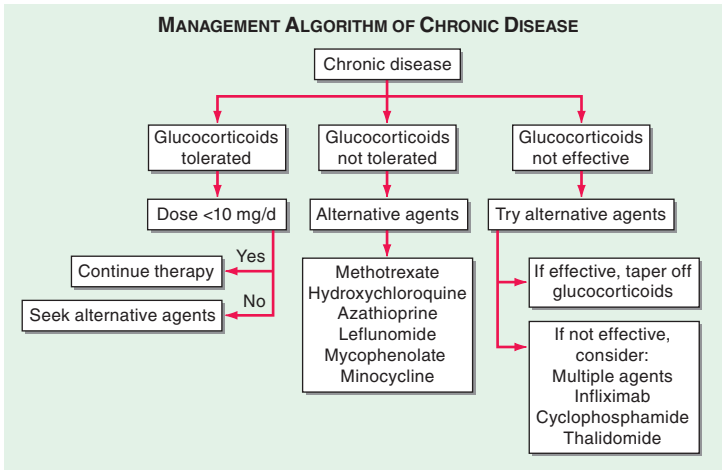


FIGURE 169-2 Approach to chronic disease is based on whether glucocorticoid therapy is tolerated or not.

Other immunomodulatory agents have been used in refractory or severe cases or when prednisone cannot be tapered.

■ OUTCOME

Sarcoidosis is usually a self-limited, non-life-threatening disease. Remission occurs in >50% within 2–5 years of diagnosis with at least 20% developing chronic diseases. Death directly due to disease is low and usually related to lung, cardiac, neurologic, or liver involvement.

170 Amyloidosis



■ DEFINITION

Amyloidosis is a term for a group of protein misfolding disorders characterized by the extracellular deposition of insoluble polymeric protein fibrils in tissues and organs. Clinical manifestations depend on anatomic distribution and intensity of amyloid protein deposition; they range from local deposition with little significance to involvement of virtually any organ system with severe pathophysiologic consequences.

■ CLASSIFICATION

Amyloid diseases are defined by the biochemical nature of the protein in the fibril deposits and are classified according to whether they are systemic or localized, acquired or inherited, and their clinical patterns. The accepted nomenclature is AX where A indicates amyloidosis and X is the protein in the fibril (Table 108-1, p. 804, HPIM-20).

- AL (immunoglobulin light chains): *primary amyloidosis*; most common form of systemic amyloidosis; arises from a clonal B-cell disorder, usually multiple myeloma.
- AA (serum amyloid A): *secondary amyloidosis*; can occur in association with almost any chronic inflammatory state (e.g., RA, SLE, periodic fever syndromes such as familial Mediterranean fever [FMF], Crohn's disease) or chronic infections.
- AF (familial amyloidoses): number of different types that are dominantly transmitted in association with a mutation that enhances protein misfolding and fibril formation; most commonly due to transthyretin.
- A β_2 M: composed of β_2 microglobulin; occurs in end-stage renal disease of long duration.
- Localized or organ-limited amyloidoses: most common form is A β found in Alzheimer's disease derived from abnormal proteolytic processing of the amyloid precursor protein.

■ CLINICAL MANIFESTATIONS

Clinical features are varied and depend entirely on biochemical nature of the fibril protein. Frequent sites of involvement:

- *Kidney*: seen with AA and AL; proteinuria, nephrosis, azotemia.
- *Liver*: occurs in AA, AL, and AF; hepatomegaly.
- *Skin*: characteristic of AL but can be seen in AA; raised waxy papules.
- *Heart*: common in AL and AF; CHF, cardiomegaly, arrhythmias.
- *GI*: common in all types; GI obstruction or ulceration, hemorrhage, protein loss, diarrhea, macroglossia, disordered esophageal motility.
- *Joints*: usually AL, frequently with myeloma; periarticular amyloid deposits, "shoulder pad sign": firm amyloid deposits in soft tissue around the shoulder, symmetric arthritis of shoulders, wrists, knees, hands.
- *Nervous system*: prominent in AF; peripheral neuropathy, postural hypotension, dementia. Carpal tunnel syndrome may occur in AL and A β_2 M.
- *Respiratory*: lower airways can be affected in AL; localized amyloid can cause obstruction along upper airways.

■ DIAGNOSIS

Diagnosis relies on the identification of fibrillar deposits in tissues and typing of the amyloid (Fig. 170-1). Congo red staining of abdominal fat will demonstrate amyloid deposits in >80% of pts with systemic amyloid.

■ PROGNOSIS

Outcome is variable and depends on type of amyloidosis and organ involvement. Average survival of AL amyloid without treatment is ~1–2 years; cardiac involvement is the leading cause of death with a median survival of ~6 months without treatment.

TREATMENT

Amyloidosis

For AL, current therapies target the clonal bone-marrow plasma cells using approaches used for multiple myeloma. High-dose IV melphalan followed by autologous stem-cell transplantation produces complete hematologic responses in ~40% but only 50% are eligible for such aggressive treatment, and peritransplant mortality is higher than for other hematologic diseases because of impaired organ function. Treatment of AA is directed toward controlling the underlying

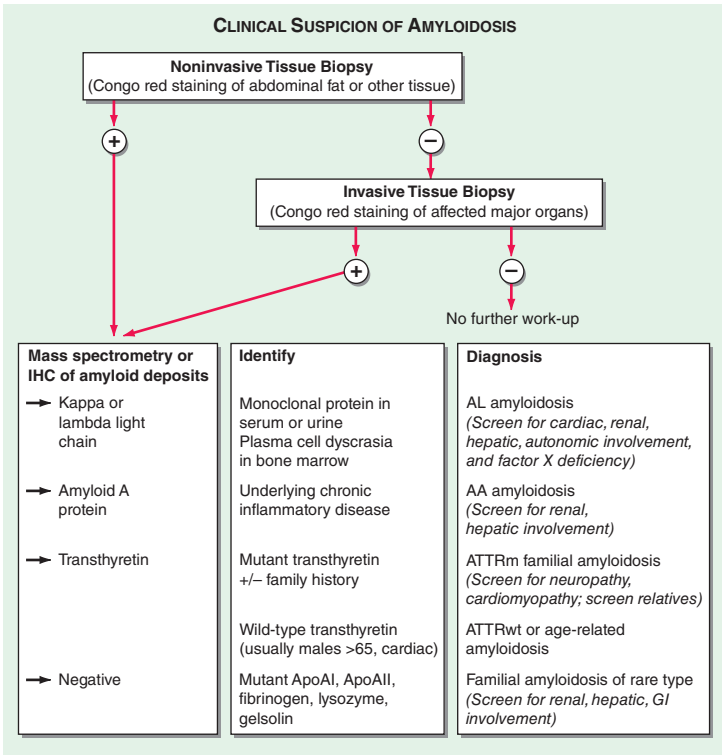


FIGURE 170-1 Algorithm for the diagnosis of amyloidosis and determination of type. Clinical suspicion: unexplained nephropathy, cardiomyopathy, neuropathy, enteropathy, arthropathy, and macroglossia. ApoAI, apolipoprotein AI; ApoAII, apolipoprotein AII; GI, gastrointestinal.

inflammatory condition. Colchicine (1.2–1.8 mg/d) is the standard treatment for FMF but has not been helpful for AA of other causes. TNF inhibitors and interleukin-1 antagonists can be effective in syndromes related to cytokine elevation. In certain forms of AF, genetic counseling is important and liver transplantation is a successful form of therapy.

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Disorders of the Anterior Pituitary and Hypothalamus



The anterior pituitary is often referred to as the “master gland” because, together with the hypothalamus, it regulates the functions of multiple other glands (Fig. 171-1). The anterior pituitary produces six major hormones: (1) prolactin (PRL), (2) growth hormone (GH), (3) adrenocorticotropin hormone (ACTH), (4) luteinizing hormone (LH), (5) follicle-stimulating hormone (FSH), and (6) thyroid-stimulating hormone (TSH). Pituitary hormones are secreted in a pulsatile manner, reflecting intermittent stimulation by specific hypothalamic-releasing factors. Each of these pituitary hormones elicits specific responses in peripheral target glands. The hormonal products of these peripheral glands, in turn, exert feedback control at the level of the hypothalamus and pituitary to modulate pituitary function. Disorders of the pituitary can be broadly divided into clinical syndromes associated with hormone excess (i.e., benign pituitary tumors) or with hormone deficiency (i.e., infarction, mass effects, autoimmune, granulomatous disease, and genetic disorders).

PITUITARY TUMORS

Pituitary adenomas are benign monoclonal tumors that arise from one of the five anterior pituitary cell types and may cause clinical effects from either overproduction of a pituitary hormone or compressive/destructive effects on surrounding structures, including the hypothalamus, pituitary, optic chiasm, and cavernous sinus. About one-third of all adenomas are clinically nonfunctioning and produce no distinct clinical hypersecretory syndrome. They are typically identified because of mass effects or as incidental findings during imaging for other reasons. Among hormonally functioning neoplasms, tumors secreting PRL are the most common (~50%); they have a greater prevalence in women than in men. GH- and ACTH-secreting tumors each account for about 10–15% of functioning pituitary tumors. Adenomas are classified as microadenomas (<10 mm) or macroadenomas (≥10 mm). Pituitary adenomas (especially PRL- and GH-producing tumors) may be part of genetic familial syndromes such as MEN 1, Carney syndrome, or mutant aryl hydrocarbon receptor inhibitor protein (AIP) syndrome. Other entities that can present as a sellar mass include craniopharyngiomas, Rathke’s cleft cysts, sella chordomas, meningiomas, pituitary metastases, gliomas, and granulomatous disease (e.g., histiocytosis X, sarcoidosis).

Clinical Features

Symptoms from mass effects include headache; visual loss through compression of the optic chiasm (classically a bitemporal hemianopia); and diplopia, ptosis, ophthalmoplegia, and decreased facial sensation from cranial nerve compression laterally. Pituitary stalk compression from the tumor may also result in mild hyperprolactinemia. Symptoms of hypopituitarism or hormonal excess may be present as well (see below).

Pituitary apoplexy, typically resulting from hemorrhage into a preexisting adenoma or post-partum as Sheehan’s syndrome, is an endocrine emergency that typically presents with features that include severe headache, bilateral visual changes, ophthalmoplegia, and, in severe cases, cardiovascular collapse and loss

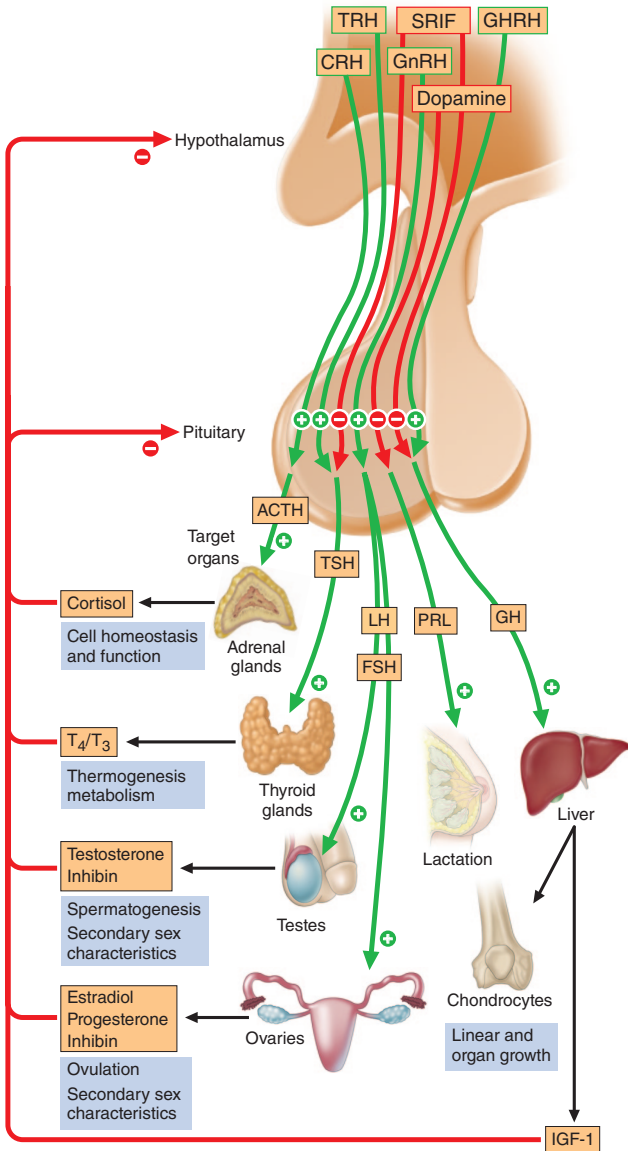


FIGURE 171-1 Diagram of pituitary axes. Hypothalamic hormones regulate anterior pituitary tropic hormones that, in turn, determine target gland secretion. Peripheral hormones feedback to regulate hypothalamic and pituitary hormones. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; IGF, insulin-like growth factor; LH, luteinizing hormone; PRL, prolactin; SRIF, somatostatin, somatotropin release-inhibiting factor; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

of consciousness. It may result in hypotension, hypoglycemia, CNS hemorrhage, and death. Pts with no evident visual loss or impaired consciousness can usually be observed and managed conservatively with high-dose glucocorticoids; surgical decompression should be considered when visual or neurologic symptoms/signs are present.

Diagnosis

Sagittal and coronal T1-weighted MRI images with specific pituitary cuts should be obtained before and after administration of gadolinium. In pts with lesions close to the optic chiasm, visual field assessment that uses perimetry techniques should be performed. In pituitary apoplexy, CT or MRI of the pituitary may reveal signs of hemorrhage in the sellar region, with deviation of the pituitary stalk and compression of pituitary tissue.

TREATMENT

Pituitary Tumors

Pituitary surgery is indicated for mass lesions that impinge on surrounding structures or to correct hormonal hypersecretion, except in the case of prolactinoma, where medical treatment is usually effective (see below). Transsphenoidal surgery, rather than transfrontal resection, is the desired surgical approach for most pts. The goal is selective resection of the pituitary mass lesion without damage to the normal pituitary tissue, to decrease the likelihood of hypopituitarism. Transient or permanent diabetes insipidus, hypopituitarism, CSF rhinorrhea, visual loss, and oculomotor palsy are potential complications. Tumor invasion outside of the sella is rarely amenable to surgical cure, but debulking procedures may relieve tumor mass effects and reduce hormonal hypersecretion. Radiation may be used as an adjunct to surgery, but efficacy is delayed and >50% of pts develop hormonal deficiencies within 10 years, usually due to hypothalamic damage. GH- and TSH-secreting tumors are also amenable to medical therapy; in PRL-secreting tumors, medical therapy is the initial treatment of choice.

PITUITARY HORMONE HYPERSECRETION SYNDROMES

■ HYPERPROLACTINEMIA

Prolactin is unique among the pituitary hormones in that the predominant central control mechanism is inhibitory, reflecting dopamine-mediated suppression of PRL release. Prolactin acts to induce and maintain lactation and decreases reproductive function and libido (via suppression of gonadotropin-releasing hormone [GnRH], gonadotropins, and gonadal steroidogenesis).

Etiology

Physiologic elevation of PRL occurs in pregnancy and lactation. Otherwise, PRL-secreting pituitary adenomas (prolactinomas) are the most common cause of PRL levels >200 µg/L. Less pronounced hyperprolactinemia is commonly caused by medications (risperidone, chlorpromazine, perphenazine, haloperidol, metoclopramide, opiates, H₂ antagonists, amitriptyline, selective serotonin reuptake inhibitors [SSRIs], verapamil, estrogens), pituitary stalk damage (tumors, lymphocytic hypophysitis, granulomas, trauma, irradiation), primary hypothyroidism, or renal failure. Nipple stimulation may also stimulate PRL secretion.

Clinical Features

In women, amenorrhea, galactorrhea, and infertility are the hallmarks of hyperprolactinemia. In men, symptoms of hypogonadism ([Chap. 177](#)) or mass effects are the usual presenting symptoms, and galactorrhea is rare.

Diagnosis

Fasting PRL levels should be measured; when clinical suspicion is high, measurement of levels on several different occasions may be required. If hyperprolactinemia is present, nonneoplastic causes should be excluded (e.g., pregnancy test, hypothyroidism, medications).

TREATMENT**Hyperprolactinemia**

If the pt is taking a medication that is known to cause hyperprolactinemia, the drug should be withdrawn, if possible. A pituitary MRI should be performed if the underlying cause of PRL elevation is unknown. Resection of hypothalamic or sellar mass lesions can reverse hyperprolactinemia due to stalk compression. Medical therapy with a dopamine agonist is indicated in microprolactinomas for control of symptomatic galactorrhea, for restoration of gonadal function, or when fertility is desired. Alternatively, estrogen replacement may be indicated if fertility is not desired, but tumor size should be carefully monitored. Dopamine agonist therapy for macroprolactinomas generally results in both adenoma shrinkage and reduction of PRL levels. Cabergoline (initial dose 0.5 mg a week, usual dose 0.5–1 mg twice a week) or bromocriptine (initial dose 0.625–1.25 mg qhs, usual dose 2.5 PO three times a day) are the two most frequently used dopamine agonists. Cabergoline is the more effective and better-tolerated drug. These medications should initially be taken at bedtime with food, followed by gradual dose increases, to reduce the side effects of nausea and postural hypotension. Other side effects include constipation, nasal stuffiness, dry mouth, nightmares, insomnia, or vertigo; decreasing the dose usually alleviates these symptoms. Dopamine agonists may also precipitate or worsen underlying psychiatric conditions. Cardiac echocardiography is prudent before starting cabergoline therapy as there has been concern about an association with valvular heart disease. In pts with microadenomas successfully treated (normal PRL, full tumors shrinkage), therapy may be withdrawn after 2 years, followed by careful monitoring for tumor recurrence. Spontaneous remission of microadenomas, presumably caused by infarction, occurs in some pts. Surgical debulking may be required for macroprolactinomas that do not adequately respond to medical therapy.

Women with microprolactinomas who become pregnant should discontinue dopaminergic therapy, as the risk for significant tumor growth during pregnancy is low. In those with macroprolactinomas, visual field testing should be performed at each trimester. A pituitary MRI should be performed if severe headache and/or visual defects occur.

■ ACROMEGALY**Etiology**

GH hypersecretion is primarily the result of pituitary somatotrope adenomas, mostly sporadic, but also in conjunction with MEN 1, Carney syndrome, McCune-Albright syndrome, and familial AIP mutations. Extrapituitary causes of acromegaly (ectopic growth hormone-releasing hormone [GHRH] production) are very rare.

Clinical Features

In children, GH hypersecretion prior to long bone epiphyseal closure results in gigantism. The presentation of acromegaly in adults is usually indolent, and diagnosis is typically delayed by up to a decade. Pts may note a change in facial

features, widened teeth spacing, deepening of the voice, snoring, increased shoe or glove size, ring tightening, hyperhidrosis, oily skin, arthropathy, and carpal tunnel syndrome. Frontal bossing, mandibular enlargement with prognathism, macroglossia, an enlarged thyroid, skin tags, thick heel pads, and hypertension may be present on examination. Associated conditions include cardiomyopathy, left ventricular hypertrophy, diastolic dysfunction, sleep apnea, glucose intolerance, diabetes mellitus, colon polyps, and colonic malignancy. Overall mortality is increased approximately threefold. Unless GH levels are controlled, survival is reduced by an average of 10 years compared with an age-matched control population.

Diagnosis

Insulin-like growth factor type I (IGF-I) levels are a useful screening measure, with elevation suggesting acromegaly. Due to the pulsatility of GH, measurement of a single random GH level is not useful for screening. The diagnosis of acromegaly is confirmed by demonstrating the failure of GH suppression to $<0.4 \mu\text{g/L}$ within 1–2 h of a 75-g oral glucose load. MRI of the pituitary usually reveals a macroadenoma.

TREATMENT

Acromegaly

The goal of treatment is to control GH and IGF-I hypersecretion, ablate or arrest tumor growth, ameliorate comorbidities, restore mortality rates to normal, and preserve pituitary function. The primary treatment modality for acromegaly is transsphenoidal surgery. GH levels are not normalized by surgery alone in many pts with macroadenomas; in those, somatostatin analogues provide adjunctive medical therapy that suppresses GH secretion with modest to no effect on tumor size. Octreotide (50 μg SC three times a day) is used for initial therapy to determine response. Once a positive response and tolerance of side effects (nausea, abdominal discomfort, diarrhea, flatulence) are established, pts are changed to long-acting depot formulations (octreotide LAR 20–30 mg IM every 2–4 weeks or lanreotide autogel 90–120 mg IM once a month). For those resistant to octreotide, pasireotide, with preferential SST5 binding, has been shown to exhibit efficacy. Dopamine agonists (bromocriptine, cabergoline) can be used as adjunctive therapy but are generally not very effective. The GH receptor antagonist pegvisomant (10–20 mg SC daily) can be added in pts who do not respond to somatostatin analogues. Pegvisomant is highly effective in lowering IGF-I levels but does not lower GH levels or decrease tumor size. Pituitary irradiation may also be required as adjuvant therapy but has a slow therapeutic onset and a high rate of late hypopituitarism.

■ CUSHING'S DISEASE (SEE CHAP. 174)

■ NONFUNCTIONING AND GONADOTROPIN-PRODUCING ADENOMAS

These tumors are the most common type of pituitary neoplasm and usually present with symptoms of one or more hormonal deficiencies or mass effect. They typically produce small amounts of intact gonadotropins (usually FSH) as well as uncombined α -subunit and LH β and FSH β subunits. Surgery is indicated for mass effects or hypopituitarism; asymptomatic small adenomas may be followed with regular MRI and visual field testing. Diagnosis is based on immunohistochemical analysis of resected tumor tissue. Medical therapy is usually ineffective in shrinking these tumors.

■ TSH-SECRETING ADENOMAS

TSH-producing adenomas are rare but often large and locally invasive when they occur. Pts present with goiter and hyperthyroidism, and/or sella mass effects. Diagnosis is based on elevated serum-free T_4 levels in the setting of inappropriately normal or high TSH secretion and MRI evidence of a pituitary adenoma. Surgery is indicated and is usually followed by somatostatin analogue therapy to treat residual tumor. Somatostatin analogue therapy (see earlier) leads to normalization of TSH and euthyroidism and some tumor shrinkage in most pts. If necessary, thyroid ablation or antithyroid drugs can be used to reduce thyroid hormone levels.

HYPOPITUITARISM

Etiology

A variety of disorders may cause deficiencies of one or more pituitary hormones. These disorders may be genetic, congenital, traumatic (pituitary surgery, cranial irradiation, head injury), neoplastic (large pituitary adenoma, parasellar mass, craniopharyngioma, metastases, meningioma), infiltrative (hemochromatosis, lymphocytic hypophysitis, sarcoidosis, histiocytosis X), vascular (pituitary apoplexy, postpartum necrosis, sickle cell disease), or infectious (tuberculous, fungal, parasitic). Automimmune hypophysitis has been associated with checkpoint inhibitor cancer immunotherapy. The most common cause of hypopituitarism is neoplastic in origin (pituitary mass, or following hypophysectomy or radiation therapy). Pituitary hormone failure due to compression, destruction, or radiation therapy follows a sequential pattern, though this is highly variable: GH>FSH>LH>TSH>ACTH. Genetic causes of hypopituitarism may affect several hormones (e.g., pituitary dysplasia, PROP-1 and PIT-1 mutations) or be restricted to single pituitary hormones or axes (e.g., isolated GH deficiency, Kallmann syndrome, isolated ACTH deficiency). Hypopituitarism following cranial irradiation develops over 5–15 years. Varying degrees of partial to complete hormone deficiencies occur during evolution of hypothalamic and pituitary damage.

Clinical Features

Each hormone deficiency is associated with specific findings:

- *GH*: growth disorders in children; increased intraabdominal fat, reduced lean body mass, hyperlipidemia, reduced bone mineral density, decreased stamina, and social isolation in adults
- *FSH/LH*: menstrual disorders and infertility in women ([Chap. 178](#)); hypogonadism in men ([Chap. 177](#))
- *ACTH*: features of hypocortisolism ([Chap. 174](#)) without mineralocorticoid deficiency
- *TSH*: growth retardation in children; features of hypothyroidism in children and adults ([Chap. 173](#))
- *PRL*: failure to lactate postpartum

Diagnosis

Biochemical diagnosis of pituitary insufficiency is made by demonstrating low or inappropriately normal levels of pituitary hormones in the setting of low target hormone levels. Initial testing should include an 8 A.M. cortisol level, TSH and free T_4 , IGF-I, testosterone in men, assessment of menstrual cycles in women, and PRL level. Note that TSH levels are often inappropriately low or normal in the setting of low free T_4 . Provocative tests are required for definitive diagnosis of

GH and ACTH deficiency. Adult GH deficiency is diagnosed by demonstrating a subnormal GH response to a standard provocative test (insulin tolerance test, L-arginine + GHRH). Acute ACTH deficiency may be diagnosed by a subnormal response in an insulin tolerance test, metyrapone test, or corticotropin-releasing hormone (CRH) stimulation test. Standard ACTH (cosyntropin) stimulation tests may be normal in acute ACTH deficiency; with adrenal atrophy, the cortisol response to cosyntropin is blunted.

TREATMENT

Hypopituitarism

Hormonal replacement should aim to mimic physiologic hormone production. Effective dose schedules are outlined in [Table 171-1](#). Doses should be individualized, particularly for GH, glucocorticoids, and L-thyroxine. GH therapy, particularly when excessive, may be associated with fluid retention, joint pain, and carpal tunnel syndrome. Glucocorticoid replacement should always precede L-thyroxine therapy to avoid precipitation of adrenal crisis. Pts requiring glucocorticoid replacement should wear a medical alert bracelet and should be instructed to take additional doses during stressful events such as acute illness, dental procedures, trauma, and acute hospitalization.

TABLE 171-1 Hormone Replacement Therapy for Adult Hypopituitarism^a

TROPHIC HORMONE DEFICIT	HORMONE REPLACEMENT
ACTH	Hydrocortisone (10–20 mg A.M.; 5–10 mg P.M.) Cortisone acetate (25 mg A.M.; 12.5 mg P.M.) Prednisone (5 mg A.M.)
TSH	L-Thyroxine (0.075–0.15 mg daily)
FSH/LH	Males Testosterone enanthate (200 mg IM every 2 weeks) Testosterone gel (5–10 g/d applied to skin) Females Conjugated estrogen (0.625–1.25 mg qd for 25 days) Estradiol skin patch (0.025–0.1 mg, every week) Progesterone (5–10 mg qd) on days 16–25 For fertility: Menopausal or biosynthetic gonadotropins, human chorionic gonadotropins
GH	Adults: Somatotropin (0.1–1.25 mg SC qd) Children: Somatotropin (0.02–0.05 [mg/kg per day])
Vasopressin	Intranasal desmopressin (5–20 µg twice daily) Oral desmopressin (300–600 µg qd)

^aAll doses shown should be individualized for specific pts and should be reassessed during stress, surgery, or pregnancy. Male and female fertility requirements should be managed as discussed in [Chaps. 177](#) and [178](#).

Abbreviations: ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

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Diabetes Insipidus and Syndrome of Inappropriate Antidiuretic Hormone



The neurohypophysis, or posterior pituitary gland, produces two hormones: (1) arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), and (2) oxytocin. AVP acts on the renal tubules to induce water retention, leading to concentration of the urine. Oxytocin stimulates postpartum milk letdown in response to suckling. Clinical syndromes may result from deficiency or excess of AVP.

DIABETES INSIPIDUS

■ ETIOLOGY

Diabetes insipidus (DI) results from insufficient AVP production by the hypothalamus or from impaired AVP action in the kidney. AVP deficiency is characterized by production of large amounts of dilute urine. In *central DI*, insufficient AVP is released in response to physiologic stimuli. Causes include acquired (head trauma; neoplastic or inflammatory conditions affecting the hypothalamus/posterior pituitary), congenital, and genetic disorders, but almost half of cases are idiopathic. In *gestational DI*, increased metabolism of plasma AVP by an aminopeptidase (vasopressinase) produced by the placenta leads to a relative deficiency of AVP during pregnancy. *Primary polydipsia* results in secondary insufficiency of AVP due to physiologic inhibition of AVP secretion by excessive fluid intake. There are three main types: (1) dipsogenic DI with inappropriate thirst; (2) psychogenic DI often associated with psychosis or obsessive compulsive disorders; and (3) iatrogenic DI often caused by efforts to consume excess fluids for presumed health benefits. *Nephrogenic DI* is caused by AVP resistance at the level of the kidney; it can be genetic or acquired from drug exposure (lithium, demeclocycline, amphotericin B), metabolic conditions (hypercalcemia, hypokalemia), or renal damage.

■ CLINICAL FEATURES

Symptoms include polyuria, excessive thirst, and polydipsia, with a 24-h urine output of >50 mL/kg per day and a urine osmolality that is less than that of serum (<300 mosmol/kg; specific gravity <1.010). DI can be partial or complete; in the latter case the urine is maximally diluted (<100 mosmol/kg) and the daily urine output can reach 10–20 L. Clinical or laboratory signs of dehydration, including hypernatremia, occur only if the pt simultaneously has a thirst defect (not uncommon in pts with CNS disease) or does not have access to water. Other etiologies of hypernatremia are described in [Chap. 1](#).

■ DIAGNOSIS

DI must be differentiated from other etiologies of polyuria ([Chap. 48](#)). Unless an inappropriately dilute urine is present in the setting of serum hyperosmolality, a fluid deprivation test is used to make the diagnosis of DI. This test should be started in the morning with careful supervision to avoid dehydration. Body weight, plasma osmolality, serum sodium, and urine volume and osmolality should be measured hourly. The test should be stopped when body weight decreases by 5% or plasma osmolality/sodium exceeds the upper limit of normal. If the urine osmolality is <300 mosmol/kg with serum hyperosmolality, desmopressin (0.03 $\mu\text{g}/\text{kg}$ SC) should be administered with repeat measurement of urine osmolality 1–2 h later. An increase of $>50\%$ indicates severe pituitary DI,

whereas a smaller or absent response suggests nephrogenic DI. Measurement of AVP levels before and after fluid deprivation may be helpful to distinguish central and nephrogenic DI. If AVP is normal or elevated (>1 pg/mL) and the concurrent urine osmolarity is low (<300 mosmol/L), the pt has nephrogenic DI and the only additional evaluation required is to determine the cause. Occasionally, hypertonic saline infusion may be required if fluid deprivation does not achieve the requisite level of hypertonic dehydration, but this should be administered with caution.

TREATMENT

Diabetes Insipidus

Pituitary DI can be treated with desmopressin (DDAVP) subcutaneously (1–2 μ g once or twice per day), via nasal spray (10–20 μ g two or three times a day), or orally (100–400 μ g two or three times a day), with recommendations to drink to thirst. Symptoms of nephrogenic DI may be ameliorated by treatment with a thiazide diuretic and/or amiloride in conjunction with a low-sodium diet, or with prostaglandin synthesis inhibitors (e.g., indomethacin).

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (SIADH)

■ ETIOLOGY

Excessive or inappropriate production of AVP predisposes to hyponatremia, reflecting water retention. The evaluation of hyponatremia is described in [Chap. 1](#). Etiologies of SIADH include neoplasms, lung infections, CNS disorders, and drugs ([Table 172-1](#)).

■ CLINICAL FEATURES

If hyponatremia develops gradually, it may be asymptomatic until it reaches a severe stage. However, if it develops acutely, symptoms of water intoxication may include mild headache, confusion, anorexia, nausea, vomiting, coma, and convulsions. Laboratory findings include low BUN, creatinine, uric acid, and albumin; serum Na <130 meq/L and plasma osmolality <270 mosmol/kg; urine is not maximally diluted and frequently hypertonic to plasma, and urinary Na⁺ is usually >20 mmol/L.

TREATMENT

SIADH

Fluid intake should be restricted to 500 mL less than urinary output. In pts with severe symptoms or signs, hypertonic (3%) saline can be infused at ≤ 0.05 mL/kg body weight IV per minute, with hourly sodium levels measured until Na increases by 12 meq/L or to 130 meq/L, whichever occurs first. However, if the hyponatremia has been present for >24 –48 h and is corrected too rapidly, saline infusion has the potential to produce central pontine myelinolysis, a serious, potentially fatal neurologic complication caused by osmotic fluid shifts. Vasopressin antagonists (conivaptan, tolvaptan) are now available. Conivaptan has been approved for short-term, in-hospital IV treatment of SIADH. It should be given as a loading dose of 20 mg IV over 30 min followed by a continuous infusion of 20 mg over 24 h. Tolvaptan can be given orally starting at a dose of 15 mg PO and increasing to 30 mg or 60 mg at 24-h intervals depending on the

TABLE 172-1 Causes of Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

Neoplasms	Neurologic
Carcinomas	Guillain-Barré syndrome
Lung	Multiple sclerosis
Duodenum	Delirium tremens
Pancreas	Amyotrophic lateral sclerosis
Ovary	Hydrocephalus
Bladder, ureter	Psychosis
Other neoplasms	Peripheral neuropathy
Thymoma	Congenital malformations
Mesothelioma	Agenesis corpus callosum
Bronchial adenoma	Cleft lip/palate
Carcinoid	Other midline defects
Gangliocytoma	Metabolic
Ewing's sarcoma	Acute intermittent porphyria
Head trauma	Pulmonary
Infections	Asthma
Pneumonia, bacterial or viral	Pneumothorax
Abscess, lung or brain	Positive-pressure respiration
Cavitation (aspergillosis)	Drugs
Tuberculosis, lung or brain	Vasopressin or desmopressin
Meningitis, bacterial or viral	Chlorpropamide
Encephalitis	Oxytocin, high dose
AIDS	Vincristine
Vascular	Carbamazepine
Cerebrovascular occlusions, hemorrhage	Nicotine
Cavernous sinus thrombosis	Phenothiazines
Genetic	Cyclophosphamide
X-linked recessive	Tricyclic antidepressants
(V ₂ receptor gene)	Monoamine oxidase inhibitors
	Serotonin reuptake inhibitors

effect. With either approach, fluid intake should be restricted to less than urine output. Regulating fluid intake so that it under-replaces urine output by 5 mL/kg body weight per hour will raise serum sodium at a rate of about 1% an hour. In any event, serum sodium should be checked every 2–4 hours to ensure it is not raised faster than ≥ 1 mEq/L per hour the lower limit of normal. In addition to fluid restriction, the best approach for the treatment of chronic SIADH is the administration of oral tolvaptan, a selective V₂ antagonist that increases urinary water excretion by blocking the antidiuretic effect of AVP. Other options include demeclocycline, 150–300 mg PO tid or qid, or fludrocortisone, 0.05–0.2 mg PO bid. The effect of the demeclocycline manifests in 7–14 days and is due to induction of a reversible form of nephrogenic DI. The effect of fludrocortisone also requires 1–2 weeks and is partly due to increased retention of sodium and possibly inhibition of thirst. It also increases urinary potassium excretion, which may require replacement through dietary adjustments or supplements and may induce hypertension.

173 Thyroid Gland Disorders



Disorders of the thyroid gland result primarily from autoimmune processes that stimulate the overproduction of thyroid hormones (*thyrotoxicosis*) or cause glandular destruction and underproduction of thyroid hormones (*hypothyroidism*). *Neoplastic processes* in the thyroid gland can lead to benign nodules or thyroid cancer.

Thyroidal production of the hormones thyroxine (T_4) and triiodothyronine (T_3) is controlled via a classic endocrine feedback loop (see Fig. 171-1). Some T_3 is secreted by the thyroid, but most is produced by deiodination of T_4 in peripheral tissues. Both T_4 and T_3 are bound to carrier proteins (thyroid-binding globulin [TBG], transthyretin [binds T_4], and albumin) in the circulation. Increased levels of total T_4 and T_3 with normal free levels are seen in states of increased carrier proteins (pregnancy, estrogens, cirrhosis, hepatitis, and inherited disorders). Conversely, decreased total T_4 and T_3 levels with normal free levels are seen in severe systemic illness, chronic liver disease, and nephrosis.

HYPOTHYROIDISM

■ ETIOLOGY

Deficient thyroid hormone production can be due to thyroid failure (primary hypothyroidism) or, less commonly, pituitary or hypothalamic disease (secondary hypothyroidism) (Table 173-1). Congenital hypothyroidism is present in 1 of 4000 newborns; the importance of its recognition and prompt treatment for child development has led to the adoption of neonatal screening programs. Transient hypothyroidism may occur in silent or subacute thyroiditis. *Subclinical* (or *mild*) *hypothyroidism* is a state of normal free thyroid hormone levels and mild elevation of thyroid-stimulating hormone (TSH). With higher TSH levels and low free T_4 levels, symptoms become more readily apparent in *clinical* (or *overt*) *hypothyroidism*. In areas of iodine sufficiency, autoimmune disease and iatrogenic causes are the most common etiologies of hypothyroidism. The peak age of occurrence is around 60 years, and prevalence increases with age. Novel anticancer and immunomodulatory treatments, such as tyrosine kinase inhibitors and alemtuzumab, can also induce thyroid autoimmunity via their effects on T cell regulation.

■ CLINICAL FEATURES

Symptoms of hypothyroidism include lethargy, dry hair and skin, cold intolerance, hair loss, difficulty concentrating, poor memory, constipation, mild weight gain with poor appetite, dyspnea, hoarse voice, muscle cramping, and menorrhagia. Cardinal features on examination include bradycardia, mild diastolic hypertension, prolongation of the relaxation phase of deep tendon reflexes, and cool peripheral extremities. Goiter may be palpated, or the thyroid may be atrophic and nonpalpable. Carpal tunnel syndrome may be present. An enlarged cardiac silhouette may be caused by pericardial effusion. The most extreme presentation is characterized by a dull, expressionless face, sparse hair, periorbital puffiness, large tongue, and pale, doughy, cool skin. The condition may progress into a hypothermic, stuporous state (*myxedema coma*) with respiratory depression. Factors that predispose to myxedema coma include cold exposure, trauma, infection, and administration of narcotics. In mild hypothyroidism, the classic findings of overt hypothyroidism may not be present, and the clinical picture may be dominated by fatigue and ill-defined symptoms.

TABLE 173-1 Causes of Hypothyroidism**Primary**

Autoimmune hypothyroidism: Hashimoto's thyroiditis, atrophic thyroiditis
 Iatrogenic: ^{131}I treatment, subtotal or total thyroidectomy, external irradiation of neck for lymphoma or cancer

Drugs: iodine excess (including iodine-containing contrast media and amiodarone), lithium, antithyroid drugs, *p*-aminosalicylic acid, interferon α and other cytokines, aminoglutethimide, sunitinib

Congenital hypothyroidism: absent or ectopic thyroid gland, dysmorphogenesis, TSH-R mutation

Iodine deficiency

Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riedel's thyroiditis

Overexpression of type 3 deiodinase in infantile hemangioma

Transient

Silent thyroiditis, including postpartum thyroiditis

Subacute thyroiditis

Withdrawal of thyroxine treatment in individuals with an intact thyroid

After ^{131}I treatment or subtotal thyroidectomy for Graves' disease

Secondary

Hypopituitarism: tumors, pituitary surgery or irradiation, infiltrative disorders, Sheehan's syndrome, trauma, genetic forms of combined pituitary hormone deficiencies

Isolated TSH deficiency or inactivity

Bexarotene treatment

Hypothalamic disease: tumors, trauma, infiltrative disorders, idiopathic

Abbreviations: TSH, thyroid-stimulating hormone; TSH-R, TSH receptor.

DIAGNOSIS

Decreased serum-free T_4 is common to all varieties of hypothyroidism. An elevated serum TSH is a sensitive marker of primary hypothyroidism but is not found in secondary hypothyroidism. A summary of the investigations used to determine the existence and cause of hypothyroidism is provided in [Fig. 173-1](#). Thyroid peroxidase (TPO) antibodies are increased in >90% of pts with autoimmune-mediated hypothyroidism. Elevated cholesterol, increased creatine phosphokinase, and anemia may be present; bradycardia, low-amplitude QRS complexes, and flattened or inverted T waves may be present on ECG.

TREATMENT**Hypothyroidism**

Adult pts <60 years without evidence of heart disease may be started on 50–100 μg of levothyroxine (T_4) daily. In the elderly or in pts with known coronary artery disease, the starting dose of levothyroxine is 12.5–25 $\mu\text{g}/\text{d}$. The dose should be adjusted in 12.5- to 25- μg increments every 6–8 weeks on the basis of TSH levels, until a normal TSH level is achieved. The average daily replacement dose is 1.6 $\mu\text{g}/\text{kg}$ per day, but dosing should be individualized and guided by TSH measurement. In *secondary* hypothyroidism, TSH levels cannot be used, and therapy needs to be guided by free T_4 measurement. Women on levothyroxine replacement should have a TSH level checked as soon as pregnancy is diagnosed, as

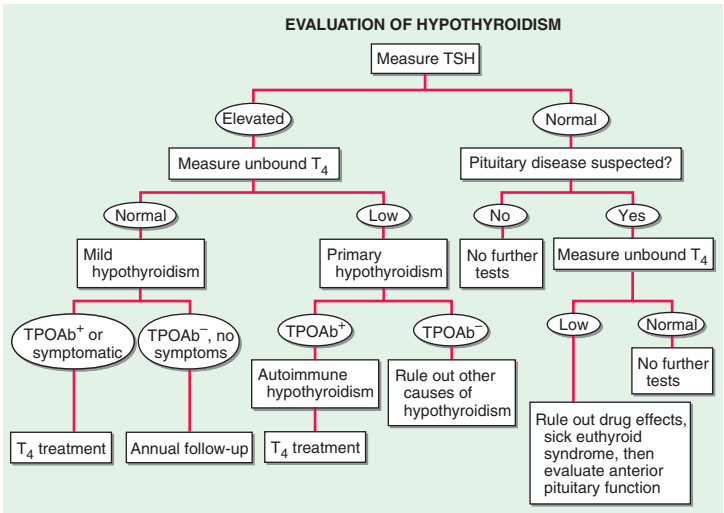


FIGURE 173-1 Evaluation of hypothyroidism. TPOAb⁺, thyroid peroxidase antibodies present; TPOAb⁻, thyroid peroxidase antibodies not present; TSH, thyroid-stimulating hormone.

the replacement dose typically increases by 30–50% during pregnancy. Failure to recognize and treat maternal hypothyroidism may adversely affect fetal neural development. Therapy for myxedema coma should include levothyroxine (200–400 µg) as a single IV bolus followed by a daily oral dose of 1.6 µg/kg per day, reduced by 25% if administered, along with hydrocortisone (50 mg every 6 h) for impaired adrenal reserve, ventilatory support, space blankets, and treatment of precipitating factors.

THYROTOXICOSIS

■ ETIOLOGY

Causes of thyroid hormone excess include primary hyperthyroidism (Graves' disease, toxic multinodular goiter [MNG], toxic adenoma, iodine excess); thyroid destruction (subacute thyroiditis, silent thyroiditis, amiodarone, radiation); extrathyroidal sources of thyroid hormone (thyrotoxicosis factitia, struma ovarii, functioning follicular carcinoma); and secondary hyperthyroidism (TSH-secreting pituitary adenoma, thyroid hormone resistance syndrome, human chorionic gonadotropin [hCG]-secreting tumors, gestational thyrotoxicosis). Graves' disease, caused by activating TSH-receptor antibodies, is the most common cause of thyrotoxicosis and accounts for 60–80% of cases. Its prevalence in women is 10-fold higher than in men; its peak occurrence is at age 20–50 years.

■ CLINICAL FEATURES

Symptoms include nervousness, irritability, heat intolerance, excessive sweating, palpitations, fatigue and weakness, weight loss with increased appetite, frequent bowel movements, and oligomenorrhea. Pts are anxious, restless, and fidgety. Skin is warm and moist, and fingernails may separate from the nail bed (Plummer's nails). Eyelid retraction and lid lag may be present. Cardiovascular findings include tachycardia, systolic hypertension, systolic murmur, and atrial

fibrillation. A fine tremor, hyperreflexia, and proximal muscle weakness also may be present. Long-standing thyrotoxicosis may lead to osteopenia. In the elderly, the classic signs of thyrotoxicosis may not be apparent, the main manifestations being weight loss and fatigue (“apathetic thyrotoxicosis”).

In Graves’ disease, the thyroid is usually diffusely enlarged to two to three times its normal size, and a bruit or thrill may be present. Infiltrative ophthalmopathy (with variable degrees of proptosis, periorbital swelling, and ophthalmoplegia) and dermopathy (pretibial myxedema) also may be found; these are extrathyroidal manifestations of the autoimmune process. In subacute thyroiditis, the thyroid is exquisitely tender and enlarged with referred pain to the jaw or ear, and sometimes accompanied by fever and preceded by an upper respiratory tract infection. Solitary or multiple nodules may be present in toxic adenoma or toxic MNG.

Thyrotoxic crisis, or thyroid storm, is rare, presents as a life-threatening exacerbation of hyperthyroidism, and can be accompanied by fever, delirium, seizures, arrhythmias, coma, vomiting, diarrhea, and jaundice.

■ DIAGNOSIS

Investigations used to determine the existence and causes of thyrotoxicosis are summarized in Fig. 173-2. Serum TSH is a sensitive marker of thyrotoxicosis caused by Graves’ disease, autonomous thyroid nodules, thyroiditis, and

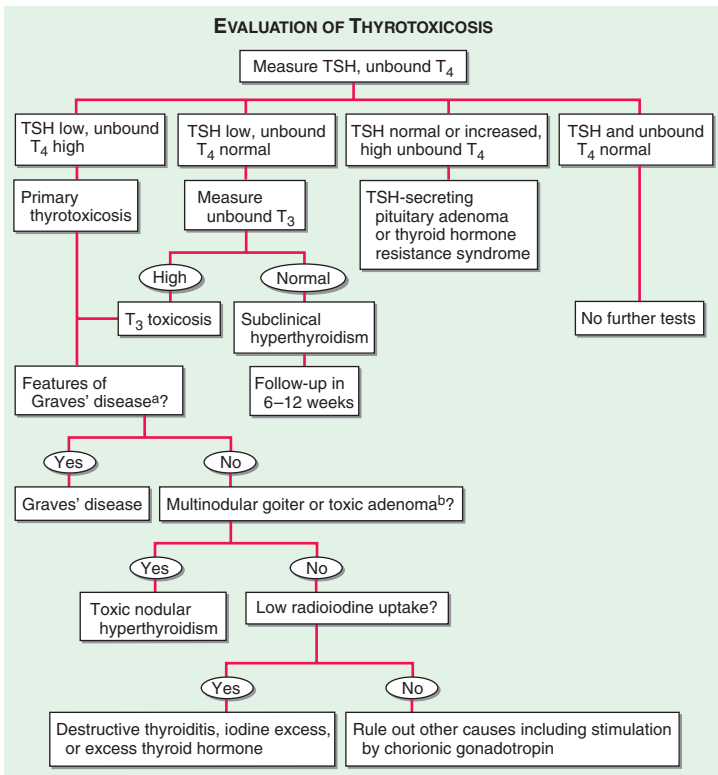


FIGURE 173-2 Evaluation of thyrotoxicosis. ^aDiffuse goiter, positive TPO antibodies, ophthalmopathy, dermopathy; ^bcan be confirmed by radionuclide scan. TSH, thyroid-stimulating hormone.

exogenous levothyroxine treatment. Associated laboratory abnormalities include elevation of bilirubin, liver enzymes, and ferritin. Thyroid radioiodine uptake may be required to distinguish the various etiologies: high uptake in Graves' disease and nodular disease versus low uptake in thyroid destruction, iodine excess, and extrathyroidal sources of thyroid hormone. (*Note:* Radioiodine is the nuclide required for quantitative thyroid uptake, whereas technetium is sufficient for imaging purposes.) The ESR is elevated in subacute thyroiditis. TRAb measurement can also be used to diagnose Graves' disease and color-flow Doppler ultrasonography may distinguish between hyperthyroidism (with increased blood flow) and destructive thyroiditis.

TREATMENT

Thyrotoxicosis

Graves' disease may be treated with antithyroid drugs or radioiodine; subtotal thyroidectomy is rarely indicated. The main antithyroid drugs are methimazole or carbimazole (10–20 mg two to three times a day initially, titrated to 2.5–10 mg/d) and propylthiouracil (PTU) (100–200 mg every 8 h initially, titrated to 50 mg once or twice a day). Methimazole is preferred in most pts because of easier dosing. Thyroid function tests should be checked 3–4 weeks after initiation of treatment, with adjustments to maintain a normal free T_4 level. Since TSH recovery from suppression is delayed, serum TSH levels should not be used for dose adjustment in the first few months. The common side effects are rash, urticaria, fever, and arthralgia (1–5% of pts). Uncommon but major side effects include hepatitis, an SLE-like syndrome, and, rarely, agranulocytosis (<1%). All pts should be given written instructions regarding the symptoms of possible agranulocytosis (sore throat, fever, mouth ulcers) and the need to stop treatment pending a complete blood count to confirm that agranulocytosis is not present. Propranolol (20–40 mg every 6 h) or longer-acting beta blockers such as atenolol (50 mg/d) may be useful at the start of treatment to control adrenergic symptoms until euthyroidism is reached. Anticoagulation with warfarin should be considered in pts with atrial fibrillation. Radioiodine can also be used as initial treatment or in pts who do not undergo remission after a 1- to 2-year trial of antithyroid drugs. Antecedent treatment with antithyroid drugs and a beta blocker should be considered in elderly pts and those with cardiac problems, with cessation of antithyroid drugs 3–5 days prior to radioiodine administration. Radioiodine treatment is contraindicated in pregnancy; instead, symptoms and hormone levels should be monitored or controlled with the lowest effective dose of PTU. (Methimazole is not recommended in pregnancy because of reports of fetal agenesis cutis.) Radioactive iodine should generally be avoided in pts with moderate to severe eye disease. Corneal drying may be relieved with artificial tears and taping the eyelids shut during sleep. Progressive exophthalmos with chemosis, ophthalmoplegia, or vision loss is treated with large doses of prednisone (40–80 mg/d) and ophthalmologic referral; orbital decompression may be required.

In thyroid storm, large doses of PTU (600-mg loading dose) should be administered orally, per nasogastric tube, or per rectum, followed 1 h later by five drops of saturated solution of KI (SSKI) q6h. PTU (200–300 mg every 6 h) should be continued, along with propranolol (40–60 mg PO q4h or 2 mg IV every 4 h) and dexamethasone (2 mg every 6 h). Any underlying precipitating cause should be identified and treated.

Radioiodine is the treatment of choice for toxic nodules. Subacute thyroiditis in its thyrotoxic phase should be treated with NSAIDs and beta blockade to control symptoms, with monitoring of the TSH and free T_4 levels every 4 weeks. Antithyroid drugs are not effective in thyroiditis. The clinical course of subacute

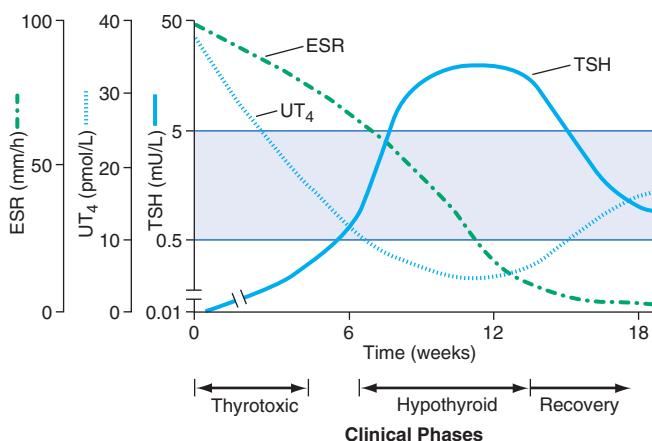


FIGURE 173-3 Clinical course of subacute thyroiditis. The release of thyroid hormones is initially associated with a thyrotoxic phase and suppressed TSH levels. A hypothyroid phase then ensues, with T_4 and TSH levels that are initially low but gradually increase. During the recovery phase, increased TSH levels combined with resolution of thyroid follicular injury lead to normalization of thyroid function, often several months after the beginning of the illness. ESR, erythrocyte sedimentation rate; TSH, thyroid-stimulating hormone; UT_4 , unbound T_4 .

thyroiditis is summarized in [Fig. 173-3](#). Transient levothyroxine replacement (50–100 $\mu\text{g}/\text{d}$) may be required if the hypothyroid phase is prolonged. Silent thyroiditis (or postpartum thyroiditis if within 3–6 months of delivery) should be treated with beta blockade during the thyrotoxic phase and levothyroxine in the hypothyroid phase, with withdrawal after 6–9 months to assess recovery.

SICK EUTHYROID SYNDROME

Any acute, severe illness can cause abnormalities of circulating thyroid hormone levels or TSH, even in the absence of underlying thyroid disease. Therefore, the routine testing of thyroid function should be avoided in acutely ill pts unless a thyroid disorder is strongly suspected. The most common pattern in sick euthyroid syndrome is a decrease in total and free T_3 levels, with normal levels of TSH and T_4 . This is considered an adaptive response to a catabolic state. More ill pts may additionally have a fall in total T_4 levels, with normal free T_4 levels. TSH levels may range from <0.1 to >20 mU/L , with normalization after recovery from illness. The pathogenesis of this condition is not fully understood but may involve altered binding of T_4 to TBG and effects of high glucocorticoid and cytokine levels. Unless there is historic or unequivocal clinical evidence of hypothyroidism, thyroid hormone should not be administered and thyroid function tests should be repeated after recovery.

AMIODARONE

Amiodarone is a type III antiarrhythmic agent that has some structural similarity to thyroid hormone and has a high iodine content. Amiodarone treatment leads to substantial iodine overload and is associated with (1) acute, transient suppression of thyroid function, (2) hypothyroidism, or (3) thyrotoxicosis. These effects

are only partially attributable to iodine overload. Hypothyroidism can occur in pts with preexisting thyroid disease, with an inability to escape from the suppressive effect of excess iodine. Pts with hypothyroidism can be easily managed with levothyroxine replacement therapy, without a need to stop amiodarone. There are two major forms of amiodarone-induced thyrotoxicosis (AIT). Type 1 AIT is associated with an underlying thyroid abnormality (preclinical Graves' disease or nodular goiter). Thyroid hormone synthesis becomes excessive as a result of increased iodine exposure. Type 2 AIT occurs in pts with no intrinsic thyroid abnormalities and is the result of destructive thyroiditis. Differentiation between type 1 and type 2 AIT may be difficult as the high iodine load interferes with thyroid scans. Color-flow Doppler ultrasonography typically increased vascularity in type 1 AIT but decreased vascularity in type 2 AIT. The drug should be stopped, if possible, although this is often difficult to achieve without compromising the arrhythmia management. Amiodarone has a long biologic half-life, and its effects persist for weeks following discontinuation. Therapy of type 1 AIT consists of high-dose antithyroid drugs, but efficacy may be limited. Potassium perchlorate (200 mg every 6 h) can be used to deplete the thyroid of iodine, but long-term use carries a risk of agranulocytosis. Glucocorticoids in high doses are partially effective. Lithium can be used to block thyroid hormone release. In some cases, subacute thyroidectomy may be necessary to control thyrotoxicosis.

NONTOXIC GOITER

Goiter refers to an enlarged thyroid gland (>20–25 g), which can be diffuse or nodular. Goiter is more common in women than men. Biosynthetic defects, iodine deficiency, autoimmune disease, dietary goitrogens (cabbage, cassava root), and nodular diseases can lead to goiter. Worldwide, iodine deficiency is the most common etiology of goiter. Nontoxic MNG is common in both iodine-deficient and iodine-replete populations, with a prevalence of up to 12%. The etiology, other than iodine deficiency, is usually not known and may be multifactorial. If thyroid function is preserved, most goiters are asymptomatic. Substernal goiter may obstruct the thoracic inlet and should be evaluated with respiratory flow measurements and CT or MRI in pts with obstructive signs or symptoms (difficulty swallowing, tracheal compression, or plethora). Thyroid function tests should be performed in all pts with goiter to exclude thyrotoxicosis or hypothyroidism. Ultrasound is not generally indicated in the evaluation of diffuse goiter, unless a nodule is palpable on physical examination.

Iodine or thyroid hormone replacement induces variable regression of goiter in iodine deficiency. Thyroid hormone replacement is rarely effective for significantly shrinking a nontoxic goiter that is not due to iodine deficiency or a biosynthetic defect. Radioiodine reduces goiter size by about 50% in the majority of pts. Surgery is rarely indicated for diffuse goiter but may be required to alleviate compression in pts with nontoxic MNG.

TOXIC MULTINODULAR GOITER AND TOXIC ADENOMA

■ TOXIC MULTINODULAR GOITER

In addition to features of goiter, the clinical presentation of toxic MNG includes subclinical hyperthyroidism or mild thyrotoxicosis. The pt is usually elderly and may present with atrial fibrillation or palpitations, tachycardia, nervousness, tremor, or weight loss. Recent exposure to iodine, from contrast dyes or other sources, may precipitate or exacerbate thyrotoxicosis; this may be prevented by prior administration of an antithyroid drug. The TSH level is low. T_4 may be normal or minimally increased; T_3 is often elevated to a greater degree than T_4 . Thyroid scan shows heterogeneous uptake with multiple regions of increased

and decreased uptake; 24-h uptake of radioiodine may not be increased. Cold nodules in an MNG should be evaluated in the same way as solitary nodules (see below). Fine-needle aspiration (FNA) may be indicated based on sonographic patterns and size cutoffs. The cytology results, if indeterminate or suspicious, may direct the therapy to surgery. Antithyroid drugs, often in combination with beta blockers, can normalize thyroid function and improve clinical features of thyrotoxicosis but do not induce remission. A trial of radioiodine should be considered before subjecting pts, many of whom are elderly, to surgery. Subtotal thyroidectomy provides definitive treatment of goiter and thyrotoxicosis. Pts should be rendered euthyroid with antithyroid drugs before surgical intervention.

■ TOXIC ADENOMA

A solitary, autonomously functioning thyroid nodule is referred to as *toxic adenoma*. Most cases are caused by somatic activating mutations of the TSH receptor. Thyrotoxicosis is typically mild. A thyroid scan provides a definitive diagnostic test, demonstrating focal uptake in the hyperfunctioning nodule and diminished uptake in the remainder of the gland, as activity of the normal thyroid is suppressed. Radioiodine ablation with relatively large doses (e.g., 10–29.9 mCi ^{131}I) is usually the treatment of choice.

THYROID NEOPLASMS

■ ETIOLOGY

Thyroid neoplasms may be benign (adenomas) or malignant (carcinomas). Carcinomas of the follicular epithelium include papillary, follicular, and anaplastic thyroid cancer. Thyroid cancer incidence is ~14/100,000 per year and increases with age. Papillary thyroid cancer is the most common type of thyroid cancer (70–90%). It tends to be multifocal and to invade locally. Follicular thyroid cancer is difficult to diagnose via FNA because the distinction between benign and malignant follicular neoplasms rests largely on evidence of invasion into vessels, nerves, or adjacent structures. It tends to spread hematogenously, leading to bone, lung, and CNS metastases. Anaplastic carcinoma is rare, highly malignant, and rapidly fatal. Thyroid lymphoma may arise in the background of Hashimoto's thyroiditis and occurs in the setting of a rapidly expanding thyroid mass. Medullary thyroid carcinoma arises from parafollicular (C) cells producing calcitonin and may occur sporadically or as a familial disorder, sometimes in association with multiple endocrine neoplasia type 2.

■ CLINICAL FEATURES

Features suggesting carcinoma include recent or rapid growth of a nodule or mass, history of neck irradiation, lymph node involvement, hoarseness, and fixation to surrounding tissues. Glandular enlargement may result in compression and displacement of the trachea or esophagus and obstructive symptoms. Age <20 or >45, male sex, and larger nodule size are associated with a worse prognosis.

■ DIAGNOSIS

An approach to the evaluation of a solitary nodule is outlined in [Fig. 173-4](#).

TREATMENT

Thyroid Neoplasms

Benign nodules should be monitored via serial examination. TSH suppression with levothyroxine does not usually reduce nodule size in iodine-sufficient populations. If suppression therapy is used, TSH levels should be reduced to just below the normal range and suppressive therapy should not exceed 6–12 months if unsuccessful.

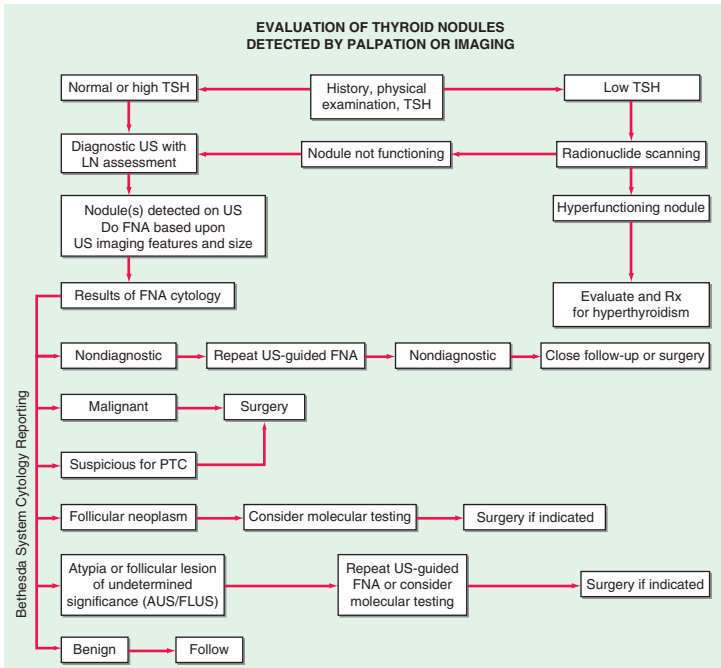


FIGURE 173-4 Approach to the pt with a thyroid nodule. FNA, fine-needle aspiration; LN, lymph node; PTC, papillary thyroid cancer; TSH, thyroid-stimulating hormone; US, ultrasound.

Follicular adenomas cannot be distinguished from follicular carcinomas on the basis of cytologic analysis of FNA specimens. The extent of surgical resection (lobectomy vs. near-total thyroidectomy) should be discussed prior to surgery.

Near-total thyroidectomy is required for papillary and follicular carcinoma and should be performed by a surgeon who is highly experienced in the procedure.

If risk factors and pathologic features indicate the need for radioiodine treatment, the pt should be treated for several weeks postoperatively with liothyronine (T_3 , 25 μg two to three times a day), followed by withdrawal for an additional 2 weeks, in preparation for postsurgical radioablation of remnant tissue. A therapeutic dose of ^{131}I is administered when the TSH level is >25 IU/L. Alternatively, recombinant TSH (0.9 mg) is administered as two daily consecutive injections followed by ^{131}I 24 h after the second injection. This appears to be equally effective as thyroid hormone withdrawal for radioablation therapy. For pts either at intermediate or high risk of recurrence, TSH levels should be kept to 0.1–0.5 mIU/L and <0.1 mIU/L, respectively, if there are no strong contraindications to mild thyrotoxicosis. TSH should be <0.1 mIU/L for those with known metastatic disease. Follow-up scans and serum thyroglobulin levels (acting as a tumor marker in an athyreotic pt) should be performed at regular intervals after either thyroid hormone withdrawal or administration of recombinant human TSH.

Kinase inhibitors are being explored as a means to target pathways known to be active in thyroid cancer, including the RAS, BRAF, RET, EGFR, VEGFR, and angiogenesis pathways.

The management of medullary thyroid carcinoma is surgical, as these tumors do not take up radioiodine. Testing for *RET* mutations should be performed to assess for the presence of MEN 2, and the family should be screened if testing is positive. Following surgery, serum calcitonin provides a marker of residual or recurrent disease.

174 Adrenal Gland Disorders



The adrenal cortex produces three major classes of steroids: (1) glucocorticoids, (2) mineralocorticoids, and (3) adrenal androgens. Clinical syndromes may result from deficiency or excess of these hormones. The adrenal medulla produces catecholamines, with excess being caused by a pheochromocytoma ([Chap. 119](#)).

HYPERFUNCTION OF THE ADRENAL GLAND

■ CUSHING'S SYNDROME

Etiology

The most common cause of Cushing's syndrome is iatrogenic, due to administration of glucocorticoids for therapeutic reasons. Endogenous Cushing's syndrome results from production of excess cortisol (and other steroid hormones) by the adrenal cortex. The major cause is bilateral adrenal hyperplasia secondary to hypersecretion of adrenocorticotrophic hormone (ACTH) by the pituitary (Cushing's disease) or from ectopic sources such as small cell carcinoma of the lung; carcinoids of the bronchus, thymus, gut and ovary, medullary carcinoma of the thyroid; or pheochromocytoma. Adenomas or carcinomas of the adrenal gland account for about 15–20% of endogenous Cushing's syndrome cases. There is a female preponderance in endogenous Cushing's syndrome except for the ectopic ACTH syndrome.

Clinical Features

Some common manifestations (central obesity, hypertension, osteoporosis, psychological disturbances, acne, hirsutism, amenorrhea, and diabetes mellitus) are relatively nonspecific. More specific findings include easy bruising, purple striae, proximal myopathy, fat deposition in the face and nuchal areas (moon faces and buffalo hump), and rarely androgenization. Thin, fragile skin, and plethoric moon faces also may be found. Hypokalemia and metabolic alkalosis are prominent, particularly with ectopic production of ACTH.

Diagnosis

The diagnosis of Cushing's syndrome requires demonstration of increased cortisol production and abnormal cortisol suppression in response to dexamethasone. For initial screening, measurement of 24-h urinary free cortisol, the 1-mg overnight dexamethasone test (8:00 A.M. plasma cortisol $<1.8 \mu\text{g/dL}$ [50 nmol/L]), or late-night salivary cortisol measurement is appropriate. Repeat testing or performance of more than one screening test may be required. Definitive diagnosis

is established in equivocal cases by inadequate suppression of urinary cortisol ($<10 \mu\text{g}/\text{d}$ [$25 \text{ nmol}/\text{d}$]) or plasma cortisol ($<5 \mu\text{g}/\text{dL}$ [$140 \text{ nmol}/\text{L}$]) after 0.5 mg dexamethasone every 6 h for 48 h. Once the diagnosis of Cushing's syndrome is established, further biochemical testing is required to localize the source. This evaluation is best performed by an experienced endocrinologist. Low levels of plasma ACTH levels suggest an adrenal adenoma, bilateral nodular hyperplasia, or carcinoma; inappropriately normal or high plasma ACTH levels suggest a pituitary or ectopic source. In 95% of ACTH-producing pituitary microadenomas, cortisol production is suppressed by high-dose dexamethasone (2 mg every 6 h for 48 h). MRI of the pituitary should be obtained but may not reveal a microadenoma because these tumors are typically very small. Furthermore, because up to 10% of ectopic sources of ACTH may also suppress after high-dose dexamethasone testing, inferior petrosal sinus sampling may be required to distinguish pituitary from peripheral sources of ACTH. Testing with corticotropin-releasing hormone (CRH) also may be helpful in determining the source of ACTH. Imaging of the chest and abdomen is required to localize the source of ectopic ACTH production; small bronchial carcinoids may escape detection by conventional CT. Pts with chronic alcoholism, depression, or obesity may have false-positive results in testing for Cushing's syndrome—a condition named pseudo-Cushing's syndrome. Similarly, pts with acute illness may have abnormal laboratory test results, since major stress alters the normal regulation of ACTH secretion. The diagnosis and management of Cushing's syndrome are summarized in [Fig. 174-1](#).

TREATMENT

Cushing's Syndrome

Uncontrolled hypercorticism carries a poor prognosis, and treatment of Cushing's syndrome is therefore necessary. Transsphenoidal surgery for pituitary ACTH-secreting microadenomas is curative in 70–80% when performed by a highly experienced surgeon, but long-term follow-up is required because these tumors may recur. Radiation therapy may be used when a surgical cure is not achieved ([Chap. 171](#)). Therapy of adrenal adenoma or carcinoma requires surgical excision; stress doses of glucocorticoids must be given pre- and postoperatively. Metastatic and unresectable adrenal carcinomas are treated with mitotane in doses gradually increased to $6 \text{ g}/\text{d}$ in three or four divided doses. On occasion, debulking of lung carcinoma or resection of carcinoid tumors can result in remission of ectopic Cushing's syndrome. If the source of ACTH cannot be resected, medical management with ketoconazole ($600\text{--}1200 \text{ mg}/\text{d}$), metyrapone ($2\text{--}3 \text{ g}/\text{d}$), or mitotane ($500\text{--}1000 \text{ mg}/\text{d}$) may relieve manifestations of cortisol excess. In some cases, bilateral total adrenalectomy is required to control hypercorticism. Pts with unresectable pituitary adenomas who have had bilateral adrenalectomy are at risk for Nelson's syndrome (aggressive pituitary adenoma enlargement).

■ HYPERALDOSTERONISM

Etiology

Aldosteronism is caused by hypersecretion of the adrenal mineralocorticoid aldosterone. *Primary hyperaldosteronism* refers to an adrenal cause and can be due to either an adrenal adenoma or bilateral adrenal hyperplasia. Rare causes include glucocorticoid-remediable hyperaldosteronism, some forms of

ALGORITHM FOR MANAGEMENT OF THE PT WITH SUSPECTED CUSHING'S SYNDROME

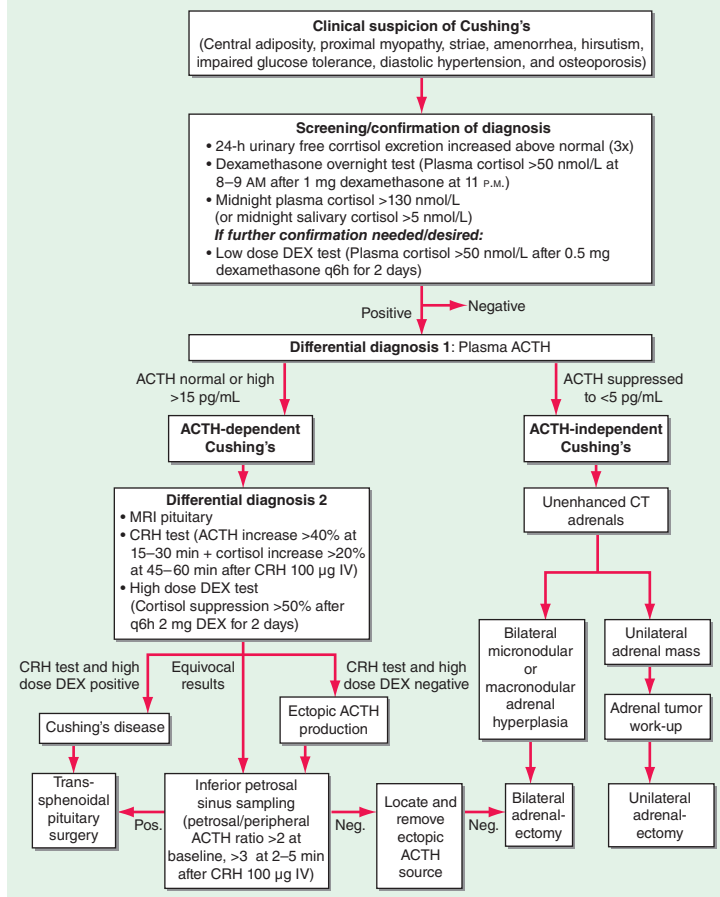


FIGURE 174-1 Management of the pt with suspected Cushing's syndrome. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; DEX, dexamethasone.

congenital adrenal hyperplasia, and other disorders of true or apparent mineralocorticoid excess (see [Table 379-3](#), HPIM-20). The term *secondary hyperaldosteronism* is used when an extraadrenal stimulus for renin secretion is present, as in renal artery stenosis, decompensated liver cirrhosis, or diuretic therapy.

Clinical Features

Most pts with primary hyperaldosteronism have difficult to control hypertension (especially diastolic) and hypokalemia. Headaches are common. Edema is characteristically absent, unless congestive heart failure or renal disease is present. Hypokalemia, caused by urinary potassium loss, may cause muscle weakness, fatigue, and polyuria, although potassium levels may be normal in mild primary hyperaldosteronism. Metabolic alkalosis is a typical feature.

Diagnosis

The diagnosis is suggested by treatment-resistant hypertension that is associated with persistent hypokalemia in a nonedematous pt who is not receiving potassium-wasting diuretics. In pts receiving potassium-wasting diuretics, the diuretic should be discontinued and potassium supplements should be administered for 1–2 weeks. If hypokalemia persists after supplementation, screening using a serum aldosterone and plasma renin activity should be performed. Ideally, antihypertensives should be stopped before testing, but that is often impractical. Aldosterone receptor antagonists, beta-adrenergic blockers, ACE inhibitors, and angiotensin receptor blockers interfere with testing and should be substituted with other antihypertensives if possible. An aldosterone to renin ratio (ARR) of aldosterone (pmol/L) to plasma renin activity (ng/mL per hour) >750 and an absolute level of aldosterone >450 pmol/L suggests primary aldosteronism. Failure to suppress plasma aldosterone after saline or sodium loading confirms primary hyperaldosteronism. The saline infusion test involves the IV administration of 2 L of physiologic saline over a 4-h period. Failure of aldosterone to suppress below 140 pmol/L (5 ng/dL) is indicative of autonomous mineralocorticoid excess. Alternative tests are the oral sodium loading test (300 mmol NaCl/d for 3 days) or the fludrocortisone suppression test (0.1 mg q6h with 30 mmol NaCl q8h for 4 days); the latter can be difficult because of the risk of hypokalemia and increased hypertension. Caution should be used with sodium loading in a hypertensive pt. Localization should then be undertaken with a high-resolution CT scan of the adrenal glands. If the CT scan is negative, bilateral adrenal vein sampling may be required to diagnose a unilateral aldosterone-producing adenoma. Secondary hyperaldosteronism is associated with elevated plasma renin activity.

TREATMENT

Hyperaldosteronism

Surgery can be curative in pts with adrenal adenoma but is not effective for adrenal hyperplasia, which is managed with sodium restriction and spironolactone (25–100 mg twice daily) or eplerenone (25–50 mg twice daily). The sodium channel blocker amiloride (5–10 mg twice a day) also can be used. Secondary hyperaldosteronism is treated with salt restriction and correction of the underlying cause.

■ SYNDROMES OF ADRENAL ANDROGEN EXCESS

See [Chap. 178](#) for discussion of hirsutism and virilization.

HYPOFUNCTION OF THE ADRENAL GLAND

Primary adrenal insufficiency is due to failure of the adrenal gland, whereas *secondary adrenal insufficiency* is due to failure of ACTH production or release.

■ ADDISON'S DISEASE

Etiology

Addison's disease occurs when >90% of adrenal tissue is destroyed. The most common cause is autoimmune destruction (alone, or as part of type I or type II polyglandular autoimmune syndromes). Tuberculosis used to be the leading etiology. Other granulomatous diseases (histoplasmosis, coccidioidomycosis, cryptococcosis, sarcoidosis), bilateral adrenalectomy, bilateral tumor metastases, bilateral hemorrhage, CMV, HIV, amyloidosis, and congenital diseases (some

types of congenital adrenal hypoplasia, adrenal hypoplasia congenita, and adrenoleukodystrophy) are additional etiologies.

Clinical Features

Manifestations include fatigue, weakness, anorexia, nausea and vomiting, weight loss, abdominal pain, cutaneous and mucosal pigmentation, salt craving, hypotension (especially orthostatic), and, occasionally, hypoglycemia. Routine laboratory parameters may be normal, but typically serum Na is reduced and serum K increased. Extracellular fluid depletion accentuates hypotension. In secondary adrenal insufficiency, pigmentation is diminished and serum potassium is not elevated. Serum Na tends to be low because of hemodilution stemming from excess vasopressin secreted in the setting of cortisol deficiency.

Diagnosis

The best screening test is the cortisol response 60 min after 250 μg ACTH (cosyntropin) IV or IM. Cortisol levels should exceed 18 $\mu\text{g}/\text{dL}$ 30–60 min after the ACTH. If the response is abnormal, then primary and secondary deficiency may be distinguished by measurement of aldosterone from the same blood samples. In secondary, but not primary, adrenal insufficiency, the aldosterone increment from baseline will be normal (≥ 5 ng/dL). Furthermore, in primary adrenal insufficiency, plasma ACTH is elevated, whereas in secondary adrenal insufficiency, plasma ACTH values are low or inappropriately normal. Pts with recent onset or partial pituitary insufficiency may have a normal response to the rapid ACTH stimulation test. In these pts, alternative testing (metyrapone test or insulin tolerance testing) can be used for diagnosis.

TREATMENT

Addison's Disease

Hydrocortisone, at 15–25 mg/d divided into 2/3 in the morning and 1/3 in the afternoon, is the mainstay of glucocorticoid replacement. Some pts benefit from doses administered three times daily, and other glucocorticoids may be given at equivalent doses. Mineralocorticoid supplementation is usually needed for primary adrenal insufficiency, with administration of 0.05–0.1 mg fludrocortisone PO qd and maintenance of adequate Na intake. Doses should be titrated to normalize Na and K levels and to maintain normal blood pressure without postural changes. Measurement of plasma renin levels may also be useful in titrating the dose. Mineralocorticoid replacement is not needed in pts with secondary adrenal insufficiency. All pts with adrenal insufficiency should be instructed in the parenteral self-administration of steroids and should be registered with a medical alert system. During periods of intercurrent illness, the dose of hydrocortisone should be doubled. During adrenal crisis, high-dose hydrocortisone (10 mg/h continuous IV or 100-mg bolus IV three times a day) should be administered along with normal saline. Thereafter, if the pt is improving and is afebrile, the dose can be tapered by 20–30% daily to usual replacement doses.

■ HYPOALDOSTERONISM

Isolated aldosterone deficiency accompanied by normal cortisol production occurs with hyporeninism, as an inherited aldosterone synthase deficiency, post-operatively following removal of aldosterone-secreting adenomas (transient), and during protracted heparin therapy. Hyporeninemic hypoaldosteronism is seen most commonly in adults with diabetes mellitus and mild renal failure; it is characterized by mild to moderate hyperkalemia. This is usually a benign

condition that can be managed by observation. If needed, oral fludrocortisone (0.05–0.15 mg/d PO) restores electrolyte balance if salt intake is adequate. In pts with hypertension, mild renal insufficiency, or congestive heart failure, an alternative approach is to reduce salt intake and to administer furosemide.

INCIDENTAL ADRENAL MASSES

Adrenal masses are common findings on abdominal CT or MRI scans (1–7% prevalence with increasing age). The majority of such “incidentalomas” are clinically nonfunctional, and the probability of an adrenal carcinoma is low (<5%) (Fig. 174-2). Genetic syndromes such as MEN 1, MEN 2, Carney syndrome, and McCune-Albright syndrome are all associated with adrenal masses. The first step in evaluation is to determine the functional status by measurement of plasma free metanephrines to screen for pheochromocytoma. In a pt with a known extraadrenal malignancy, there is a 30–50% chance that the incidentaloma is a metastasis. Additional hormonal evaluation should include 24-h urine for urinary free cortisol or overnight 1-mg dexamethasone suppression testing, aldosterone/renin ratio in hypertensives, DHEAS in women with signs of androgen excess, and estradiol in males with feminization. Fine-needle aspiration is rarely indicated and absolutely contraindicated if a pheochromocytoma is suspected. Adrenocortical cancer is suggested by large size (>4–6 cm), irregular margins, tumor inhomogeneity, soft tissue calcifications, and high unenhanced CT attenuation values (>10 HU).

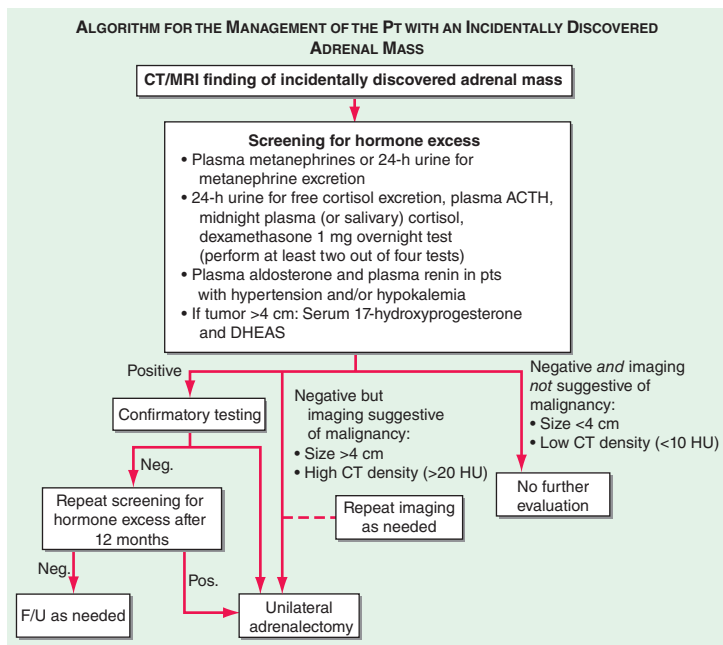


FIGURE 174-2 Management of the pt with an incidentally discovered adrenal mass. CT, computed tomography; F/U, follow-up; MRI, magnetic resonance imaging.

175 Obesity



Obesity is a state of excess adipose tissue mass. About 70% of U.S. adults are categorized as overweight or obese, and the prevalence of obesity is increasing rapidly in most of the industrialized world. Children and adolescents also are becoming more obese, indicating that the current trends will accelerate over time. Obesity is associated with an increased risk of multiple health problems, including hypertension, type 2 diabetes, dyslipidemia, obstructive sleep apnea, non-alcoholic fatty liver disease, degenerative joint disease, and some malignancies.

Obesity should not be defined by body weight alone, as muscular individuals may be overweight by arbitrary standards without having increased adiposity. The most widely used method to classify weight status and risk of disease is the body mass index (BMI), which is equal to weight/height² in kg/m². At a similar BMI, women have more body fat than men. Furthermore, regional fat distribution may influence the risks associated with obesity. Central (primarily visceral) obesity (high ratio of the circumference of the waist to the circumference of the hips [waist-to-hip ratio], >0.9 in women and 1.0 in men) is independently associated with a higher risk for metabolic syndrome, diabetes mellitus, hyperandrogenism in women, and cardiovascular disease.

■ ETIOLOGY

Obesity can result from increased energy intake, decreased energy expenditure, or a combination of the two. Excess accumulation of body fat is the consequence of environmental and genetic factors; social factors and economic conditions also represent important influences. The recent increase in obesity can be attributed to a combination of excess caloric intake and decreasing physical activity. Poorly understood reasons for increased food assimilation due to dietary composition have also been postulated, as have sleep deprivation and an unfavorable gut flora. The susceptibility to obesity is polygenic in nature, and 30–50% of the variability in total fat stores is believed to be genetically determined. Among monogenic causes, mutations in the melanocortin receptor 4 are most common and account for ~1% of obesity in the general population and ~6% in severe, early-onset obesity. Syndromic obesity forms include Prader-Willi syndrome and Laurence-Moon-Biedl syndrome. Other monogenic or syndromic causes are extremely rare. Secondary causes of obesity include hypothalamic injury, hypothyroidism, Cushing's syndrome, and hypogonadism. Drug-induced weight gain is also common in those who use antidiabetes agents (insulin, sulfonylureas, thiazolidinediones), glucocorticoids, psychotropic agents, mood stabilizers (lithium), antidepressants (tricyclics, monoamine oxidase inhibitors, paroxetine, mirtazapine), or antiepileptic drugs (valproate, gabapentin, carbamazepine). Insulin-secreting tumors can cause overeating and weight gain.

■ CLINICAL FEATURES

Obesity has major adverse effects on health. Increased mortality from obesity is primarily due to cardiovascular disease, hypertension, gall bladder disease, diabetes mellitus, and several types of cancer, such as cancer of the esophagus, colon, rectum, pancreas, liver, and prostate, and gallbladder, bile ducts, breasts, endometrium, cervix, and ovaries in women. Sleep apnea in severely obese individuals poses serious health risks. Obesity is also associated with an increased incidence of steatohepatitis, gastroesophageal reflux, osteoarthritis, gout, back

pain, skin infections, and depression. Hypogonadism in men and infertility in both sexes are prevalent in obesity; in women this may be associated with hyperandrogenism (polycystic ovarian syndrome).

TREATMENT

Obesity

Obesity is a chronic medical condition that requires ongoing treatment and lifestyle modifications. Treatment is important because of the associated health risks, but is made difficult by a limited repertoire of effective therapeutic options. Weight regain after weight loss is common with all forms of therapy. The urgency and selection of treatment modalities should be based on BMI and a risk assessment.

Diet, exercise, and behavior therapy are recommended for all pts with a BMI ≥ 25 kg/m². Behavior modification including group counseling, diet diaries, and changes in eating patterns should be initiated. Food-related behaviors should be monitored carefully (avoid cafeteria-style settings, eat small and frequent meals, eat breakfast). A deficit of 7500 kcal will produce a weight loss of approximately 1 kg. Therefore, eating 100 kcal/d less for a year should cause a 5-kg weight loss, and a deficit of 1000 kcal/d should cause a loss of ~1 kg per week. Physical activity should be increased to a minimum of 150 min of moderate intensity per week.

Pharmacotherapy may be added to a lifestyle program for pts with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with concomitant obesity-related diseases. Medications for obesity have traditionally fallen into two major categories: appetite suppressants (*anorexiant*s) and gastrointestinal fat blockers. Four anti-obesity medications were approved by the U.S. Food and Drug Administration (FDA) since 2012: lorcaserin, phentermine/topiramate (PHEN/TPM) extended release, naltrexone sustained release (SR)/bupropion SR, and liraglutide. Gastrointestinal fat blockers (Orlistat) reduce the absorption of selective macronutrients, such as fat, from the gastrointestinal tract. Response to medications should be assessed after 3 months. Metformin, exenatide, and liraglutide tend to decrease body weight in pts with obesity and type 2 diabetes mellitus, but they are not indicated for pts without diabetes.

Bariatric surgery should be considered for pts with severe obesity (BMI ≥ 40 kg/m²) or moderate obesity (BMI ≥ 35 kg/m²) associated with a serious medical condition, with repeated failures of other therapeutic approaches, at eligible weight for >3 years, capable of tolerating surgery, and without addictions or major psychopathology. Weight-loss surgeries are either restrictive (limiting the amount of food the stomach can hold and slowing gastric emptying), such as laparoscopic adjustable silicone gastric banding, or restrictive-malabsorptive, such as Roux-en-Y gastric bypass (Fig. 175-1). These procedures generally produce a 30–35% weight loss that is maintained in about 40% of pts at 4 years. In many pts, there is significant improvement in co-morbid conditions including type 2 diabetes mellitus, hypertension, sleep apnea, hyperlipidemia, and cardiovascular events. The metabolic benefits appear to be the combined result of weight loss and physiologic responses of gut hormones and adipose tissue metabolism. Complications include stomal stenosis, marginal ulcers, and dumping syndrome. Procedures with a malabsorptive component require lifelong supplementation of micronutrients (iron, folate, calcium, vitamins B₁₂ and D) and are associated with a risk of islet cell hyperplasia and hypoglycemia.

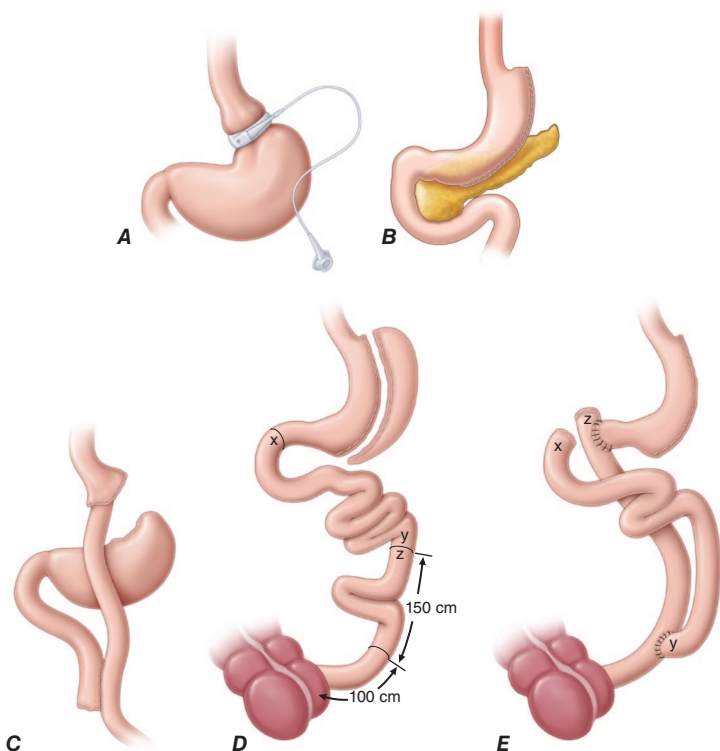


FIGURE 175-1 Bariatric surgical procedures. Examples of operative interventions used for surgical manipulation of the gastrointestinal tract. **A.** Laparoscopic adjustable gastric banding. **B.** Laparoscopic sleeve gastrectomy. **C.** The Roux-en-Y gastric bypass. **D.** Biliopancreatic diversion with duodenal switch. **E.** Biliopancreatic diversion. (From Kendrick ML, Dakin GF: *Mayo Clin Proc* 815:518, 2006; with permission.)

176 Diabetes Mellitus

■ ETIOLOGY AND PREVALENCE

Diabetes mellitus (DM) comprises a group of metabolic disorders that share the common feature of hyperglycemia. DM is currently classified on the basis of the pathogenic process that leads to hyperglycemia. Type 1 DM is characterized by insulin deficiency and a tendency to develop ketosis—it is most commonly caused by autoimmune destruction of the pancreatic islet beta cells. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and excessive hepatic glucose production—it is strongly associated with obesity. Other specific types include DM caused by genetic defects (maturity-onset diabetes of the young [MODY] and other rare monogenic disorders), diseases of the exocrine pancreas (chronic

pancreatitis, cystic fibrosis, hemochromatosis), endocrinopathies (acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism), drugs (nicotinic acid, glucocorticoids, thiazides, protease inhibitors), and pregnancy (gestational DM). The phenotype of these monogenetic and secondary types of DM typically resembles type 2 DM; its severity depends on the degree of beta cell dysfunction and prevailing insulin resistance.

The worldwide prevalence of DM is increasing rapidly; type 2 DM frequency in particular is rising in parallel with the epidemic of obesity (Chap. 175). In the past two decades, the worldwide prevalence of DM has increased more than 10-fold, from as estimated 30 million to >400 million cases. In the United States, the adult prevalence of DM ranges from 7–11% of the population, increasing with age. A significant portion of persons with DM are undiagnosed.

DM is attended by serious morbidity and significant mortality; it is consistently a leading cause of death worldwide.

■ DIAGNOSIS

Criteria for the diagnosis of DM are summarized in Table 176-1.

Screening with a fasting plasma glucose level or HbA_{1c} is recommended every 3 years for individuals aged ≥45, as well as for younger individuals who are overweight (body mass index ≥25 kg/m²) and have one or more additional risk factors (Table 176-2).

The *metabolic syndrome* (also known as *insulin resistance syndrome* or *syndrome X*) is a term used to describe a commonly found constellation of metabolic derangements that includes insulin resistance (with or without diabetes), hypertension, dyslipidemia, central or visceral obesity, and endothelial dysfunction and is associated with accelerated cardiovascular disease (Chap. 120).

■ CLINICAL FEATURES

Common presenting symptoms of DM include polyuria, polydipsia, weight loss, fatigue, weakness, blurred vision, frequent superficial infections, and poor wound healing. In early type 2 DM, symptoms may be more subtle and consist of fatigue, poor wound healing, and paresthesias. The lack of symptoms is the main reason for the delayed diagnosis of type 2 DM. Many pts are diagnosed based on screening or during blood tests taken for other reasons. A complete medical history should be obtained with special emphasis on weight, exercise, smoking, ethanol use, family

TABLE 176-1 Criteria for the Diagnosis of Diabetes Mellitus

- Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL)^a or
- Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL)^b or
- Hemoglobin A_{1c} ≥ 6.5%^c or
- 2-h plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test^d

^aRandom is defined as without regard to time since the last meal.

^bFasting is defined as no caloric intake for at least 8 h.

^cHemoglobin A_{1c} test should be performed in a laboratory using a method approved by the National Glycohemoglobin Standardization Program and correlated to the reference assay of the Diabetes Control and Complications Trial. Point-of-care hemoglobin A_{1c} should not be used for diagnostic purposes.

^dThe test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water, not recommended for routine clinical use.

Note: In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

Source: Adapted from American Diabetes Association: 2. Classification and diagnosis of diabetes. *Diabetes Care* 40(Suppl 1):S11–24, 2017.

TABLE 176-2 Risk Factors for Type 2 Diabetes Mellitus

Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
Overweight or obese (BMI ≥ 25 kg/m ² , ≥ 23 kg/m ² in Asian Americans, or other ethnically relevant definition for overweight)
Physical inactivity
Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
Previously identified with IFG, IGT, or a hemoglobin A _{1c} of 5.7–6.4%
History of GDM
Hypertension (blood pressure $\geq 140/90$ mmHg)
HDL cholesterol level < 35 mg/dL (0.90 mmol/L) and/or a triglyceride level > 250 mg/dL (2.82 mmol/L)
Polycystic ovary syndrome or acanthosis nigricans
History of cardiovascular disease

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Source: Adapted from American Diabetes Association: 2. Classification and diagnosis of diabetes. *Diabetes Care* 40(Suppl 1): S13, 2017.

history of DM, and risk factors for cardiovascular disease. In a pt with established DM, assessment of prior diabetes care, HbA_{1c} levels, self-monitoring blood glucose results, frequency of hypoglycemia, and pt's knowledge about DM should be obtained. Special attention should be given on physical examination to retinal examination, bp, foot examination (including vibratory sensation and monofilament testing), peripheral pulses, and insulin injection sites. Acute complications of DM that may be seen on presentation include diabetic ketoacidosis (DKA) (type 1 DM) and hyperglycemic hyperosmolar state (type 2 DM) ([Chap. 25](#)).

The chronic complications of DM are listed below:

- *Ophthalmologic:* nonproliferative or proliferative diabetic retinopathy, macular edema, rubeosis of iris, glaucoma, cataracts
- *Renal:* proteinuria, end-stage renal disease (ESRD), type IV renal tubular acidosis
- *Neurologic:* distal symmetric polyneuropathy, polyradiculopathy, mononeuropathy, autonomic neuropathy
- *Gastrointestinal:* fatty liver, gastroparesis, diarrhea, constipation
- *Genitourinary:* cystopathy, erectile dysfunction, female sexual dysfunction, vaginal candidiasis
- *Cardiovascular:* coronary artery disease, congestive heart failure, peripheral vascular disease, stroke
- *Lower extremity:* foot deformity (hammer toe, claw toe, Charcot foot), ulceration, amputation
- *Dermatologic:* Infections (folliculitis, furunculosis, cellulitis), necrobiosis, poor healing, ulcers, gangrene
- *Dental:* Periodontal disease

TREATMENT

Diabetes Mellitus

Optimal treatment of DM requires more than plasma glucose management. Comprehensive diabetes care should also detect and manage DM-specific complications and modify risk factors for DM-associated diseases. The pt with type 1

TABLE 176-3 Properties of Insulin Preparations^a

PREPARATION	TIME OF ACTION		
	ONSET, h	PEAK, h	EFFECTIVE DURATION, h
Short-Acting^b			
Aspart	<0.25	0.5–1.5	2–4
Glulisine	<0.25	0.5–1.5	2–4
Lispro ^f	<0.25	0.5–1.5	2–4
Regular ^g	0.5–1.0	2–3	3–6
Inhaled human insulin	0.5–1.0	2–3	3
Long-Acting^g			
Degludec	1–9	— ^c	42 ^d
Detemir	1–4	— ^c	12–24 ^d
Glargine ^f	2–4	— ^c	20–24
NPH	2–4	4–10	10–16
Examples of Insulin Combinations^e			
75/25–75% protamine lispro, 25% lispro	<0.25	Dual ^f	10–16
70/30–70% protamine aspart, 30% aspart	<0.25	Dual ^f	15–18
50/50–50% protamine lispro, 50% lispro	<0.25	Dual ^f	10–16
70/30–70% NPH, 30% regular	0.5–1	Dual ^f	10–16
Combination of long-acting insulin and GLP-1 receptor agonist	See text		

^aInjectable insulin preparations (with exception of inhaled formulation) available in the United States; others are available in the United Kingdom and Europe.

^bFormulation with niacinamide has a slightly more rapid onset and offset.

^cDegludec, detemir, and glargine have minimal peak activity.

^dDuration is dose-dependent.

^eOther insulin combinations are available.

^fDual: two peaks—one at 2–3 h and the second one several hours later.

^gAlso available in concentrations >U-100.

or type 2 DM should receive education about nutrition, exercise, care of diabetes during illness, and medications to lower the plasma glucose. In general, the target HbA_{1c} level should be <7.0%, although individual considerations (age, ability to implement a complex treatment regimen, risk of hypoglycemia, and presence of other medical conditions) should also be taken into account. Intensive therapy reduces long-term complications but is associated with more frequent and more severe hypoglycemic episodes. Goal preprandial capillary plasma glucose levels should be 4.4–7.2 mmol/L (80–130 mg/dL) and postprandial levels should be <10.0 mmol/L (<180 mg/dL) 1–2 h after a meal.

In general, pts with type 1 DM require 0.4–1.0 U/kg per day of insulin divided into multiple doses. Combinations of insulin preparations with different times of onset and duration of action should be used (Table 176-3). Preferred regimens include injection of long-acting insulin at bedtime with preprandial short-acting insulin (lispro, glulisine, or insulin aspart) or continuous SC insulin using an infusion device. Pramlintide, an injectable amylin analogue, can be used as adjunct therapy to control postprandial glucose excursions.

Pts with type 2 DM may be managed with diet and exercise alone or in conjunction with oral glucose-lowering agents, insulin, or a combination of oral agents and insulin. The classes of oral glucose-lowering agents and dosing regimens are listed in Table 176-4. In addition, injectable glucagon-like peptide 1

TABLE 176-4 Agents Used for Treatment of Type 1 or Type 2 Diabetes

	MECHANISM OF ACTION	EXAMPLES ^a	HbA _{1c} REDUCTION (%) ^b	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
Oral						
Biguanides ^{c*}	↓ Hepatic glucose production	Metformin	1–2	Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, ↓ CV events	Diarrhea, nausea, lactic acidosis, vitamin B12 deficiency	Renal insufficiency (see text for GFR <45 mL/min), CHF, radiographic contrast studies, hospitalized pts, acidosis
α-Glucosidase inhibitors ^{c**}	↓ GI glucose absorption	Acarbose, miglitol, voglibose	0.5–0.8	Reduce postprandial glycemia	GI flatulence, liver function tests	Renal/liver disease
Dipeptidyl peptidase IV inhibitors ^{c***}	Prolong endogenous GLP-1 action; ↑ Insulin, ↓ glucagon	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin	0.5–0.8	Well tolerated, do not cause hypoglycemia	Angioedema/urticarial and immune-mediated dermatologic effects	Reduced dose with renal disease
Insulin secretagogues: Sulfonylureas ^{c*}	↑ Insulin secretion	Glibornuride, gliclazide, glimepiride, glipizide, glyliquidone, glyburide, glycopyramide	1–2	Short onset of action, lower postprandial glucose, inexpensive	Hypoglycemia, weight gain	Renal/liver disease

Insulin secretagogues: Nonsulfonylureas ^{c,***}	↑ Insulin secretion	Mitiglinide nateglinide, repaglinide	0.5–1.0	Short onset of action, lower postprandial glucose	Hypoglycemia	Renal/liver disease
Sodium-glucose cotransporter 2 inhibitors ^{***}	↑ renal glucose excretion	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	0.5–1.0	Do not cause hypoglycemia, ↓ weight and BP; see text for CVD effect	Urinary and genital infections, polyuria, dehydration, exacerbate tendency to hyperkalemia and DKA; see text	Moderate renal insufficiency, insulin-deficient DM
Thiazolidinediones ^{c,***}	↓ Insulin resistance, ↑ glucose utilization	Pioglitazone, rosiglitazone	0.5–1.4	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures, macular edema	CHF, liver disease
Parenteral						
Amylin agonists ^{c,d,***}	Slow gastric emptying, ↓ glucagon	Pramlintide	0.25–0.5	Reduce postprandial glycemia, weight loss	Injection, nausea, ↑ risk of hypoglycemia with insulin	Agents that also slow GI motility
GLP-1 receptor agonists ^{c,***}	↑ Insulin, ↓ glucagon, slow gastric emptying, satiety	Albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide	0.5–1.0	Weight loss, do not cause hypoglycemia; see text for CVD effect	Injection, nausea, ↑ risk of hypoglycemia with insulin secretagogues	Renal disease, agents that also slow GI motility; medullary carcinoma of thyroid, pancreatic disease

(Continued)

TABLE 176-4 Agents Used for Treatment of Type 1 or Type 2 Diabetes (Continued)

	MECHANISM OF ACTION	EXAMPLES ^a	HbA _{1c} REDUCTION (%) ^b	AGENT-SPECIFIC ADVANTAGES	AGENT-SPECIFIC DISADVANTAGES	CONTRAINDICATIONS
Insulin ^{c,d****}	↑ Glucose utilization, ↓ hepatic glucose production, and other anabolic actions	See text	Not limited	Known safety profile	Injection, weight gain, hypoglycemia	
Medical nutrition therapy and physical activity^c	↓ Insulin resistance, ↑ insulin secretion	Low-calorie, low-fat diet, exercise	1–3	Other health benefits	Compliance difficult, long-term success low	

^aExamples are approved for use in the United States; others are available in other countries. Examples may not include all agents in the class.

^bHbA_{1c} reduction (absolute) depends partly on starting HbA_{1c}.

^cUsed for treatment of type 2 diabetes.

^dUsed in conjunction with insulin for treatment of type 1 diabetes. Cost of agent in the United States: *low, **moderate, ***high, ****variable.

Note: Some agents used to treat type 2 DM are not included in table (see text).

Abbreviations: ACE, angiotensin-converting enzyme; CHF, congestive heart failure; CV, cardiovascular; GI, gastrointestinal; HbA_{1c}, hemoglobin A_{1c}.

(GLP-1, an incretin) analogues may be used in combination with metformin or sulfonylureas. A reasonable treatment algorithm for initial therapy proposes metformin as initial therapy because of its efficacy (1–2% decrease in HbA_{1c}), known side-effect profile, and relatively low cost (Fig. 176-1). Metformin has the advantage that it promotes mild weight loss, lowers insulin levels, improves the lipid profile slightly, lowers cancer risk, and does not cause hypoglycemia when used as monotherapy, although it is contraindicated in renal insufficiency, congestive heart failure, any form of acidosis, liver disease, or severe hypoxia, and should be temporarily discontinued in pts who are seriously ill or receiving radiographic contrast material. Metformin therapy can be followed by addition of a second oral agent (insulin secretagogue, DPP-IV inhibitor, thiazolidinedione, α -glucosidase inhibitor, or SGLT2 inhibitor). Combinations of two oral agents may be used with additive effects, with stepwise addition of bedtime insulin or a third oral agent if adequate control is not achieved. As endogenous insulin production falls, multiple injections of long-acting and short-acting insulin may be required, as in type 1 DM. Individuals who require >1 U/kg per day

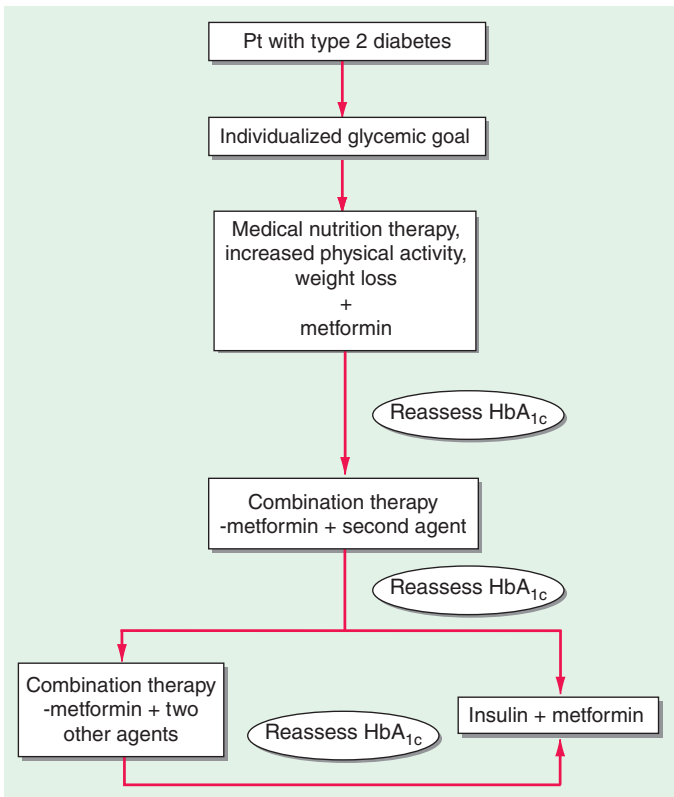


FIGURE 176-1 Glycemic management of type 2 diabetes. Agents that can be combined with metformin include insulin secretagogues, thiazolidinediones, α -glucosidase inhibitors, DPP-IV inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and insulin. HbA_{1c} , hemoglobin HbA_{1c} .

of long-acting insulin should be considered for combination therapy with an insulin-sensitizing agent such as metformin or a thiazolidinedione. Insulin-requiring type 2 DM pts may also benefit from addition of pramlintide. Based on demonstrations of a beneficial cardiovascular effect in certain individuals with type 2 DM and CVD, or at high risk of CVD, empagliflozin and liraglutide (and possibly canagliflozin) should now be considered in these populations.

Bariatric surgery should be considered in selected pts (**Chap. 175**).

The morbidity and mortality of DM-related complications can be greatly reduced by timely and consistent surveillance procedures (**Table 176-5**). A routine urinalysis may be performed as an initial screen for diabetic nephropathy. If it is positive for protein, quantification of protein on a 24-h urine collection should be performed. If the urinalysis is negative for protein, a spot collection for albuminuria should be performed (present if 30–300 $\mu\text{g}/\text{mg}$ creatinine on two of three tests within a 3- to 6-month period). A resting ECG should be performed in adults, with more extensive cardiac testing for high-risk pts. Therapeutic goals to prevent complications of DM include management of proteinuria with ACE inhibitor or angiotensin receptor blocker therapy, bp control ($<140/90$ mmHg, and $<130/80$ in individuals with CVD or chronic kidney disease), and dyslipidemia management (LDL <2.6 mmol/L [<100 mg/dL], HDL >1.1 mmol/L [>40 mg/dL] in men and >1.38 mmol/L [50 mg/dL] in women, triglycerides <1.7 mmol/L [<150 mg/dL]). In addition, any diabetic pt >40 years should take a statin, regardless of the LDL cholesterol, and in those with existing cardiovascular disease, the LDL target should be <1.8 mmol/L (70 mg/dL). If LDL cholesterol remains elevated despite statin therapy in a high risk, consider addition of ezetimibe or PCSK9 inhibitor.

TABLE 176-5 Guidelines for Ongoing, Comprehensive Medical Care for Pts with Diabetes

- Individualized glycemic goal and therapeutic plan
- Self-monitoring of blood glucose (individualized frequency)
- HbA_{1c} testing (2–4 times/year)
- Lifestyle management in the care of diabetes, including:
 - Diabetes-self-management education and support
 - Nutrition therapy
 - Physical activity
 - Psychosocial care, including evaluation for depression, anxiety
- Detection, prevention, or management of diabetes-related complications, including:
 - Diabetes-related eye examination (annual or biannual)
 - Diabetes-related foot examination (1–2 times/year by provider; daily by pt)
 - Diabetes-related neuropathy examination (annual)
 - Diabetes-related kidney disease testing (annual)
- Manage or treat diabetes-relevant conditions, including:
 - Blood pressure (assess quarterly)
 - Lipids (annual)
 - Consider antiplatelet therapy
 - Influenza/pneumococcal/hepatitis B immunizations

Abbreviation: HbA_{1c}, hemoglobin A_{1c}.

MANAGEMENT OF THE HOSPITALIZED PT

The goals of diabetes management during hospitalization are near-normal glycemic control, avoidance of hypoglycemia, and transition back to the outpatient diabetes treatment regimen. Pts with type 1 DM undergoing general anesthesia and surgery, or with serious illness, should receive continuous insulin, either through an IV insulin infusion or by SC administration of a reduced dose of long-acting insulin. Short-acting insulin alone is insufficient to prevent the onset of diabetic ketoacidosis. Oral hypoglycemic agents should be discontinued in most pts with type 2 DM at the time of hospitalization. Either regular insulin infusion (0.05–0.15 U/kg per hour) or a reduced dose (by 30–50%) of long-acting insulin and short-acting insulin (held, or reduced by 30–50%), with infusion of a solution of 5% dextrose, should be administered when pts are NPO for a procedure. A regimen of long- and short-acting SC insulin should be used in type 2 pts who are eating. The glycemic goal for hospitalized pts with DM should be a preprandial glucose of <7.8 mmol/L (<140 mg/dL) and <10 mmol/L (<180 mg/dL) at post-meal times. For critically ill pts, glucose levels of 7.8–10.0 mmol/L (140–180 mg/dL) are recommended. Those with DM undergoing radiographic procedures with contrast dye should be well hydrated before and after dye exposure, and the serum creatinine should be monitored after the procedure.

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Disorders of the Male Reproductive System



The testes produce sperm and testosterone. Inadequate production of sperm can occur in isolation or in the presence of androgen deficiency, which impairs spermatogenesis secondarily.

ANDROGEN DEFICIENCY

■ ETIOLOGY

Androgen deficiency can be due to either testicular failure (*primary hypogonadism*) or hypothalamic-pituitary defects (*secondary hypogonadism*).

Primary hypogonadism is diagnosed when testosterone levels are low and gonadotropin levels (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) are high. Klinefelter's syndrome is the most common cause (~1 in 1000 male births) and is due to the presence of one or more extra X chromosomes, usually a 47,XXY karyotype. Other genetic causes of testicular development, androgen biosynthesis, or androgen action are uncommon. Acquired primary testicular failure usually results from viral orchitis but may be due to trauma, testicular torsion, cryptorchidism, radiation damage, or systemic diseases such as amyloidosis, Hodgkin's disease, sickle cell disease, or granulomatous diseases. Testicular failure can occur as a part of polyglandular autoimmune failure syndrome. Malnutrition, AIDS, renal failure, liver cirrhosis, myotonic dystrophy, paraplegia, and toxins such as alcohol, marijuana, heroin, methadone, lead, and antineoplastic and chemotherapeutic agents also can cause testicular failure. Testosterone synthesis may be blocked by drugs such as ketoconazole or abiraterone, and testosterone action may be blocked at the androgen receptor level by spironolactone or cimetidine.

Secondary hypogonadism is diagnosed when levels of both testosterone and gonadotropins are low (*hypogonadotropic hypogonadism*). Kallmann syndrome is

due to maldevelopment of neurons producing gonadotropin-releasing hormone (GnRH) and is characterized by GnRH deficiency, low levels of LH and FSH, and anosmia. Several other types of GnRH deficiency or gonadotropin deficiency occur without anosmia. Acquired causes of isolated hypogonadotropic hypogonadism include critical illness, malnutrition, excessive stress, obesity, Cushing's syndrome, opioid and marijuana use, hemochromatosis, and hyperprolactinemia (due to pituitary adenomas or drugs such as phenothiazines). Destruction of the pituitary gland by tumors, infection, trauma, or metastatic disease causes hypogonadism in conjunction with deficiency of other pituitary hormones (see [Chap. 171](#)). Normal aging is associated with a progressive decline of testosterone production, which is due to downregulation of the entire hypothalamo-pituitary-testicular axis.

■ CLINICAL FEATURES

The history should focus on developmental stages such as puberty and growth spurts, as well as androgen-dependent events such as early morning erections, frequency and intensity of sexual thoughts, and frequency of masturbation or intercourse. The physical examination should focus on secondary sex characteristics such as hair growth on the face, axilla, chest, and pubic regions; gynecomastia; testicular volume; prostate; and height and body proportions. Eunuchoidal proportions are defined as an arm span >2 cm greater than height and suggest that androgen deficiency occurred prior to epiphyseal fusion. Normal testicular size ranges from 3.5 to 5.5 cm in length, which corresponds to a volume of 12–25 mL. The presence of varicocele should be sought by palpation of the testicular veins with the pt standing. Pts with Klinefelter's syndrome have small (1–2 mL), firm testes.

A morning total testosterone level <10.4 nmol/L (<300 ng/dL), in association with symptoms, suggests testosterone deficiency. A level of >12.1 nmol/L (>350 ng/dL) makes the diagnosis of androgen deficiency unlikely. In men with testosterone levels between 6.9 and 12.1 nmol/L (200 and 350 ng/dL), the total testosterone level should be repeated and a free testosterone level should be measured by a reliable method. In older men and in pts with other clinical states that are associated with alterations in sex hormone-binding globulin levels, a direct measurement of free testosterone can be useful to confirm testosterone deficiency. When androgen deficiency has been found, LH should be measured to classify the pt as having primary (high LH) or secondary (low or inappropriately normal LH) hypogonadism. In men with primary hypogonadism of unknown cause, a karyotype should be performed to exclude Klinefelter's syndrome. Measurement of a prolactin level and MRI of the hypothalamic-pituitary region should be considered in men with secondary hypogonadism. Gynecomastia in the absence of androgen deficiency should be further evaluated ([Fig. 177-1](#)).

TREATMENT

Androgen Deficiency

Treatment of hypogonadal men with androgens restores normal male secondary sexual characteristics (beard, body hair, external genitalia), male sexual drive, and masculine somatic development (hemoglobin, muscle mass), but not fertility. Administration of gradually increasing doses of testosterone is recommended for disorders in which hypogonadism occurred prior to puberty. Testosterone levels in the normal range may be achieved through daily application of transdermal testosterone patches (5–10 mg/d) or gel (50–100 mg/d), parenteral administration of a long-acting testosterone ester (e.g., 150–200 mg testosterone enanthate at 1- to 3-week intervals), injectable long-acting testosterone undecanoate in oil (after loading, 750 mg IM q10wks), or buccal testosterone tablets (30 mg/d).

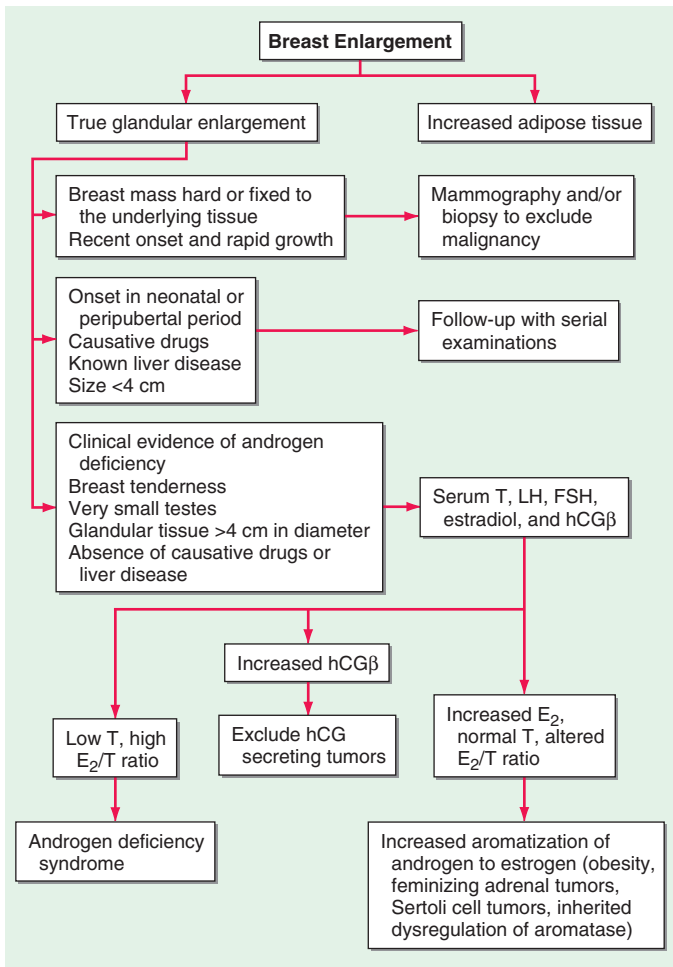


FIGURE 177-1 Evaluation of gynecomastia. E₂, 17β-estradiol; FSH, follicle-stimulating hormone; hCGβ, human chorionic gonadotropin β; LH, luteinizing hormone; T, testosterone.

Hct should be monitored initially during testosterone therapy and the dose lowered if Hct is >54%. Prostate cancer, severe symptoms of lower urinary tract obstruction, baseline Hct >50%, severe sleep apnea, and class IV congestive heart failure are contraindications for androgen replacement. Gonadotropin therapy for secondary hypogonadism should be reserved for fertility induction.

MALE INFERTILITY

■ ETIOLOGY

Male infertility plays a role in 25% of infertile couples (couples who fail to conceive after 1 year of unprotected intercourse). Known causes of male

infertility include primary hypogonadism (30–40%), disorders of sperm transport (10–20%), and secondary hypogonadism (2%), with an unknown etiology in up to half of men with suspected male factor infertility. Impaired spermatogenesis occurs with testosterone deficiency but may also be present without testosterone deficiency. Y chromosome microdeletions and substitutions, viral orchitis, tuberculosis, STDs, radiation, chemotherapeutic agents, and environmental toxins have all been associated with isolated impaired spermatogenesis. Prolonged elevations of testicular temperature, as in varicocele, in cryptorchidism, or after an acute febrile illness, may impair spermatogenesis. Ejaculatory obstruction can be a congenital (cystic fibrosis, in utero diethylstilbestrol exposure, or idiopathic) or acquired (vasectomy, accidental ligation of the vas deferens, or obstruction of the epididymis). Androgen abuse by male athletes can lead to testicular atrophy and a low sperm count.

■ CLINICAL FEATURES

Evidence of hypogonadism may or may not be present. Testicular size and consistency may be abnormal, and a varicocele may be apparent on palpation. When the seminiferous tubules are damaged prior to puberty, the testes are small (usually <12 mL) and firm, whereas postpubertal damage causes the testes to be soft (the capsule, once enlarged, does not contract to its previous size). The key diagnostic test is a *semen analysis*. Sperm counts of <13 million/mL, motility of <32%, and <9% normal morphology are associated with subfertility. Testosterone levels should be measured if the sperm count is low on repeated examination or if there is clinical evidence of hypogonadism.

TREATMENT

Male Infertility

Men with primary hypogonadism occasionally respond to androgen therapy if there is minimal damage to the seminiferous tubules, whereas those with secondary hypogonadism require gonadotropin therapy to achieve fertility. Fertility occurs in about half of men with varicocele who undergo surgical repair. In vitro fertilization is an option for men with mild to moderate defects in sperm quality; intracytoplasmic sperm injection (ICSI) has been a major advance for men with severe defects in sperm quality.

ERECTILE DYSFUNCTION

■ ETIOLOGY

Erectile dysfunction (ED) is the failure to achieve erection, ejaculation, or both. It affects 10–25% of middle-aged and elderly men. ED may result from three basic mechanisms: (1) failure to initiate (psychogenic, endocrinologic, or neurogenic); (2) failure to fill (arteriogenic); or (3) failure to store adequate blood volume within the lacunar network (venoocclusive dysfunction). Diabetic, atherosclerotic, and drug-related causes account for >80% of cases of ED in older men. The most common organic cause of ED is vasculogenic; 35–75% of men with diabetes have ED due to a combination of vascular and neurologic complications. Psychogenic causes of ED include performance anxiety, depression, relationship conflict, sexual inhibition, history of sexual abuse in childhood, and fear of pregnancy or sexually transmitted disease. Among the antihypertensive agents, the thiazide diuretics and beta blockers have been implicated most frequently. Estrogens, GnRH agonists and antagonists, H₂ antagonists, and spironolactone suppress gonadotropin production or block androgen action. Antidepressant and

antipsychotic agents—particularly neuroleptics, tricyclics, and selective serotonin reuptake inhibitors—are associated with erectile, ejaculatory, orgasmic, and sexual desire difficulties. Recreational drugs, including ethanol, cocaine, and marijuana, also may cause ED. Any disorder that affects the sacral spinal cord or the sensory nerves or autonomic fibers innervating the penis may lead to ED.

■ CLINICAL FEATURES

Men with sexual dysfunction may complain of loss of libido, inability to initiate or maintain an erection, ejaculatory failure, premature ejaculation, or inability to achieve orgasm, but frequently are embarrassed to bring up the subject unless specifically asked by the physician. Initial questions should focus on the onset of symptoms, the presence and duration of partial erections, the progression of ED, and ejaculation. Psychosocial history, libido, relationship issues, sexual orientation, and sexual practices should be part of the clinical assessment. A history of nocturnal or early morning erections is useful for distinguishing physiologic from psychogenic ED. Relevant risk factors should be identified, such as diabetes mellitus, coronary artery disease, lipid disorders, hypertension, peripheral vascular disease, smoking, alcoholism, and endocrine or neurologic disorders. The pt's surgical history should be explored, with an emphasis on bowel, bladder, prostate, or vascular procedures. Evaluation includes a detailed general as well as genital physical examination. Penile abnormalities (Peyronie's disease), testicular size, and gynecomastia should be noted. Peripheral pulses should be palpated, and bruits should be sought. Neurologic examination should assess anal sphincter tone, perineal sensation, and bulbocavernosus reflex. Serum testosterone and prolactin should be measured. Penile arteriography, electromyography, or penile Doppler ultrasound is occasionally performed.

TREATMENT

Erectile Dysfunction

Correction of the underlying disorders or discontinuation of responsible medications should be attempted as an initial step. Oral inhibitors of phosphodiesterase-5 (sildenafil, tadalafil, vardenafil, and avanafil) enhance erections after sexual stimulation, with an onset of approximately 60–120 min ([Table 177-1](#)). They are contraindicated in men receiving any form of nitrate therapy and should be avoided in those with congestive heart failure. Vacuum constriction devices or

TABLE 177-1 PDE5 Inhibitors for Sexual Dysfunction

DRUG	T 1/2	DOSE	ADVERSE EFFECTS	CONTRAINDICATIONS
Sildenafil	2–5 h	25–100 mg Starting dose 50 mg	Headache, flushing, dyspepsia Nasal congestion, altered vision	Nitrates Hypotension CV risk factors Retinitis pigmentosa Change dose with some antiretrovirals Should be on stable dose of alpha-blockers

(Continued)

TABLE 177-1 PDE5 Inhibitors for Sexual Dysfunction (Continued)

DRUG	T 1/2	DOSE	ADVERSE EFFECTS	CONTRAINDICATIONS
Vardenafil	4.5 h	5–10 mg	Headache, flushing, rhinitis, dyspepsia	Same as sildenafil May have minor prolongation of QT interval Concomitant use of Class I anti-arrhythmic
Tadalafil	17.5 h	10 mg, 20 mg 2.5 or 5 mg for daily dose	Headache, dyspepsia, back pain Nasal congestion, myalgia	Same as sildenafil
Avandafil	3–5 h	50 mg, 100 mg, and 200 mg dose	Headache, flushing, nasal congestion, nasopharyngitis, back pain	Same as sildenafil

injection of alprostadil into the urethra or corpora cavernosa may also be effective. The insertion of a penile prosthesis is reserved for pts with refractory ED.

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Disorders of the Female Reproductive System



The pituitary hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), stimulate ovarian follicular development and result in ovulation at about day 14 of the 28-day menstrual cycle.

AMENORRHEA

■ ETIOLOGY

Amenorrhea refers to the absence of menstrual periods. It is classified as *primary*, if menstrual bleeding has never occurred by age 15 in the absence of hormonal treatment, or *secondary*, if menstrual periods are absent for >3 months in a woman with previous periodic menses. Pregnancy should be excluded in women of childbearing age with amenorrhea, even when history and physical examination are not suggestive. *Oligomenorrhea* is defined as a cycle length of >35 days or <10 menses per year. Both the frequency and amount of bleeding are irregular in oligomenorrhea. Frequent or heavy irregular bleeding is termed *dysfunctional uterine bleeding* if anatomic uterine lesions or a bleeding diathesis has been excluded.

The causes of primary and secondary amenorrhea overlap, and it is generally more useful to classify disorders of menstrual function into disorders of the uterus and outflow tract and different causes for abnormal ovulation (Fig. 178-1).

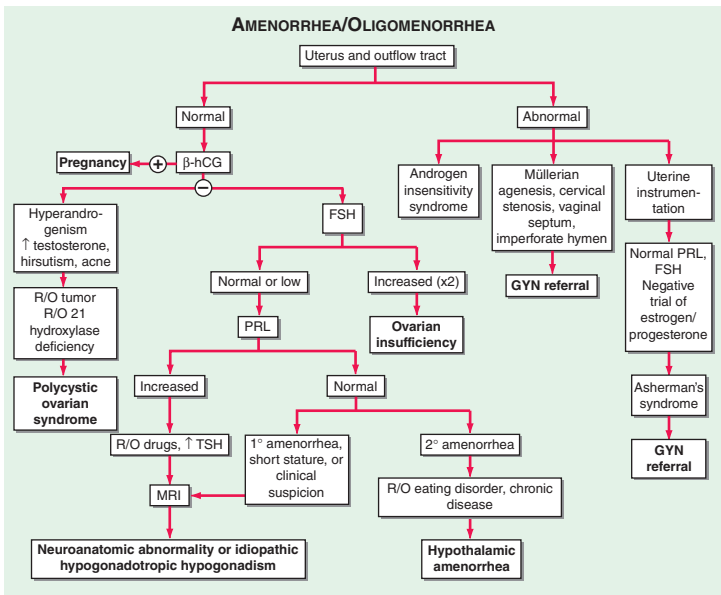


FIGURE 178-1 Algorithm for evaluation of amenorrhea. β -hCG, beta-human chorionic gonadotropin; FSH, follicle-stimulating hormone; GYN, gynecologist; PRL, prolactin; R/O, rule out; TSH, thyroid-stimulating hormone.

Anatomic defects of the outflow tract that prevent vaginal bleeding include absence of vagina or uterus, imperforate hymen, transverse vaginal septae, and cervical stenosis.

Women with amenorrhea and low FSH and LH levels have hypogonadotropic hypogonadism due to disease of either the hypothalamus or the pituitary. Hypothalamic causes include congenital idiopathic hypogonadotropic hypogonadism, hypothalamic lesions (craniopharyngiomas and other tumors, tuberculosis, sarcoidosis, metastatic tumors), hypothalamic trauma or irradiation, vigorous exercise, eating disorders, stress, and chronic debilitating diseases (end-stage renal disease, malignancy, malabsorption). The most common form of hypothalamic amenorrhea is functional, reversible gonadotropin-releasing hormone (GnRH) deficiency due to psychological or physical stress, including excess exercise, malnutrition, and anorexia nervosa. Disorders of the pituitary include rare developmental defects, pituitary adenomas, granulomas, postradiation hypopituitarism, and Sheehan's syndrome. They can lead to amenorrhea by two mechanisms: direct interference with gonadotropin production, or inhibition of GnRH secretion via excess prolactin production ([Chap. 171](#)).

Women with amenorrhea and high FSH levels have ovarian failure, which may be due to Turner's syndrome, pure gonadal dysgenesis, premature ovarian insufficiency, the resistant-ovary syndrome, and chemotherapy or radiation therapy for malignancy. The diagnosis of premature ovarian insufficiency is applied to women who cease menstruating before age 40.

Polycystic ovarian syndrome (PCOS) is characterized by the presence of clinical or biochemical hyperandrogenism (hirsutism, acne, male pattern baldness) in association with amenorrhea or oligomenorrhea. The metabolic syndrome and infertility are often present; these features are worsened with coexistent obesity.

Additional disorders with a similar presentation include excess androgen production from adrenal or ovarian tumors and adult-onset congenital adrenal hyperplasia. Hyperthyroidism may be associated with oligo- or amenorrhea; hypothyroidism more typically with metrorrhagia.

■ DIAGNOSIS

The initial evaluation involves careful physical examination including assessment of hyperandrogenism, serum or urine human chorionic gonadotropin (hCG), and serum FSH levels (Fig. 178-1). Anatomic defects may be diagnosed by physical examination, though hysterosalpingography or direct visual examination by hysteroscopy is often required. A karyotype should be performed when gonadal dysgenesis is suspected. The diagnosis of PCOS is based on the coexistence of chronic anovulation and androgen excess, after ruling out other etiologies for these features. The evaluation of pituitary function and hyperprolactinemia is described in [Chap. 171](#). In the absence of a known etiology for hypogonadotropic hypogonadism, MRI of the pituitary-hypothalamic region should be performed when gonadotropins are low or inappropriately normal.

TREATMENT

Amenorrhea

Disorders of the outflow tract are managed surgically. Decreased estrogen production, whether from ovarian failure or hypothalamic/pituitary disease, should be treated with cyclic estrogens, either in the form of oral contraceptives or conjugated estrogens (0.625–1.25 mg/d PO) and medroxyprogesterone acetate (2.5 mg/d PO or 5–10 mg during the last 5 days of the month). PCOS may be treated with medications to induce periodic withdrawal menses (medroxyprogesterone acetate 5–10 mg or progesterone 200 mg daily for 10–14 days of each month, or oral contraceptive agents) and weight reduction, along with treatment of hirsutism and, if desired, ovulation induction (see below). Individuals with PCOS may benefit from insulin-sensitizing drugs, such as metformin, and should be screened for diabetes mellitus. Pts with ovarian failure can consider oocyte donation, which has a high rate of success in this population.

PELVIC PAIN

■ ETIOLOGY

Pelvic pain may be associated with normal or abnormal menstrual cycles and may originate in the pelvis or be referred from another region of the body. A high index of suspicion must be entertained for extrapelvic disorders that refer to the pelvis, such as appendicitis, diverticulitis, cholecystitis, intestinal obstruction, and urinary tract infections. A thorough history including the type, location, radiation, and status with respect to increasing or decreasing severity can help to identify the cause of acute pelvic pain. Associations with vaginal bleeding, sexual activity, defecation, urination, movement, or eating should be sought. Determination of whether the pain is acute versus chronic, constant versus spasmodic, and cyclic versus noncyclic will direct further investigation ([Table 178-1](#)).

■ ACUTE PELVIC PAIN

Pelvic inflammatory disease most commonly presents with bilateral lower abdominal pain. Testing for *C. trachomatis* and *N. gonorrhoea* should be considered for women at increased risk. Unilateral pain suggests adnexal pathology from rupture, bleeding, or torsion of ovarian cysts, or, less commonly, neoplasms of

TABLE 178-1 Causes of Pelvic Pain

	ACUTE	CHRONIC
Cyclic pelvic pain		Mittelschmerz Dysmenorrhea Endometriosis
Noncyclic pelvic pain	Pelvic inflammatory disease Ruptured or hemorrhagic ovarian cyst, endometrioma, or ovarian torsion Ectopic pregnancy Endometritis Acute growth or degeneration of uterine myoma Threatened abortion	Pelvic congestion syndrome Adhesions and retroversion of the uterus Pelvic malignancy Vulvodynia Chronic pelvic inflammatory disease Tuberculous salpingitis History of sexual abuse

the ovary, fallopian tubes, or paraovarian areas. Ectopic pregnancy is associated with right- or left-sided lower abdominal pain, vaginal bleeding, and menstrual cycle abnormalities, with clinical signs appearing 6–8 weeks after the last normal menstrual period. Orthostatic signs and fever may be present. Uterine pathology includes endometritis and degenerating leiomyomas.

■ CHRONIC PELVIC PAIN

Many women experience lower abdominal discomfort with ovulation (*mittelschmerz*), characterized as a dull, aching pain at midcycle that lasts minutes to hours. In addition, ovulatory women may experience somatic symptoms during the few days prior to menses, including edema, breast engorgement, and abdominal bloating or discomfort. A symptom complex of cyclic irritability, depression, and lethargy is known as *premenstrual syndrome* (PMS). Severe or incapacitating cramping with ovulatory menses in the absence of demonstrable disorders of the pelvis is termed *primary dysmenorrhea*. *Secondary dysmenorrhea* is caused by underlying pelvic pathology such as endometriosis, adenomyosis, or cervical stenosis.

■ DIAGNOSIS

Evaluation includes a history, pelvic examination, hCG measurement, tests for chlamydial and gonococcal infections, and pelvic ultrasound. Laparoscopy or laparotomy is indicated in some cases of pelvic pain of undetermined cause.

TREATMENT

Pelvic Pain

Primary dysmenorrhea is best treated with NSAIDs or oral contraceptive agents. Secondary dysmenorrhea not responding to NSAIDs suggests pelvic pathology, such as endometriosis. Infections should be treated with the appropriate antibiotics. Symptoms from PMS may improve with selective serotonin reuptake inhibitor (SSRI) therapy. The majority of unruptured ectopic pregnancies are treated with methotrexate, which has 85–95% success rate. Surgery may be required for structural abnormalities.

HIRSUTISM

■ ETIOLOGY

Hirsutism, defined as excessive male-pattern hair growth, affects ~10% of women. It may be familial or caused by PCOS, ovarian or adrenal neoplasms, congenital adrenal hyperplasia, Cushing's syndrome, pregnancy, and drugs (androgens, oral contraceptives containing androgenic progestins). Other drugs, such as minoxidil, phenytoin, diazoxide, and cyclosporine, can cause excessive growth of non-androgen-dependent vellus hair, leading to hypertrichosis.

■ CLINICAL FEATURES

An objective clinical assessment of hair distribution and quantity is central to the evaluation. A commonly used method to grade hair growth is the Ferriman-Gallwey score (see Fig. 387-1, p. 2801, HPIM-20). Associated manifestations of androgen excess include acne and male-pattern balding (androgenic alopecia). *Virilization* or *androgenization*, on the other hand, refers to the state in which androgen levels are sufficiently high to cause deepening of the voice, breast atrophy, increased muscle bulk, clitoromegaly, and increased libido. Historic elements include menstrual history and the age of onset, rate of progression, and distribution of hair growth. Sudden development of hirsutism, rapid progression, and virilization suggests an ovarian or adrenal neoplasm.

■ DIAGNOSIS

An approach to testing for androgen excess is depicted in Fig. 178-2. PCOS is a relatively common cause of hirsutism. The dexamethasone androgen-suppression

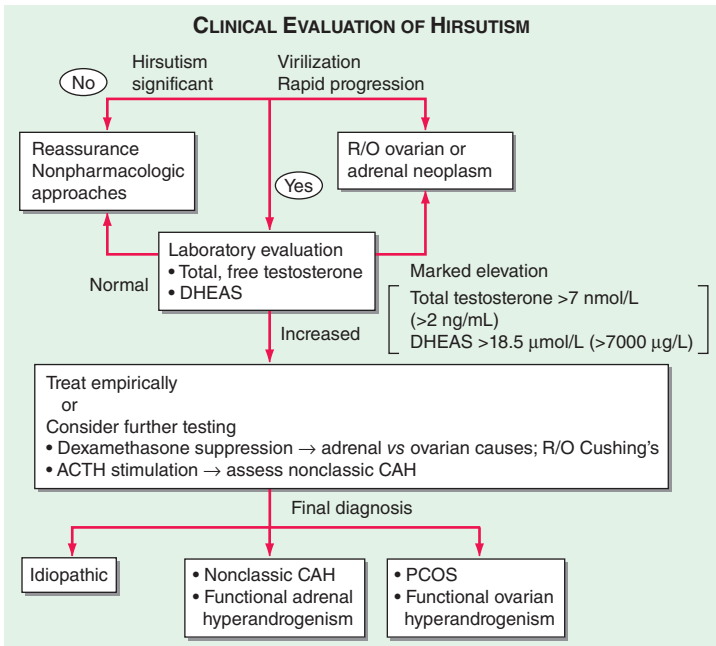


FIGURE 178-2 Algorithm for the evaluation and differential diagnosis of hirsutism. ACTH, adrenocorticotrophic hormone; CAH, congenital adrenal hyperplasia; DHEAS, sulfated form of dehydroepiandrosterone; PCOS, polycystic ovarian syndrome; R/O, rule out.

test (0.5 mg PO every 6 h \times 4 days, with free testosterone levels obtained before and after administration of dexamethasone) may distinguish ovarian from adrenal overproduction. Incomplete suppression suggests ovarian androgen excess. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency can be excluded by a 17-hydroxyprogesterone level that is <6 nmol/L (<2 μ g/L) either in the morning during the follicular phase or 1 h after administration of 250 μ g of cosyntropin. CT may localize an adrenal mass, and ultrasound may identify an ovarian mass, if evaluation suggests these possibilities.

TREATMENT

Hirsutism

Treatment of a remediable underlying cause (e.g., Cushing's syndrome, adrenal or ovarian tumor) also improves hirsutism. In idiopathic hirsutism or PCOS, symptomatic physical or pharmacologic treatment is indicated. Nonpharmacologic treatments include (1) bleaching; (2) depilatory such as shaving and chemical treatments; and (3) epilatory such as plucking, waxing, electrolysis, and laser or intense pulsed light (IPL). Pharmacologic therapy includes oral contraceptives with a low androgenic progestin and spironolactone (100–200 mg/d PO), often in combination. Flutamide is also effective as an antiandrogen, but its use is limited by hepatotoxicity. Glucocorticoids (dexamethasone, 0.25–0.5 mg at bedtime, or prednisone, 5–10 mg at bedtime) are the mainstay of treatment in pts with congenital adrenal hyperplasia. Attenuation of hair growth with pharmacologic therapy is typically not evident until 6 months after initiation of medical treatment and therefore should be used in conjunction with nonpharmacologic treatments.

MENOPAUSE

■ ETIOLOGY

Menopause is defined as the final episode of menstrual bleeding and occurs at a median age of 51 years. It is the consequence of depletion of ovarian follicles or of oophorectomy. The onset of *perimenopause*, when fertility wanes and menstrual irregularity increases, precedes the final menses by 2–8 years.

■ CLINICAL FEATURES

The most common menopausal symptoms are vasomotor instability (hot flashes and night sweats), mood changes (nervousness, anxiety, irritability, and depression), insomnia, and atrophy of the urogenital epithelium and skin. FSH levels are elevated to ≥ 40 IU/L with estradiol levels that are <30 pg/mL.

TREATMENT

Menopause

During perimenopause, low-dose combined oral contraceptives may be of benefit. The rational use of postmenopausal hormone therapy requires balancing the potential benefits and risks. Concerns include increased risks of endometrial cancer, breast cancer, thromboembolic disease, and gallbladder disease, as well as increased risks of stroke, cardiovascular events, and ovarian cancer. Benefits include a delay in postmenopausal bone loss and probably decreased risks of colorectal cancer and diabetes mellitus. Short-term therapy (<5 years) may be beneficial in controlling intolerable symptoms of menopause, as long as no contraindications exist (Fig. 178-3). These include unexplained vaginal bleeding, active liver disease, venous thromboembolism, history of endometrial cancer,

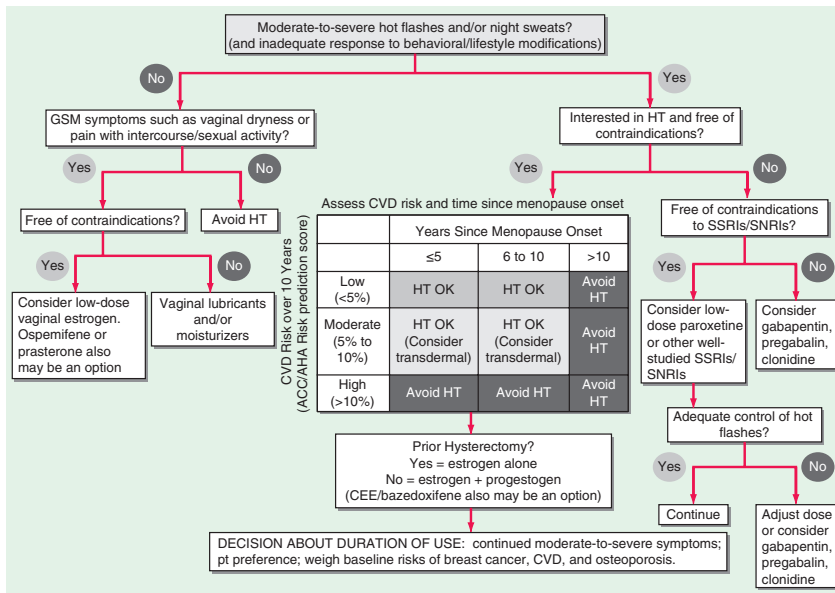


FIGURE 178-3 Algorithm for menopausal symptom management. The algorithm was developed in collaboration with the North American Menopause Society and is available in a free mobile app called *MenoPro* (dual mode for clinicians and pts). ACC, American College of Cardiology; AHA, American Heart Association; CEE, conjugated equine estrogens; CVD, cardiovascular disease; GSM, genitourinary syndrome of menopause; HT, hormone therapy; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors. (From Manson JE et al: *Algorithm and mobile app for menopausal symptom management and hormonal/non-hormonal therapy decision making*. *Menopause* 22:247, 2015. Used with permission.)

breast cancer, preexisting cardiovascular disease, and diabetes. Hypertriglyceridemia (>400 mg/dL) and active gallbladder disease are relative contraindications. Alternative therapies for symptoms include venlafaxine, fluoxetine, paroxetine, gabapentin, clonidine, vitamin E, or soy-based products. Vaginal estradiol tablets or creams may be used for genitourinary symptoms. Long-term therapy (≥ 5 years) should be undertaken only after careful consideration, particularly in light of alternative therapies for osteoporosis (bisphosphonates, raloxifene) and of the risks of venous thromboembolism and breast cancer. Estrogens should be given in the minimal effective doses (conjugated estrogen, 0.625 mg/d PO; micronized estradiol, 1.0 mg/d PO; or transdermal estradiol, 0.05–1.0 mg once or twice a week). Women with an intact uterus should be given estrogen in combination with a progestin (medroxyprogesterone either cyclically, 5–10 mg/d PO for days 15–25 each month, or continuously, 2.5 mg/d PO) to avoid the increased risk of endometrial carcinoma seen with unopposed estrogen use.

CONTRACEPTION

The most widely used methods for fertility control include (1) barrier methods, (2) oral contraceptives, (3) intrauterine devices, (4) long-acting progestins, (5) sterilization, and (6) abortion.

Oral contraceptive agents are widely used for both prevention of pregnancy and control of dysmenorrhea and anovulatory bleeding. Combination oral contraceptive agents contain synthetic estrogen (ethinyl estradiol or mestranol) and synthetic progestins. Some progestins possess an inherent androgenic action. Low-dose norgestimate and third-generation progestins (desogestrel, gestodene, drospirenone) have a less androgenic profile; levonorgestrel appears to be the most androgenic of the progestins and should be avoided in pts with hyperandrogenic symptoms. The three major formulation types include fixed-dose estrogen-progestin, phasic estrogen-progestin, and progestin only.

Despite overall safety, oral contraceptive users are at risk for venous thromboembolism, hypertension, and cholelithiasis. Risks for myocardial infarction and stroke are increased with smoking and aging. Side effects, including breakthrough bleeding, amenorrhea, breast tenderness, and weight gain, are often responsive to a change in formulation.

Absolute contraindications to the use of oral contraceptives include previous thromboembolic disorders, cerebrovascular or coronary artery disease, carcinoma of the breasts or other estrogen-dependent neoplasia, liver disease, hypertriglyceridemia, heavy smoking with age >35 , undiagnosed uterine bleeding, or known or suspected pregnancy. Relative contraindications include hypertension and anticonvulsant drug therapy.

New methods include a weekly contraceptive patch, a monthly contraceptive injection, and a monthly vaginal ring. Long-term progestins may be administered in the form of Depo-Provera or a subdermal progestin implant.

Emergency contraceptive pills, containing progestin only, can be used within 72 h of unprotected intercourse for prevention of pregnancy. Mifepristone (RU486) also may be used but is not available in most countries.

INFERTILITY

■ ETIOLOGY

Infertility is defined as the inability to conceive after 12 months of unprotected sexual intercourse. The causes of infertility are outlined in [Fig. 178-4](#). Male infertility is discussed in [Chap. 177](#).

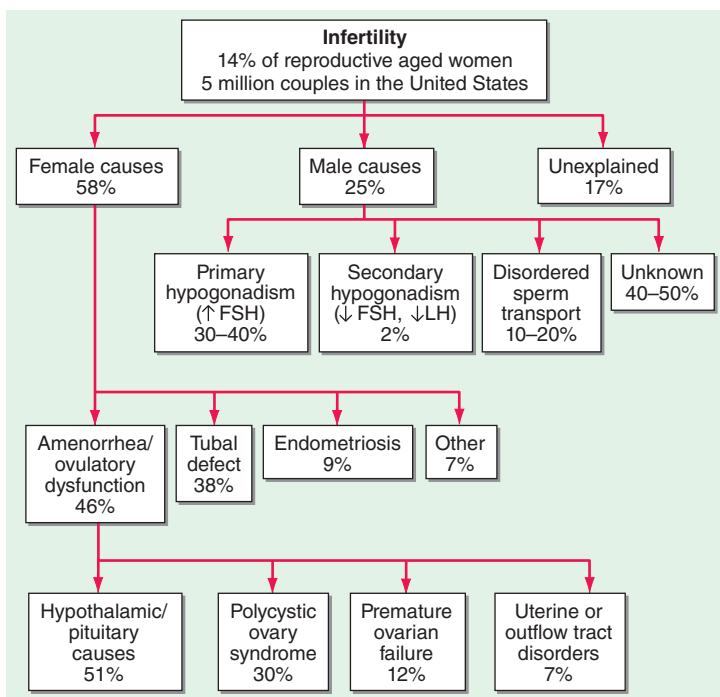


FIGURE 178-4 Causes of infertility. FSH, follicle-stimulating hormone; LH, luteinizing hormone.

■ CLINICAL FEATURES

The initial evaluation includes discussion of the appropriate timing of intercourse, semen analysis in the male, confirmation of ovulation in the female, and, in the majority of situations, documentation of tubal patency in the female. Abnormalities in menstrual function constitute the most common cause of female infertility (Fig. 178-1). A history of regular, cyclic, predictable, spontaneous menses usually indicates ovulatory cycles, which may be confirmed by urinary ovulation predictor kits, basal body temperature graphs, or plasma progesterone measurements during the luteal phase of the cycle. An FSH level <10 IU/mL on day 3 of the cycle predicts adequate ovarian oocyte reserve. Tubal disease can be evaluated by obtaining a hysterosalpingogram or by diagnostic laparoscopy. Endometriosis may be suggested by history and examination, but is often clinically silent and can only be excluded definitively by laparoscopy.

TREATMENT

Infertility

The treatment of infertility should be tailored to the problems unique to each couple. Treatment options include expectant management, clomiphene citrate with or without intrauterine insemination (IUI), gonadotropins with or without IUI, and in vitro fertilization (IVF). In specific situations, surgery, gonadotropin therapy, intracytoplasmic sperm injection (ICSI), or assisted reproductive technologies with donor egg or sperm may be required.

179

Hypercalcemia and Hypocalcemia

**HYPERCALCEMIA**

Hypercalcemia from any cause can result in fatigue, depression, mental confusion, anorexia, nausea, constipation, renal tubular defects, polyuria, a short QT interval, and arrhythmias. CNS and GI symptoms can occur at levels of serum calcium >2.9 mmol/L (>11.5 mg/dL), and nephrocalcinosis and impairment of renal function occur when serum calcium is >3.2 mmol/L (>13 mg/dL). Severe hypercalcemia, usually defined as >3.7 mmol/L (>15 mg/dL), can be a medical emergency, leading to coma and cardiac arrest.

■ ETIOLOGY

The regulation of the calcium homeostasis is depicted in [Fig. 179-1](#). The causes of hypercalcemia are listed in [Table 179-1](#). Hyperparathyroidism and malignancy account for $>90\%$ of cases.

Primary hyperparathyroidism is a generalized disorder of bone metabolism due to increased secretion of parathyroid hormone (PTH) by an adenoma (80%) or rarely a carcinoma in a single gland, or by parathyroid hyperplasia (15%). Familial hyperparathyroidism may be part of multiple endocrine neoplasia type 1 (MEN 1), which also includes pituitary and pancreatic islet tumors, or of MEN 2A, in which hyperparathyroidism occurs with pheochromocytoma and medullary carcinoma of the thyroid.

Hypercalcemia associated with malignancy is often severe and difficult to manage. Mechanisms for this include excess production and release of PTH-related protein (PTHrP) in lung, kidney, squamous cell carcinoma, and other cancers (humoral hypercalcemia of malignancy); local bone destruction in myeloma and breast carcinoma; activation of lymphocytes leading to release of cytokines in myeloma and lymphoma; or an increased synthesis of $1,25(\text{OH})_2\text{D}$ in lymphoma.

Several other conditions have been associated with hypercalcemia. These include sarcoidosis and other granulomatous diseases, which lead to increased synthesis of $1,25(\text{OH})_2\text{D}$; vitamin D intoxication from chronic ingestion of large vitamin doses ($50\text{--}100 \times$ physiologic requirements); lithium therapy, which results in hyperfunctioning of the parathyroid glands; and familial hypocalciuric hypercalcemia (FHH) due to autosomal dominant inheritance of an inactivating mutation in the calcium-sensing receptor, which results in inappropriately normal or even high secretion of PTH, despite hypercalcemia and enhanced renal calcium resorption. Severe secondary hyperparathyroidism associated with end-stage renal disease may progress to tertiary hyperparathyroidism, in which PTH hypersecretion becomes autonomous, causes hypercalcemia, and is no longer responsive to medical therapy.

■ CLINICAL FEATURES

Most pts with mild to moderate hyperparathyroidism are asymptomatic, even when the disease involves the kidneys and the skeletal system. Pts frequently have hypercalciuria and polyuria, and calcium can be deposited in the renal parenchyma (nephrocalcinosis) or form calcium oxalate stones. The characteristic skeletal lesion is osteopenia or osteoporosis; rarely, the more severe disorder osteitis fibrosa cystica occurs as a manifestation of long-standing, more severe hyperparathyroidism. Increased bone resorption primarily involves cortical rather than trabecular bone. Hypercalcemia may be intermittent or sustained, and serum phosphate is usually low but may be normal.

■ DIAGNOSIS

Primary hyperparathyroidism is confirmed by demonstration of an inappropriately high PTH level for the degree of hypercalcemia. Hypercalciuria helps to

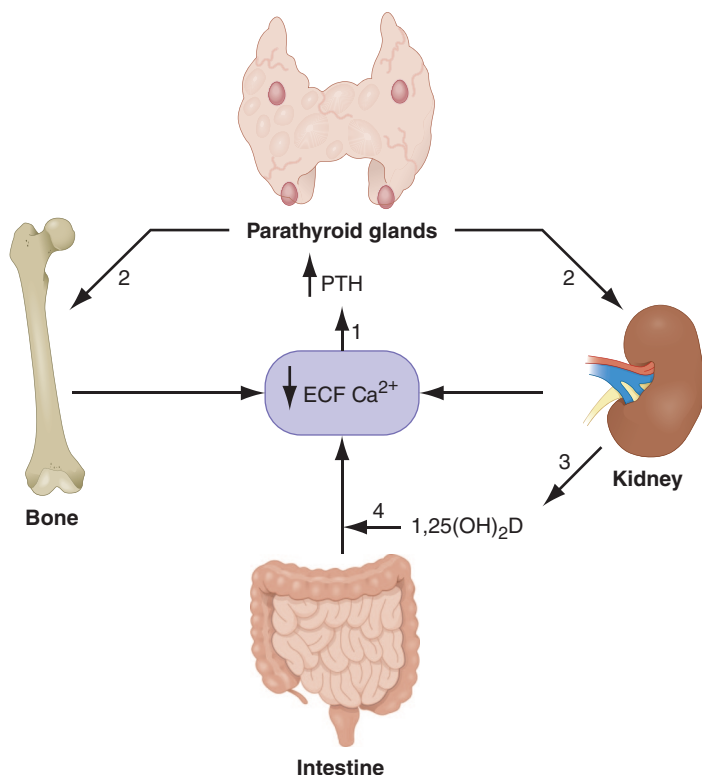


FIGURE 179-1 Feedback mechanisms maintaining extracellular calcium concentrations within a narrow, physiologic range (8.9–10.1 mg/dL [2.2–2.5 mM]). A decrease in extracellular fluid (ECF) calcium (Ca^{2+}) triggers an increase in parathyroid hormone (PTH) secretion (1) via the calcium sensor receptor on parathyroid cells. PTH, in turn, results in increased tubular reabsorption of calcium by the kidney (2) and resorption of calcium from bone (2) and also stimulates renal $1,25(\text{OH})_2\text{D}$ production (3). $1,25(\text{OH})_2\text{D}$, in turn, acts principally on the intestine to increase calcium absorption (4). Collectively, these homeostatic mechanisms serve to restore serum calcium levels to normal.

distinguish this disorder from FHH, in which PTH levels are usually in the normal range and the urine calcium level is low. Differentiation between primary hyperparathyroidism and FHH is important because the latter does not respond to parathyroid surgery. Levels of PTH are low in hypercalcemia of malignancy.

Total serum calcium should be corrected when serum albumin is abnormal (addition of 0.2 mM [0.8 mg/dL] to calcium value for every 1.0-g/dL decrement in albumin <4.1 g/dL, or the converse for an increase in albumin). Alternatively, ionized calcium can be measured.

TREATMENT

Hypercalcemia

The type of treatment is based on the severity of the hypercalcemia and the nature of the associated symptoms. [Table 179-2](#) shows general recommendations that

TABLE 179-1 Classification of Causes of Hypercalcemia**I. Parathyroid-Related**

- A. Primary hyperparathyroidism
 - 1. Adenoma(s)
 - 2. Multiple endocrine neoplasia
 - 3. Carcinoma
- B. Lithium therapy
- C. Familial hypocalciuric hypercalcemia

II. Malignancy-Related

- A. Solid tumor with metastases (breast)
- B. Solid tumor with humoral mediation of hypercalcemia (lung, kidney)
- C. Hematologic malignancies (multiple myeloma, lymphoma, leukemia)

III. Vitamin D-Related

- A. Vitamin D intoxication
- B. ↑ 1,25(OH)₂D; sarcoidosis and other granulomatous diseases
- C. ↑ 1,25(OH)₂D; impaired 1,25(OH)₂D metabolism due to 24-hydroxylase deficiency and inactivating mutations in the sodium-dependent phosphate co-transporters

IV. Associated with High Bone Turnover

- A. Hyperthyroidism
- B. Immobilization
- C. Thiazides
- D. Vitamin A intoxication
- E. Fat necrosis

V. Associated with Renal Failure

- A. Severe secondary hyperparathyroidism
- B. Aluminum intoxication
- C. Milk-alkali syndrome

apply to therapy of severe hypercalcemia (levels of >3.2 mmol/L [>13 mg/dL]) from any cause.

In pts with severe primary hyperparathyroidism, surgical parathyroidectomy should be performed promptly. Asymptomatic disease may not require surgery; usual surgical indications include age <50, nephrolithiasis, creatinine clearance <60 mL/min, reduction in bone mass (T score <-2.5), or serum calcium >0.25 mmol/L (>1 mg/dL) above the normal range. A minimally invasive approach may be used if preoperative localization via sestamibi scans with single-photon emission computed tomography (SPECT) or neck ultrasound demonstrates a solitary adenoma and intraoperative PTH assays are available. Otherwise, neck exploration is required. Surgery in a center experienced in parathyroid interventions is recommended. Postoperative management requires close monitoring of calcium and phosphorus, as transient hypocalcemia is common. Calcium supplementation is given for symptomatic hypocalcemia.

Hypercalcemia of malignancy is managed by treating the underlying tumor. Adequate hydration and parenteral bisphosphonates can be used to reduce calcium levels. Long-term control of hypercalcemia is difficult unless the underlying cause can be eliminated.

No therapy is recommended for FHH. Secondary hyperparathyroidism should be treated with phosphate restriction, the use of nonabsorbable

TABLE 179-2 Therapies for Severe Hypercalcemia

TREATMENT	ONSET OF ACTION	DURATION OF ACTION	ADVANTAGES	DISADVANTAGES
Most useful therapies				
Hydration with normal saline	Hours	During infusion	Rehydration invariably needed	Volume overload
Forced diuresis; normal saline plus loop diuretic	Hours	During treatment	Rapid action	Volume overload, cardiac decompensation, intensive monitoring, electrolyte disturbance, inconvenience
Pamidronate	1–2 days	10–14 days to weeks	High potency; intermediate onset of action	Fever in 20%, hypophosphatemia, hypocalcemia, hypomagnesemia, rarely jaw necrosis, atypical femoral fracture
Zoledronate	1–2 days	>3 weeks	Same as for pamidronate (lasts longer)	Same as pamidronate above
Denosumab	1–2 days	>3 weeks	Strongest antiresorptive	Occasional severe hypocalcemia, rarely jaw necrosis, skin infections, atypical femoral fracture
Special-use therapies				
Calcitonin	Hours	1–2 days	Rapid onset of action; useful as adjunct in severe hypercalcemia	Rapid tachyphylaxis
Phosphate oral	24 h	During use	Chronic management (with hypophosphatemia); low toxicity if P < 4 mg/dL	Limited use except as adjuvant or chronic therapy
Glucocorticoids	Days	Days, weeks	Oral therapy, antitumor agent	Active only in certain malignancies, vitamin D excess and sarcoidosis; glucocorticoid side effects
Dialysis	Hours	During use and 24–48 h afterward	Useful in renal failure; onset of effect in hours; can immediately reverse life-threatening hypercalcemia	Complex procedure, reserved for extreme or special circumstances

antacids or sevelamer, and calcitriol. Tertiary hyperparathyroidism requires parathyroidectomy.

HYPOCALCEMIA

Chronic hypocalcemia is less common than hypercalcemia, and is usually symptomatic and requires treatment. Symptoms include peripheral and perioral paresthesia, muscle spasms, carpopedal spasm, tetany, laryngeal spasm, seizure, and respiratory arrest. Increased intracranial pressure and papilledema may occur with long-standing hypocalcemia, and other manifestations may include irritability, depression, psychosis, intestinal cramps, and chronic malabsorption. Chvostek's and Trousseau's signs are frequently positive, and the QT interval is prolonged. Both hypomagnesemia and alkalosis lower the threshold for tetany.

■ ETIOLOGY

Transient hypocalcemia often occurs in critically ill pts with burns, sepsis, and acute renal failure; following transfusion with citrated blood; or with medications such as protamine and heparin. Hypoalbuminemia can reduce serum calcium below normal, although ionized calcium levels remain normal. The above-mentioned correction (see "Hypercalcemia") can be used to assess whether the serum calcium concentration is abnormal when serum proteins are low. Alkalosis increases calcium binding to proteins, and in this setting direct measurements of ionized calcium should be used.

The causes of hypocalcemia can be divided into those in which PTH is absent (hereditary or acquired hypoparathyroidism, hypomagnesemia), PTH is ineffective (chronic renal failure, vitamin D deficiency, anticonvulsant therapy, intestinal malabsorption, pseudohypoparathyroidism), or PTH is overwhelmed (severe, acute hyperphosphatemia in tumor lysis, acute renal failure, or rhabdomyolysis; hungry bone syndrome following parathyroidectomy). The most common forms of chronic severe hypocalcemia are autoimmune hypoparathyroidism and postoperative hypoparathyroidism following neck surgery. Chronic renal insufficiency is associated with mild hypocalcemia compensated for by secondary hyperparathyroidism. The cause of hypocalcemia associated with acute pancreatitis is unclear.

TREATMENT

Hypocalcemia

Symptomatic hypocalcemia may be treated with IV calcium gluconate (bolus of 1–2 g IV over 10–20 min followed by infusion of 10 ampoules of 10% calcium gluconate diluted in 1 L D₅W infused at 30–100 mL/h). Management of chronic hypocalcemia requires a high oral calcium intake, usually with vitamin D supplementation. Hypoparathyroidism requires administration of calcium (1–3 g/d) and calcitriol (0.25–1 µg/d), adjusted according to serum calcium levels and urinary excretion. Restoration of magnesium stores may be required to reverse hypocalcemia in the setting of severe hypomagnesemia. PTH (1-84) (Natpara) has been approved for the treatment of refractory hypoparathyroidism, representing an important advance in treatment of these pts.

HYPOPHOSPHATEMIA

Mild hypophosphatemia is not usually associated with clinical symptoms. In severe hypophosphatemia, pts may have muscle weakness, numbness, paresthesia, and confusion. Rhabdomyolysis may develop during rapidly progressive

hypophosphatemia. Respiratory insufficiency can result from diaphragm muscle weakness.

■ ETIOLOGY

The causes of hypophosphatemia include decreased intestinal absorption (vitamin D deficiency, phosphorus-binding antacids, malabsorption); urinary losses (hyperparathyroidism, hyperglycemic states, X-linked hypophosphatemic rickets, oncogenic osteomalacia, alcoholism, or certain toxins); and shifts of phosphorus from extracellular to intracellular compartments (administration of insulin in diabetic ketoacidosis or by hyperalimentation or refeeding in a malnourished pt). In syndromes of severe primary renal phosphate wasting (X-linked hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets, oncogenic osteomalacia), the phosphatonin hormone FGF23 (fibroblast growth factor 23) plays a key pathogenetic role.

TREATMENT

Hypophosphatemia

Mild hypophosphatemia can be replaced orally with milk, carbonated beverages, or Neutra-Phos or K-Phos (up to 2 g/d in divided doses). For severe hypophosphatemia (0.75 mmol/L; [<2.0 mg/dL]), IV phosphate may be administered at initial doses of 0.2–0.8 mmol/kg of elemental phosphorus over 6 h. The total body phosphate depletion cannot be predicted from the serum phosphate level; careful monitoring of therapy is therefore required. Hypocalcemia should be corrected first, and the dose reduced 50% in hypercalcemia. Serum calcium and phosphate levels should be measured every 6–12 h; a serum calcium \times phosphate product of >50 must be avoided.

HYPERPHOSPHATEMIA

In adults, hyperphosphatemia is defined as a level >1.8 mmol/L (>5.5 mg/dL). The most common causes are acute and chronic renal failure, but it may also be seen in hypoparathyroidism, vitamin D intoxication, acromegaly, acidosis, rhabdomyolysis, and hemolysis. Hyperphosphatemia in chronic kidney disease lowers blood calcium levels by several mechanisms, including extraosseous deposition of calcium and phosphate, impairment of the bone-resorbing action of PTH, and reduction in $1,25(\text{OH})_2\text{D}$ production due to elevated FGF23 and diminished renal tissue. The clinical consequences of severe hyperphosphatemia are hypocalcemia and calcium phosphate deposition in tissues. Depending on the location of tissue calcifications, serious chronic or acute complications may ensue (e.g., nephrocalcinosis, cardiac arrhythmias). Therapy consists of treating the underlying disorder and limiting dietary phosphorus intake and absorption. Oral aluminum phosphate binders or sevelamer may be used, and hemodialysis should be considered in severe cases.

HYPOMAGNESEMIA

Hypomagnesemia usually indicates significant whole body magnesium depletion. Muscle weakness, prolonged PR and QT intervals, and cardiac arrhythmias are the most common manifestations of hypomagnesemia. Magnesium is important for effective PTH secretion as well as the renal and skeletal responsiveness to PTH. Therefore, hypomagnesemia is often associated with hypocalcemia.

■ ETIOLOGY

Hypomagnesemia generally results from a derangement in renal or intestinal handling of magnesium and is classified as primary (hereditary) or secondary

(acquired). Hereditary causes include both disorders of absorption and those of renal loss (e.g., Bartter's and Gitelman syndromes). Secondary causes are much more common, with renal losses being due to volume expansion, hypercalcemia, osmotic diuresis, loop diuretics, alcohol, aminoglycosides, cisplatin, cyclosporine, and amphotericin B, and gastrointestinal losses from vomiting and diarrhea or surgical drainage procedures. Proton pump inhibitors (omeprazole and others) may produce hypomagnesemia by an unknown mechanism that does not involve renal wasting of magnesium.

TREATMENT

Hypomagnesemia

For mild deficiency, oral replacement in divided doses totaling 20–30 mmol/d (40–60 meq/d) is effective, although diarrhea may result. Parenteral magnesium administration is usually needed for serum levels <0.5 mmol/L (<1.2 mg/dL), with a continuous infusion of magnesium chloride IV to deliver 50 mmol/d over a 24-h period (dose reduced by 50–75% in renal failure). Therapy may be required for several days in order to replete tissue magnesium stores; serum Mg should be monitored every 12–24 h during treatment. Pts with associated seizures or acute arrhythmias can be given 1–2 g of magnesium sulfate IV over 5–10 min. Vitamin D deficiency frequently coexists and should be treated with oral or parenteral vitamin D or 25(OH)D (but not with 1,25[OH]₂D, which may impair tubular magnesium reabsorption, possibly via PTH suppression). Other electrolytes should be monitored simultaneously and corrected as well.

HYPERMAGNESEMIA

Hypermagnesemia is rare but can be seen in renal failure when pts are taking magnesium-containing antacids, laxatives, enemas, or infusions, or in acute rhabdomyolysis. The most readily detectable clinical sign of hypermagnesemia is the disappearance of deep tendon reflexes, but hypocalcemia, hypotension, paralysis of respiratory muscles, complete heart block, and cardiac arrest can occur. Treatment includes stopping the preparation, clearing the intestines of residual offending laxatives or antacids with magnesium-free enemas or cathartics, dialysis against a low magnesium bath, or, if associated with life-threatening complications, 100–200 mg of elemental calcium IV over 1–2 h.

180

Osteoporosis and Osteomalacia



OSTEOPOROSIS

Osteoporosis is defined as a reduction in the strength of bone that leads to increased risk of fractures. It is defined operationally as a bone density that falls 2.5 SD below the mean for a young normal individual (a T-score of <-2.5). Those with a T-score of <1.0 (osteopenia) have low bone density and are at increased risk for osteoporosis. The most common sites for osteoporosis-related fractures are the vertebrae, hip, and distal radius.

Osteoporosis is a common condition in the elderly; women are at particularly high risk. In the United States, 8 million women and 2 million men have

TABLE 180-1 Risk Factors for Osteoporosis Fracture

NONMODIFIABLE	POTENTIALLY MODIFIABLE
Personal history of fracture as an adult	Current cigarette smoking
History of fracture in first-degree relative	Estrogen deficiency
Female gender	Early menopause (<45 years) or bilateral ovariectomy
Advanced age	Prolonged premenstrual amenorrhea (>1 year)
White race	Poor nutrition especially low calcium and vitamin D intake
Dementia	Alcoholism
	Impaired eyesight despite adequate correction
	Recurrent falls
	Inadequate physical activity
	Poor health/frailty

osteoporosis; an additional 18 million have osteopenia. The annual incidence of osteoporosis-related fractures is at least 2 million; almost half of them are vertebral crush fractures, followed in frequency by hip and wrist fractures. Hip fractures are associated with significant morbidity (thromboembolism) and a 5–20% mortality within a year.

■ ETIOLOGY

Low bone density may result from low peak bone mass or increased bone loss. Risk factors for an osteoporotic fracture are listed in [Table 180-1](#), and conditions associated with osteoporosis are listed in [Table 180-2](#). Certain drugs, primarily glucocorticoids, cyclosporine, cytotoxic drugs, thiazolidinediones, anticonvulsants, aluminum, heparin, excessive levothyroxine, GnRH agonists, and aromatase inhibitors also have detrimental effects on the skeleton.

■ CLINICAL FEATURES

Pts with multiple vertebral crush fractures may have loss of height, kyphosis, and secondary pain from altered biomechanics of the back. Thoracic fractures can be associated with restrictive lung disease, whereas lumbar fractures are sometimes associated with abdominal symptoms or nerve compression leading to sciatica. Dual-energy x-ray absorptiometry (DXA) has become the standard for measuring bone density. Women aged ≥ 65 should be screened routinely for osteoporosis, and screening should begin in younger postmenopausal women with increased risk. Indications for bone mass measurement are summarized in [Table 180-3](#). A general laboratory evaluation includes complete blood count, serum and 24-h urine calcium, 25(OH)D level, and renal and hepatic function tests. Further testing is based on clinical suspicion and may include thyroid-stimulating hormone (TSH), urinary free cortisol, parathyroid hormone (PTH), serum and urine electrophoresis, and testosterone levels (in men). Tissue transglutaminase Ab testing may identify asymptomatic celiac disease. Markers of bone resorption (e.g., urine cross-linked N-telopeptide) may be helpful in detecting an early response to antiresorptive therapy if measured prior to and 4–6 months after initiating therapy.

TREATMENT

Osteoporosis

Treatment involves the management of acute fractures, modifying risk factors, and treating any underlying disorders that lead to reduced bone mass.

TABLE 180-2 Conditions, Diseases, and Medications That Contribute to Osteoporosis and Fractures

Lifestyle factors		
Alcohol abuse	High salt intake	Falling
Low calcium intake	Inadequate physical activity	Excessive thinness
Vitamin D insufficiency	Immobilization	Prior fractures
Excess vitamin A	Smoking (active or passive)	
Genetic factors		
Cystic fibrosis	Homocystinuria	Osteogenesis imperfecta
Ehlers-Danlos syndrome	Hypophosphatasia	Parental history of hip fracture
Gaucher's disease	Idiopathic hypercalciuria	Porphyria
Glycogen storage diseases	Marfan's syndrome	Riley-Day syndrome
Hemochromatosis	Menkes' steely hair syndrome	
Hypogonadal states		
Androgen insensitivity	Hyperprolactinemia	Athletic amenorrhea
Anorexia nervosa and bulimia	Premature menopause	Panhypopituitarism
Turner's & Klinefelter's syndromes	Premature ovarian failure	
Endocrine disorders		
Adrenal insufficiency	Cushing's syndrome	Central adiposity
Diabetes mellitus (types 1 and 2)	Hyperparathyroidism	Thyrotoxicosis
Gastrointestinal disorders		
Celiac disease	Inflammatory bowel disease	Primary biliary cirrhosis
Gastric bypass	Malabsorption	
Gastrointestinal surgery	Pancreatic disease	
Hematologic disorders		
Multiple myeloma	Monoclonal gammopathies	Sickle cell disease
Hemophilia	Leukemia and lymphomas	Systemic mastocytosis
Thalassemia		
Rheumatologic and autoimmune diseases		
Ankylosing spondylitis	Lupus	Rheumatoid arthritis
Other rheumatic and autoimmune diseases		
Central nervous system disorders		
Epilepsy	Parkinson's disease	Stroke
Multiple sclerosis	Spinal cord injury	

(Continued)

TABLE 180-2 Conditions, Diseases, and Medications That Contribute to Osteoporosis and Fractures (Continued)

Miscellaneous conditions and diseases		
AIDS/HIV	Congestive heart failure	Posttransplant bone disease
Alcoholism	Depression	Sarcoidosis
Amyloidosis	End-stage renal disease	Weight loss
Chronic metabolic acidosis	Hypercalciuria	
Chronic obstructive lung disease	Idiopathic scoliosis	
	Muscular dystrophy	
Medications		
Aluminum (in antacids)	Glucocorticoids (≥5 mg/d prednisone or equivalent for ≥3 months)	Tamoxifen (premenopausal use)
Anticoagulants (heparin)	Gonadotropin-releasing hormone antagonists and agonists	Thiazolidinediones (such as pioglitazone and rosiglitazone)
Anticonvulsants	Lithium	Thyroid hormones (in excess)
Aromatase inhibitors	Methotrexate	Parenteral nutrition
Barbiturates	Proton pump inhibitors	
Cancer chemotherapeutic drugs	Selective serotonin reuptake inhibitors	
Cyclosporine A and tacrolimus		
Depo-medroxyprogesterone (premenopausal contraception)		

Source: From the 2014 National Osteoporosis Foundation Clinician's Guide to the Prevention and Treatment of Osteoporosis. © National Osteoporosis Foundation.

Treatment decisions are based on an individual's risk factors, but active treatment is generally recommended if the T-score is ≤ -2.5 . Risk factor reduction is a key part of management; smoking cessation and reduced alcohol intake should be encouraged; offending drugs should be discontinued or doses minimized (e.g., glucocorticoids), an exercise program should be instituted, and fall prevention strategies should be put in place. Oral calcium (1–1.2 g/d of elemental calcium in divided doses) and vitamin D (400–800 IU/d) should be initiated in all pts with osteoporosis. Adequate vitamin D status should be verified by measuring serum 25(OH)D, the value of which should be at least 75 nmol/L (30 ng/mL). Some pts may require higher vitamin D supplements than those recommended earlier. Moderate sun exposure also generates vitamin D, although recommending

TABLE 180-3 Indications for BMD Testing

- Women aged ≥ 65 and men aged ≥ 70 ; regardless of clinical risk factors
- Younger postmenopausal women, women in the menopausal transition, and men aged 50–69 with clinical risk factors for fracture
- Adults who have a fracture at or after age 50
- Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids at a daily dose >5 mg prednisone or equivalent for >3 months associated with low bone mass or bone loss)

outdoor exposure is controversial because of concerns about skin cancer. Bisphosphonates (alendronate, 70 mg PO weekly; risedronate, 35 mg PO weekly; ibandronate, 150 mg PO monthly or 3 mg IV every 3 mo; zoledronic acid, 5 mg IV annually) inhibit bone resorption, augment bone density, and decrease fracture rates. Oral bisphosphonates are poorly absorbed and should be taken in the morning on an empty stomach with 0.25 L (8 oz) of tap water. Long-term bisphosphonate treatment may be associated with atypical femur fractures; a tentative recommendation is to limit therapy to 5 years. Osteonecrosis of the jaw is a rare complication of bisphosphonate treatment mainly seen with high-dose IV zoledronic acid or pamidronate administered in cancer pts. Estrogen decreases the rate of bone reabsorption, but therapy should be carefully weighed in the context of increased risks of cardiovascular disease and breast cancer. Raloxifene (60 mg/d PO), a selective estrogen receptor modulator (SERM), is an alternative antiresorptive agent that can be used in lieu of estrogen. It increases bone density and decreases total and LDL cholesterol without stimulating endometrial hyperplasia, although it may precipitate hot flashes. A new antiresorptive agent is denosumab, a monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (RANKL), an osteoclast differentiation factor. It is approved for pts at high risk for fracture and is given as an injection twice a year (60 mg SC every 6 months).

The only available drug that induces bone *formation* is teriparatide [PTH(1-34)] 20 µg SC qd. It is indicated for treatment of severe osteoporosis for a maximum of 2 years. Teriparatide therapy should be followed by antiresorptive agent therapy to prevent rapid loss of the newly formed bone.

OSTEOMALACIA

■ ETIOLOGY

Defective mineralization of the organic matrix of bone results in *osteomalacia*. The childhood form of osteomalacia is called rickets. Osteomalacia is caused by inadequate intake or malabsorption of vitamin D (chronic pancreatic insufficiency, gastrectomy, malabsorption) and disorders of vitamin D metabolism (anticonvulsant therapy, chronic renal failure, genetic disorders of vitamin D activation or action). Osteomalacia can also be caused by long-standing hypophosphatemia, which can be due to renal phosphate wasting (e.g., X-linked hypophosphatemic rickets or oncogenic osteomalacia) or excessive use of phosphate binders.

■ CLINICAL FEATURES

Skeletal deformities may be overlooked until fractures occur after minimal trauma. Symptoms include diffuse skeletal pain and bony tenderness and may be subtle. Proximal muscle weakness is a feature of vitamin D deficiency and may mimic primary muscle disorders. A decrease in bone density is usually associated with loss of trabeculae and thinning of the cortices. Characteristic x-ray findings are radiolucent bands (looser's zones or pseudofractures) ranging from a few millimeters to several centimeters in length, usually perpendicular to the surface of the femur, pelvis, and scapula. Changes in serum calcium, phosphorus, 25(OH)D, and 1,25(OH)₂D levels vary depending on the cause. The most specific test for vitamin D deficiency in an otherwise healthy individual is a low serum 25(OH)D level. Even modest vitamin D deficiency leads to compensatory secondary hyperparathyroidism characterized by increased levels of PTH and alkaline phosphatase, hyperphosphaturia, and low serum phosphate. With advancing osteomalacia, hypocalcemia may develop due to impaired calcium mobilization from undermineralized bone. 1,25-Dihydroxyvitamin D levels may be preserved, reflecting upregulation of 1 α -hydroxylase activity.

TREATMENT**Osteomalacia**

In osteomalacia due to vitamin D deficiency [serum 25(OH)D <50 nmol/L (<20 ng/mL)], vitamin D₂ (ergocalciferol) is given orally in doses of 50,000 IU weekly for 8 weeks, followed by maintenance therapy with 800 IU daily. Osteomalacia due to malabsorption requires larger doses of vitamin D (up to 50,000 IU/d orally or 250,000 IU IM biannually). In pts taking anticonvulsants or those with disorders of abnormal vitamin D activation, vitamin D should be administered in doses that maintain the serum calcium and 25(OH)D levels in the normal range. Calcitriol (0.25–0.5 µg/d PO) is effective in treating hypocalcemia or osteodystrophy caused by chronic renal failure. Vitamin D deficiency should always be repleted in conjunction with calcium supplementation (1.5–2.0 g of elemental calcium daily). Serum and urinary calcium measurements are efficacious for monitoring resolution of vitamin D deficiency, with a goal of 24-h urinary calcium excretion of 100–250 mg/24 h.

181**Hypercholesterolemia and
Hypertriglyceridemia**

Hyperlipoproteinemia is characterized by hypercholesterolemia, isolated hypertriglyceridemia, or both. Genetic causes of hyperlipoproteinemia are summarized in [Table 181-1](#). Diabetes mellitus, obesity, ethanol consumption, oral contraceptives, glucocorticoids, renal disease, hepatic disease, and hypothyroidism can cause secondary hyperlipoproteinemias or worsen underlying hyperlipoproteinemic states.

Standard lipoprotein analysis assesses total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. Both LDL and HDL cholesterol levels are temporarily decreased for several weeks after myocardial infarction or acute inflammatory states, but can be accurately measured if blood is obtained within 8 h of the event.

ISOLATED HYPERCHOLESTEROLEMIA

Elevated levels of fasting plasma total cholesterol (>5.2 mmol/L [>200 mg/dL]) in the presence of normal levels of triglycerides are almost always associated with increased concentrations of plasma LDL cholesterol. Elevations of LDL cholesterol can result from single-gene defects, from polygenic disorders, or from the secondary effects of other disease states.

■ FAMILIAL HYPERCHOLESTEROLEMIA (FH)

FH is a codominant genetic disorder caused by mutations in the gene for the LDL receptor. Plasma LDL levels are elevated at birth and remain so throughout life. In untreated heterozygous adults, total cholesterol levels range from 7.1 to 12.9 mmol/L (275–500 mg/dL). Plasma triglyceride levels are typically normal, and HDL cholesterol levels are normal or reduced. Heterozygotes are prone to accelerated atherosclerosis and premature coronary artery disease (CAD). *Tendon xanthomas* (most commonly of the Achilles tendons and the extensor

TABLE 181-1 Primary Hyperlipoproteinemias Caused by Known Single-Gene Mutations

GENETIC DISORDER	PROTEIN (GENE) DEFECT	LIPOPROTEINS ELEVATED	CLINICAL FINDINGS	GENETIC TRANSMISSION	ESTIMATED INCIDENCE
Hypertriglyceridemia					
Lipoprotein lipase deficiency	LPL (<i>LPL</i>)	Chylomicrons, VLDL	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	~1/1,000,000
Familial apoC-II deficiency	ApoC-II (<i>APOC2</i>)	Chylomicrons, VLDL	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	<1/1,000,000
ApoA-V deficiency	ApoA-V (<i>APOA5</i>)	Chylomicrons, VLDL	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	<1/1,000,000
GPIIIBP1 deficiency	<i>GPIIIBP1</i>	Chylomicrons	Eruptive xanthomas, pancreatitis	AR	<1/1,000,000
Combined hyperlipidemia					
Familial hepatic lipase deficiency	Hepatic lipase (<i>LIPC</i>)	VLDL remnants, HDL	Pancreatitis, CHD	AR	<1/1,000,000
Familial dysbetalipoproteinemia	ApoE (<i>APOE</i>)	Chylomicron remnants, VLDL remnants	Palmar and tuberoeruptive xanthomas, CHD, PVD	AR	~1/10,000
Hypercholesterolemia					
Familial hypercholesterolemia	LDL receptor (<i>LDLR</i>)	LDL	Tendon xanthomas, CHD	AD	~1/250 to 1/500
Familial defective apoB-100	ApoB-100 (<i>APOB</i>)	LDL	Tendon xanthomas, CHD	AD	<~1/1500
Autosomal dominant hypercholesterolemia, type 3	PCSK9 (<i>PCSK9</i>)	LDL	Tendon xanthomas, CHD	AD	<1/1,000,000
Autosomal recessive hypercholesterolemia	ARH (<i>LDLRAP</i>)	LDL	Tendon xanthomas, CHD	AR	<1/1,000,000
Sitosterolemia	<i>ABCG5</i> or <i>ABCG8</i>	LDL	Tendon xanthomas, CHD	AR	<1/1,000,000

Abbreviations: AD, autosomal dominant; apo, apolipoprotein; AR, autosomal recessive; ARH, autosomal recessive hypercholesterolemia; CHD, coronary heart disease; LDL, low-density lipoprotein; LPL, lipoprotein lipase; PVD, peripheral vascular disease; VLDL, very-low density lipoprotein.

tendons of the knuckles), *tuberous xanthomas* (softer, painless nodules on the ankles and buttocks), and *xanthelasma*s (deposits on the eyelids) are common. In its homozygous form, FH leads to severe atherosclerosis during childhood.

■ FAMILIAL DEFECTIVE APO B-100

This autosomal dominant disorder impairs the synthesis and/or function of apo B-100, thereby reducing the affinity for the LDL receptor, slowing LDL catabolism, and causing a phenocopy of FH.

■ POLYGENIC HYPERCHOLESTEROLEMIA

Most moderate hypercholesterolemia (<9.1 mmol/L [<350 mg/dL]) arises from an interaction of multiple genetic defects and environmental factors such as diet, age, and exercise. Plasma HDL and triglyceride levels are normal, and xanthomas are not present.

TREATMENT

Isolated Hypercholesterolemia

Therapy for all of these disorders includes restriction of dietary cholesterol and HMG-CoA reductase inhibitors (statins). Cholesterol absorption inhibitors and bile acid sequestrants or nicotinic acid may also be required (Table 181-2).

ISOLATED HYPERTRIGLYCERIDEMIA

The diagnosis of hypertriglyceridemia is made by measuring plasma lipid levels after an overnight fast (≥ 12 h). Hypertriglyceridemia in adults is defined as a triglyceride level >2.3 mmol/L (>200 mg/dL). An isolated increase in plasma triglycerides indicates that chylomicrons and/or very low-density lipoprotein (VLDL) are increased. Plasma is usually clear when triglyceride levels are <4.5 mmol/L (<400 mg/dL) and cloudy when levels are higher due to VLDL (and/or chylomicron) particles becoming large enough to scatter light. When chylomicrons are present, a creamy layer floats to the top of plasma after refrigeration for several hours. Tendon xanthomas and xanthelasma do not occur with isolated hypertriglyceridemia, but *eruptive xanthomas* (small orange-red papules) can appear on the trunk and extremities and *lipemia retinalis* (orange-yellow retinal vessels) may be seen when the triglyceride levels are >11.3 mmol/L (>1000 mg/dL). Pancreatitis is associated with these high concentrations.

■ FAMILIAL HYPERTRIGLYCERIDEMIA

In this relatively common (~ 1 in 500), likely polygenic disorder, increased plasma VLDL causes elevated plasma triglyceride concentrations. Obesity, hyperglycemia, and hyperinsulinemia are characteristic, and diabetes mellitus, ethanol consumption, oral contraceptives, and hypothyroidism may exacerbate the condition. The diagnosis is suggested by the triad of elevated plasma triglycerides (2.8–11.3 mmol/L [250–1000 mg/dL]), normal or only mildly increased cholesterol levels (<6.5 mmol/L [<250 mg/dL]), and reduced plasma HDL. Secondary forms of hypertriglyceridemia should be ruled out before making the diagnosis of familial hypertriglyceridemia. The identification of other first-degree relatives with hypertriglyceridemia is useful in making the diagnosis. Familial dysbetalipoproteinemia and familial combined hyperlipidemia (FCHL) should be ruled out, as these two conditions are associated with accelerated atherosclerosis.

■ LIPOPROTEIN LIPASE DEFICIENCY

This rare autosomal recessive disorder results from the absence or deficiency of lipoprotein lipase, which in turn impairs the metabolism of chylomicrons.

TABLE 181-2 Summary of the Major Approved Drugs Used for the Treatment of Dyslipidemia

DRUG	MAJOR INDICATIONS	STARTING DOSE	MAXIMAL DOSE	MECHANISM	COMMON SIDE EFFECTS
HMG-CoA reductase inhibitors (statins)	Elevated LDL-C; increased CV risk			↓ Cholesterol synthesis, ↑ Hepatic LDL receptors, ↓ VLDL production	Myalgias and myopathy ↑ transaminases, ↑ diabetes risk
Lovastatin		20–40 mg daily	80 mg daily		
Pravastatin		40–80 mg daily	80 mg daily		
Simvastatin		20–40 mg daily	80 mg daily		
Fluvastatin		20–40 mg daily	80 mg daily		
Atorvastatin		20–40 mg daily	80 mg daily		
Rosuvastatin		5–20 mg daily	40 mg daily		
Pitavastatin		1–2 mg daily	4 mg daily		
Cholesterol absorption inhibitor	Elevated LDL-C			↓ Cholesterol absorption, ↑ LDL receptors	Elevated transaminases
Ezetimibe		10 mg daily	10 mg daily		
Bile acid sequestrants	Elevated LDL-C			↑ Bile acid excretion and ↑ LDL receptors	Bloating, constipation, elevated triglycerides
Cholestyramine		4 g daily	32 g daily		
Colestipol		5 g daily	40 g daily		
Colesevelam		3750 mg daily	4375 mg daily		

(Continued)

TABLE 181-2 Summary of the Major Approved Drugs Used for the Treatment of Dyslipidemia (Continued)

DRUG	MAJOR INDICATIONS	STARTING DOSE	MAXIMAL DOSE	MECHANISM	COMMON SIDE EFFECTS
PCSK9 inhibitors Evolocumab Alirocumab	Elevated LDL-C	140 mg SQ q 2 weeks 75 mg SQ q 2 weeks	420 mg SQ q 1 month (hoFH) 150 mg SQ q 2 weeks	↓ PCSK9 activity, ↑ LDL receptors	Injection site reactions
MTP inhibitor Lomitapide	HoFH	5 mg daily	60 mg daily	↓ VLDL production	Nausea, diarrhea, increased hepatic fat
ApoB inhibitor Mipomersen	HoFH	200 mg SC weekly	200 mg SC weekly	↓ VLDL production	Injection site reactions, flu- like symptoms, increased hepatic fat
Fibric acid derivatives Gemfibrozil Fenofibrate	Elevated TG	600 mg bid 145 mg qd	600 mg bid 145 mg qd	↑ LPL, ↓ VLDL synthesis	Dyspepsia, myalgia, gallstones, elevated transaminases
Omega-3 fatty acids Omega-3 acid ethyl esters Icosapent ethyl	Elevated TG	4 g daily 4 g daily	4 g daily 4 g daily	↑ TG catabolism	Dyspepsia, fishy odor to breath

Abbreviations: GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; LDL, low-density lipoprotein; LDL-C, LDL-cholesterol; LPL, lipoprotein lipase; TG, triglyceride; VLDL, very-low-density lipoprotein.

Accumulation of chylomicrons in plasma causes recurrent bouts of pancreatitis, usually beginning in childhood, and hepatosplenomegaly is present. Accelerated atherosclerosis is not a feature.

■ APO CII DEFICIENCY

This rare autosomal recessive disorder is due to the absence of apo CII, an essential cofactor for lipoprotein lipase. As a result, chylomicrons and triglycerides accumulate and cause manifestations similar to those in lipoprotein lipase deficiency.

TREATMENT

Isolated Hypertriglyceridemia

Pts with severe hypertriglyceridemia should be placed on a fat-free diet with fat-soluble vitamin supplementation. Pts with moderate hypertriglyceridemia should restrict fat, carbohydrate, and alcohol intake. In those with familial hypertriglyceridemia, fibric acid derivatives, omega-3 fatty acids, or niacin can be administered if dietary measures are insufficient (Table 181-2).

HYPERCHOLESTEROLEMIA AND HYPERTRIGLYCERIDEMIA

Elevations of both triglycerides and cholesterol are caused by elevations in both VLDL and LDL or in VLDL remnant particles.

■ FAMILIAL COMBINED HYPERLIPIDEMIA

This inherited disorder, present in 1/200 persons, can cause different lipoprotein abnormalities in affected individuals, including hypercholesterolemia (elevated LDL), hypertriglyceridemia (elevated triglycerides and VLDL), or both. Atherosclerosis is accelerated. A mixed dyslipidemia (plasma triglycerides 2.3–9.0 mmol/L [200–800 mg/dL], cholesterol levels 5.2–10.3 mmol/L [200–400 mg/dL], and HDL levels <10.3 mmol/L [<40 mg/dL] in men and <12.9 mmol/L [<50 mg/dL] in women) and a family history of hyperlipidemia and/or premature cardiovascular disease suggest the diagnosis of FCHL. Many of these pts also have the metabolic syndrome ([Chap. 120](#)), and it may be difficult to differentiate familial from secondary causes of hyperlipidemia. All pts should restrict dietary cholesterol and fat and avoid alcohol and oral contraceptives; pts with diabetes should be treated aggressively. An HMG-CoA reductase inhibitor is usually required, and many pts will require a second drug (cholesterol absorption inhibitor, niacin, or fibrate) for optimal control.

■ DYSBETALIPOPROTEINEMIA

This rare genetic disorder is associated with homozygosity for an apoprotein variant (apoE2) that has reduced affinity for the LDL receptor. Development of disease requires additional environmental and/or genetic factors. Plasma cholesterol (6.5–13.0 mmol/L [250–500 mg/dL]) and triglycerides (2.8–5.6 mmol/L [250–500 mg/dL]) are increased due to accumulation of VLDL and chylomicron remnant particles. Pts usually present in adulthood with xanthomas and premature coronary and peripheral vascular disease. Cutaneous xanthomas are distinctive, in the form of *palmar* and *tuberoeruptive xanthomas*. Triglycerides and cholesterol are both elevated. Diagnosis is established by lipoprotein electrophoresis (showing a broad beta band) or a ratio of VLDL (by ultracentrifugation) to total plasma triglycerides of >0.3. The disorder is associated with accelerated atherosclerosis. Dietary modifications should be instituted, and HMG-CoA reductase inhibitors, fibrates, and/or niacin may be necessary. Comorbidities, such as diabetes mellitus, obesity, or hypothyroidism, should be optimally managed.

PREVENTION OF THE COMPLICATIONS OF ATHEROSCLEROSIS

Abundant and compelling data demonstrate that interventions to reduce LDL-C substantially reduce the risk of cardiovascular disease, including MI and stroke, as well as total mortality. Thus, is it imperative that pts with hypercholesterolemia be assessed for cardiovascular risk and for the need for intervention. Pts at high risk for cardiovascular disease who have plasma LDL-C levels in the “normal” range also benefit from intervention to reduce LDL-C levels.

Lifestyle The first approach to a pt with hypercholesterolemia and high cardiovascular risk is to make any necessary lifestyle changes. In obese pts, efforts should be made to reduce body weight to the ideal level. Dietary counseling to reduce the content of saturated fats, trans fats, and cholesterol in the diet. Regular aerobic exercise has relatively little impact on reducing plasma LDL-C levels, though has cardiovascular benefits independent of LDL lowering.

Pharmacologic therapy for hypercholesterolemia The decision to use LDL-lowering drug therapy—with a statin being first-line therapy—depends on the level of LDL-C as well as the level of cardiovascular risk. In general, pts with a Mendelian disorder of elevated LDL-C such as FH must be treated to reduce the very high lifetime risk of cardiovascular disease, and treatment should be initiated as early as possible in adulthood, and in some cases during childhood. Otherwise, the decision to initiate LDL-lowering drug therapy is generally determined by the level of cardiovascular risk. In pts with established CVD, statin therapy is well supported by clinical trial data and should be used regardless of the LDL-C level. For pts >40 years old without clinical CVD, the AHA/ACC risk calculator (http://professional.heart.org/professional/GuidelinesStatements/PreventionGuidelines/UCM_457698_Prevention-Guidelines.jsp) can be used to determine the 10-year absolute risk for CVD, and current guidelines suggest that a 10-year risk >7.5% merits consideration of statin therapy regardless of plasma LDL-C level. For younger pts, the assessment of lifetime risk of CVD may help inform the decision to start a statin. For those who do not respond adequately to statins, or cannot tolerate them, additional therapeutic options include ezetimibe, bile acid sequestrants, nicotinic acid, and PCSK9 inhibitors (Table 181-2).

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Hemochromatosis, Porphyrrias, and Wilson's Disease



HEMOCHROMATOSIS

Hemochromatosis is a disorder of iron storage that results in increased intestinal iron absorption with Fe deposition and damage to many tissues. The classic clinical constellation of hemochromatosis is a pt presenting with bronze skin, liver disease, diabetes, arthropathy, cardiac conduction abnormalities, and hypogonadism. Two major causes of hemochromatosis exist: hereditary (due to inheritance of mutant *HFE* genes) and secondary iron overload (usually the result of ineffective erythropoiesis, such as thalassemia or sideroblastic anemia). *HFE* encodes a protein that is involved in cellular iron sensing and in regulating intestinal iron absorption. *HFE* mutations are very common in populations of Northern European origin (1 in 10 is a carrier). Heterozygotes are asymptomatic; homozygotes show a disease penetrance of ~30%.

There is progressive iron overload, with clinical manifestations appearing after age 30–40, typically earlier in men than in women. Alcoholic liver disease and chronic excessive Fe ingestion may also be associated with a moderate increase in hepatic Fe and elevated body Fe stores.

Clinical Features

Early symptoms include weakness, lassitude, weight loss, a bronze pigmentation or darkening of skin, abdominal pain, and loss of libido. Hepatomegaly occurs in 95% of pts, sometimes in the presence of normal LFTs. If untreated, liver disease progresses to cirrhosis, and further to hepatocellular carcinoma in ~30% of pts with cirrhosis. Other manifestations include skin pigmentation (bronzing), diabetes mellitus (65% of pts), arthropathy (25–59%), cardiac arrhythmias and CHF (15%), and hypogonadotropic hypogonadism. Diabetes mellitus is more common in pts with a family history of diabetes, and hypogonadism may be an isolated early manifestation. Typical signs of portal hypertension and decompensated hepatic cirrhosis may appear late in the clinical course. Adrenal insufficiency, hypothyroidism, and hypoparathyroidism rarely occur.

Diagnosis

Serum Fe, percent transferrin saturation, and serum ferritin levels are increased. In an otherwise-healthy person, a fasting serum transferrin saturation >50% is abnormal and suggests homozygosity for hemochromatosis. In most untreated pts with hemochromatosis, the serum ferritin level is also greatly increased. If either the percent transferrin saturation or the serum ferritin level is abnormal, genetic testing for hemochromatosis should be performed. All first-degree relatives of pts with hemochromatosis should be tested for the C282Y and H63D mutations in *HFE*. Liver biopsy may be required in affected individuals to evaluate possible cirrhosis and to quantify tissue iron. An algorithm for evaluating pts with possible hemochromatosis is shown in [Fig. 182-1](#). Death in untreated pts results from cardiac failure (30%), cirrhosis (25%), and hepatocellular carcinoma (30%); the latter may develop despite adequate Fe removal.

TREATMENT

Hemochromatosis

Therapy involves removal of excess body Fe, usually by intermittent phlebotomy, and supportive treatment of damaged organs. Since 1 unit of blood contains ~250 mg Fe, and since up to 25 g of Fe must be removed, phlebotomy is performed weekly for 1–2 years. Less frequent phlebotomy is then used to maintain serum Fe at 9–18 $\mu\text{mol/L}$ (50–100 $\mu\text{g/dL}$). Chelating agents such as deferoxamine (infused subcutaneously using a portable pump) remove 10–20 mg iron per day, a fraction of that mobilized by weekly phlebotomy. An effective oral iron chelating agent, deferasirox (Exjade), is effective in thalassemia and secondary iron overload, but it is expensive and carries the risk of significant side effects. Chelation therapy is indicated, however, when phlebotomy is inappropriate, such as with anemia or hypoproteinemia. Alcohol consumption should be eliminated. End-stage liver disease may require liver transplantation.

PORPHYRIAS

The porphyrias are inherited disturbances in heme biosynthesis. Each of the nine major types causes a unique pattern of overproduction, accumulation, and excretion of intermediates of heme synthesis. These disorders are classified as either hepatic or erythropoietic, depending on the primary site of overproduction and

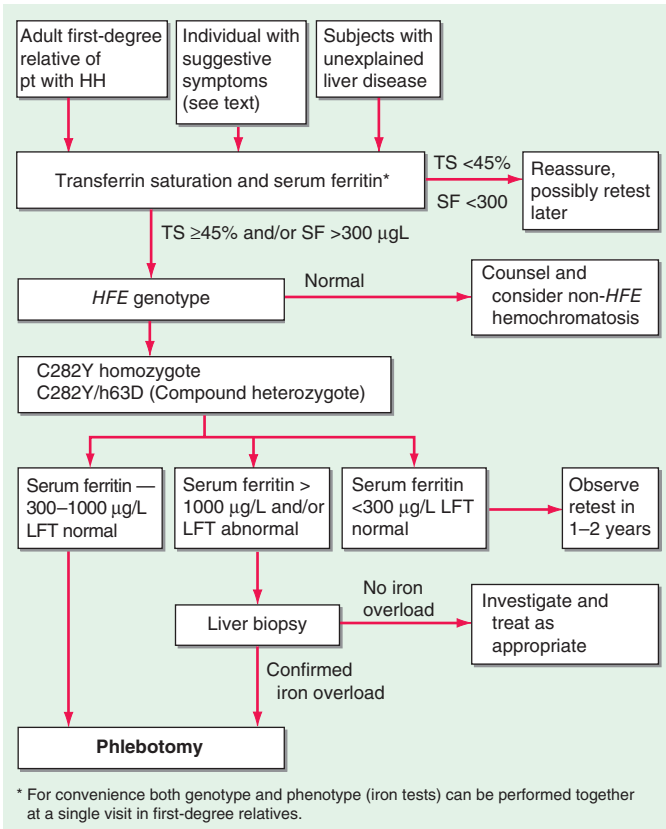


FIGURE 182-1 Algorithm for screening for *HFE*-associated hemochromatosis. HH, hereditary hemochromatosis, homozygous subject (C282Y +/+); LFT, liver function tests; SF, serum ferritin concentration; TS, transferrin saturation. (From EJ Eijkelkamp et al: *Can J Gastroenterol* 14:2, 2000; with permission.)

accumulation of the porphyrin precursor or porphyrin. The major manifestations of the hepatic porphyrias are neurologic (neuropathic abdominal pain, neuropathy, and mental disturbances), whereas the erythropoietic porphyrias characteristically cause cutaneous photosensitivity. Laboratory testing is required to confirm or exclude the various types of porphyria. However, a definite diagnosis requires demonstration of the specific enzyme deficiency or gene defect. Only the three most common porphyrias are discussed here.

■ ACUTE INTERMITTENT PORPHYRIA

This is an autosomal dominant disorder with variable expressivity caused by partial (50%) deficiency in hydroxymethylbilane (HMB) synthase. It has a prevalence of 1–3 in 100,000 but is much more common in certain parts of the world (Northern Sweden, Great Britain). Manifestations include colicky abdominal pain, vomiting, constipation, port wine-colored urine, and neurologic and psychiatric disturbances. Acute attacks rarely occur before puberty and may last from days to months. Photosensitivity does not occur. Clinical and biochemical

manifestations may be precipitated by barbiturates, anticonvulsants, estrogens, oral contraceptives, the luteal phase of the menstrual cycle, alcohol, or low-calorie diets. Diagnosis is established by demonstrating elevation of urinary porphobilinogen (PBG) and γ -aminolevulinic acid (ALA) during an acute attack. Genetic testing, if available, should be used to confirm the diagnosis.

TREATMENT

Acute Intermittent Porphyrria

As soon as possible after the onset of an attack, 3–4 mg of heme, in the form of heme arginate, heme albumin, or hematin, should be infused daily for 4 days. Heme acts by inhibiting ALA synthase, thereby restraining ALA and PBG production. Administration of IV glucose at rates up to 20 g/h or parenteral nutrition, if oral feeding is not possible for long periods, can be effective in acute attacks. Narcotic analgesics may be required during acute attacks for abdominal pain, and phenothiazines are useful for nausea, vomiting, anxiety, and restlessness. Treatment between attacks involves adequate nutritional intake, avoidance of drugs known to exacerbate the disease, and prompt treatment of other intercurrent diseases or infections. Liver transplantation has been effective in selected pt and gene replacement trials are underway.

■ PORPHYRIA CUTANEA TARDA (PCT)

This is the most common porphyria (2–4 in 100,000) and is characterized by cutaneous photosensitivity and, usually, hepatic disease. It is due to partial deficiency (familial, sporadic, or acquired) of hepatic uroporphyrinogen decarboxylase. Photosensitivity causes facial pigmentation, increased fragility of skin, erythema, and vesicular and ulcerative lesions, typically involving face, forehead, and forearms. Neurologic manifestations are not observed. Contributing factors include excess alcohol, iron, and estrogens. The incidence of the common hemochromatosis-causing mutations, hemochromatosis gene (*HFE*) mutations C282Y and H63D, are increased in pts with types 1 and 2 PCT, underscoring the importance of excess hepatic iron as a precipitating factor. Pts with liver disease are at risk for cirrhosis and hepatocellular carcinoma. Plasma and urine uroporphyrin and 7-carboxylate porphyrin are increased.

TREATMENT

Porphyria Cutanea Tarda

Avoidance of precipitating factors, including abstinence from alcohol, estrogens, iron supplements, and other exacerbating drugs, is the first line of therapy. A complete response can almost always be achieved by repeated phlebotomy (every 1–2 weeks) until hepatic iron is reduced. Chloroquine or hydroxychloroquine may be used in low doses (e.g., 125-mg chloroquine phosphate twice weekly) to promote porphyrin excretion in pts unable to undergo or unresponsive to phlebotomy.

■ ERYTHROPOIETIC PROTOPORPHYRIA

Erythropoietic protoporphyria is an autosomal dominant disorder due to partial deficiency of ferrochelatase, the last enzyme in the heme biosynthetic pathway. Its prevalence is 1 in 100,000. Porphyrins (primarily protoporphyrin IX) from bone marrow erythrocytes and plasma are deposited in the skin and lead to

cutaneous photosensitivity. Skin photosensitivity usually begins in childhood. The skin manifestations differ from those of other porphyrias, in that vesicular lesions are uncommon. Redness, swelling, burning, and itching can develop within minutes of sun exposure and resemble angioedema. Symptoms may seem out of proportion to the visible skin lesions. Chronic skin changes may include lichenification, leathery pseudovesicles, labial grooving, and nail changes. Liver function is usually normal, but liver disease and gallstones may occur. Protoporphyrin levels are increased in bone marrow, circulating erythrocytes, plasma, bile, and feces; protoporphyrin in erythrocytes is free rather than zinc complexed as it is in other types of porphyria or hematologic disorders. Urinary porphyrin levels are normal. Diagnosis is confirmed by identifying a mutation in the ferroxidase gene.

TREATMENT

Erythropoietic Protoporphyria

Avoidance of sun exposure is essential. Oral β -carotene (120–180 mg/d) improves tolerance to sunlight in many pts. The dosage may be adjusted to maintain serum carotene levels between 10 and 15 $\mu\text{mol/L}$ (600–800 $\mu\text{g/dL}$). Cholestyramine or activated charcoal may promote fecal excretion of protoporphyrin. Plasmapheresis or IV heme therapy may be beneficial.

WILSON'S DISEASE

Wilson's disease is a rare inherited disorder of copper metabolism, resulting in the toxic accumulation of copper in the liver, brain, and other organs. Individuals with Wilson's disease have mutations in the *ATP7B* gene, which encodes a membrane-bound copper-transporting adenosine triphosphatase (ATPase). Deficiency of this protein impairs copper excretion into the bile and copper incorporation into ceruloplasmin, leading to its rapid degradation.

Clinical Features

Clinical manifestations typically appear in the mid- to late-teen years but may occur later. Hepatic disease may present as hepatitis, cirrhosis, or hepatic decompensation. In other pts, neurologic or psychiatric disturbances are the first clinical sign and are always accompanied by Kayser-Fleischer rings (corneal deposits of copper). Dystonia, incoordination, or tremor may be present, and dysarthria and dysphagia are common. Autonomic disturbances also may be present. Microscopic hematuria is common. In about 5% of pts, the first manifestation may be primary or secondary amenorrhea or repeated spontaneous abortions.

Diagnosis

Serum ceruloplasmin levels are often low but may be normal in up to 10% of pts. Urine copper levels are elevated. The "gold standard" for diagnosis is an elevated copper level on liver biopsy. The disorder can be caused by a large number of different mutations but genetic testing, if available, can confirm the diagnosis in the majority of pts.

TREATMENT

Wilson's Disease

Hepatitis or cirrhosis without decompensation should be treated with zinc acetate (50-mg elemental Zn PO three times a day). Zinc is effective by blocking intestinal copper absorption and inducing metallothionein, which sequesters

copper in a nontoxic complex. For pts with hepatic decompensation, the chelator trientine (500 mg PO twice a day) plus zinc (separated by at least 1 h to avoid zinc chelation in the intestinal lumen) is recommended, although liver transplantation should be considered for severe hepatic decompensation. For initial neurologic therapy, trientine and zinc are recommended for 8 weeks, followed by therapy with zinc alone. For initial neurologic therapy, tetrathiomolybdate is emerging as the drug of choice because of its rapid control of free copper, preservation of neurologic function, and low toxicity. Penicillamine is no longer first-line therapy. Zinc treatment does not require monitoring for toxicity, and 24-h urine copper can be followed for a therapeutic response. Trientine may induce bone marrow suppression and proteinuria. With chelation therapy, measuring free serum copper levels (adjusting total serum copper for ceruloplasmin copper) rather than urine copper is used to monitor therapeutic response. Anti-copper therapy must be lifelong.

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183 The Neurologic Examination



MENTAL STATUS EXAMINATION

- *The bare minimum: During the interview, look for difficulties with communication and determine whether the pt has recall and insight into recent and past events.*

The mental status examination is underway as soon as the physician begins observing and talking with the pt. The goal is to evaluate attention, orientation, memory, insight, judgment, and grasp of general information. Attention: ask pt to respond every time a specific item recurs in a list. Orientation: ask about the day, date, and location. Memory: ask pt to immediately recall a sequence of numbers and test recall of a series of objects after defined times (e.g., 5 and 15 min). Remote memory is also evaluated by assessing pt's ability to provide a cogent chronologic history of the illness or personal life events. Recall of historic events or dates of current events can be used to assess knowledge. Evaluation of language function should include assessment of spontaneous speech, naming, repetition, reading, writing, and comprehension. Additional tests such as ability to draw and copy, perform calculations, interpret proverbs or logic problems, identify right versus left, name and identify body parts, etc., are also important.

A useful screening examination of cognitive function is the mini-mental status examination (MMSE), a 30-point test of cognitive function, with each correct answer being scored as 1 point. It includes tests in the areas of orientation (e.g., identify season/date/month/year/floor/hospital/town/state/country); registration (e.g., name and restate 3 objects); recall (e.g., remember the same three objects 5 minutes later); and language (e.g., name pencil and watch; repeat "no if's and's or but's"; follow a three-step command; obey a written command; and write a sentence and copy a design).

CRANIAL NERVE (CN) EXAMINATION

- *The bare minimum: Check the fundi, visual fields (VFs), pupil size and reactivity, extraocular movements, and facial movements.*

■ CN I

Occlude each nostril sequentially and ask pt to gently sniff and identify a mild test stimulus, such as toothpaste or coffee.

■ CN II

Check visual acuity with eyeglasses or contact lens correction using a Snellen chart or similar tool. Map VFs by confrontation testing in each quadrant of VF for each eye individually. The best method is to sit facing pt (2–3 ft apart) and then have pt cover one eye gently and fix uncovered eye on examiner's nose. A small white object (e.g., a cotton-tipped applicator) is then moved slowly from periphery of field toward center until seen. Pt's VF should be mapped against examiner's for comparison. Formal perimetry and tangent screen examination are essential to identify small defects. Optic fundi should be examined with an ophthalmoscope, and the color, size, and degree of swelling or elevation of the optic disc recorded. The retinal vessels should be checked for size, regularity,

arteriovenous (AV) nicking at crossing points, hemorrhage, exudates, and aneurysms. The retina, including the macula, should be examined for abnormal pigmentation and other lesions.

■ CN III, IV, VI

Describe size, regularity, and shape of pupils; reaction (direct and consensual) to light; and convergence (pt follows an object as it moves closer). Check for lid drooping, lag, or retraction. Ask pt to follow your finger (and report any double vision) as you move it horizontally to left and right and vertically with each eye first fully adducted then fully abducted. Check for failure to move fully in particular directions and for presence of regular, rhythmic, involuntary oscillations of eyes (nystagmus). Test quick voluntary eye movements (saccades) as well as pursuit (e.g., follow the finger).

■ CN V

Feel the masseter and temporalis muscles as pt bites down and test jaw opening, protrusion, and lateral motion against resistance. Examine sensation over entire face. Testing of the corneal reflex is indicated when suggested by the history.

■ CN VII

Look for asymmetry of face at rest and with spontaneous movements. Test eyebrow elevation, forehead wrinkling, eye closure, smiling, frowning; check puff, whistle, lip pursing, and chin muscle contraction. Observe for differences in strength of lower and upper facial muscles. Taste on the anterior two-thirds of tongue can be affected by lesions of the seventh CN proximal to the chorda tympani.

■ CN VIII

Check ability to hear tuning fork, finger rub, watch tick, and whispered voice at specified distances with each ear. Check for air versus mastoid bone conduction (Rinne) and lateralization of a tuning fork placed on center of forehead (Weber). Accurate, quantitative testing of hearing requires formal audiometry. Remember to examine tympanic membranes.

■ CN IX, X

Check for symmetric elevation of palate-uvula with phonation (“ahh”), as well as position of uvula and palatal arch at rest. Sensation in region of tonsils, posterior pharynx, and tongue may also require testing. Pharyngeal (“gag”) reflex is evaluated by stimulating posterior pharyngeal wall on each side with a blunt object (e.g., tongue blade). Direct examination of vocal cords by laryngoscopy is necessary in some situations.

■ CN XI

Check shoulder shrug (trapezius muscle) and head rotation to each side (sternocleidomastoid muscle) against resistance.

■ CN XII

Examine bulk and power of tongue. Look for atrophy, deviation from midline with protrusion, tremor, and small flickering or twitching movements (fasciculations).

■ MOTOR EXAMINATION

- *The bare minimum: Look for muscle atrophy and check extremity tone. Assess upper limb strength by checking for pronator drift and strength of wrist or finger extensors. Test for lower limb strength by asking pt to walk normally and on heels and toes and testing power of the toe extensors.*

Power should be systematically tested for major movements at each joint (Table 183-1). Strength should be recorded using a reproducible scale (e.g., 0 = no

TABLE 183-1 Muscles That Move Joints

	MUSCLE	NERVE	SEGMENTAL INNERVATION	FUNCTION
Shoulder	Supraspinatus	Suprascapular n.	C5,6	Abduction of upper arm
	Deltoid	Axillary n.	C5,6	Abduction of upper arm
Forearm	Biceps	Musculocutaneous n.	C5,6	Flexion of the supinated forearm
	Brachioradialis	Radial n.	C5,6	Forearm flexion with arm between pronation and supination
	Triceps	Radial n.	C6,7,8	Extension of forearm
	Ext. carpi radialis	Radial n.	C5,6	Extension and abduction of hand at the wrist
	Ext. carpi ulnaris	P. interosseous n.	C7,8	Extension and adduction of hand at the wrist
	Ext. digitorum	P. interosseous n.	C7,8	Extension of fingers at the MCP joints
	Supinator	P. interosseous n.	C6,7	Supination of the extended forearm
	Flex. carpi radialis	Median n.	C6,7	Flexion and abduction of hand at the wrist
	Flex. carpi ulnaris	Ulnar n.	C7,8,T1	Flexion and adduction of hand at the wrist
	Pronator teres	Median n.	C6,7	Pronation of the forearm
	Wrist	Ext. carpi ulnaris	Ulnar n.	C7,8,T1
Flex. carpi radialis		Median n.	C6,7	Flexion/abduction at the wrist
Hand	Lumbricals	Median + ulnar n.	C8,T1	Extension of fingers at PIP joint with the MCP joint extended and fixed
	Interossei	Ulnar n.	C8,T1	Abduction/adduction of the fingers
	Flex. digitorum	Median + A. interosseous n.	C7,C8,T1	Flexion of the fingers
Thumb	Opponens pollicis	Median n.	C8,T1	Touching the base of the 5th finger with thumb
	Ext. pollicis	P. interosseous n.	C7,8	Extension of the thumb
	Add. pollicis	Ulnar n.	C8,T1	Adduction of the thumb
	Abd. pollicis	Median n.	C8,T1	Abduction of the thumb
	Flex. pollicis br.	Ulnar n.	C8,T1	Flexion of the thumb

(Continued)

TABLE 183-1 Muscles That Move Joints (Continued)

	MUSCLE	NERVE	SEGMENTAL INNERVATION	FUNCTION
Thigh	Iliopsoas	Femoral n.	L1,2,3	Flexion of the thigh
	Glutei	Sup. + inf. gluteal n.	L4,L5,S1,S2	Abduction, extension, and internal rotation of the leg
	Quadriceps	Femoral n.	L2,3,4	Extension of the leg at the knee
	Adductors	Obturator n.	L2,3,4	Adduction of the leg
	Hamstrings	Sciatic n.	L5,S1,S2	Flexion of the leg at the knee
Foot	Gastrocnemius	Tibial n.	S1,S2	Plantar flexion of the foot
	Tibialis ant.	Deep peroneal n.	L4,5	Dorsiflexion of the foot
	Peronei	Deep peroneal n.	L5,S1	Eversion of the foot
	Tibialis post.	Tibial n.	L4,5	Inversion of the foot
Toes	Ext. hallucis l.	Deep peroneal n.	L5,S1	Dorsiflexion of the great toe

Abbreviations: MCP, metacarpophalangeal; PIP, proximal interphalangeal.

movement, 1 = flicker or trace of contraction with no associated movement at a joint, 2 = movement present but cannot be sustained against gravity, 3 = movement against gravity but not against applied resistance, 4 = movement against some degree of resistance, and 5 = full power; 4 values can be supplemented with + and – signs to provide additional gradations). Speed of movement, ability to relax contractions promptly, and fatigue with repetition should all be noted. Loss in bulk and size of muscle (atrophy) should be noted, as well as the presence of irregular involuntary contraction (twitching) of groups of muscle fibers (fasciculations). Any involuntary movements should be noted at rest, during maintained posture, and with voluntary action.

REFLEXES

- *The bare minimum: Tap the biceps, patellar, and Achilles reflexes.*

Important muscle-stretch reflexes to test routinely and the spinal cord segments involved in their reflex arcs include biceps (C5, 6); brachioradialis (C5, 6); triceps (C6, 7); patellar (L3, 4); and Achilles (S1, 2). A common grading scale is 0 = absent, 1 = present but diminished, 2 = normal, 3 = hyperactive, and 4 = hyperactive with clonus (repetitive rhythmic contractions with maintained stretch). The plantar reflex should be tested by using a blunt-ended object such as the point of a key to stroke the outer border of the sole of the foot from the heel toward the base of the great toe. An abnormal response (Babinski sign) is extension (dorsiflexion) of the great toe at the metatarsophalangeal joint. In some cases, this may be associated with abduction (fanning) of other toes and variable degrees of flexion at ankle, knee, and hip. Normal response is plantar flexion of the toes. Superficial abdominal and anal reflexes are important in certain situations; unlike muscle stretch reflexes, these cutaneous reflexes disappear with CNS lesions.

SENSORY EXAMINATION

- *The bare minimum: Ask whether the pt can feel light touch and the temperature of a cool object in each distal extremity. Check double simultaneous stimulation using light touch on the hands.*

For most purposes it is sufficient to test sensation to pinprick, touch, position, and vibration in each of the four extremities (Figs. 183-1 and 183-2). The Romberg maneuver, primarily a test of proprioception, is tested as follows: pt is asked to stand with feet together while eyes are open, and eyes are then closed; loss of balance with the eyes closed is an abnormal response. Specific problems often require more thorough evaluation. Pts with cerebral lesions may have abnormalities in “discriminative sensation” such as the ability to perceive double simultaneous stimuli, to localize stimuli accurately, to identify closely approximated stimuli as separate (two-point discrimination), to identify objects by touch alone (stereognosis), or to judge weights, evaluate texture, or identify letters or numbers written on the skin surface (graphesthesia).

COORDINATION AND GAIT

- *The bare minimum: Test rapid alternating movements of the hands and feet, and the finger-to-nose maneuver. Observe the pt while he or she is walking along a straight line.*

The ability to move the index finger accurately from the nose to the examiner’s outstretched finger and the ability to slide the heel of each foot from the knee

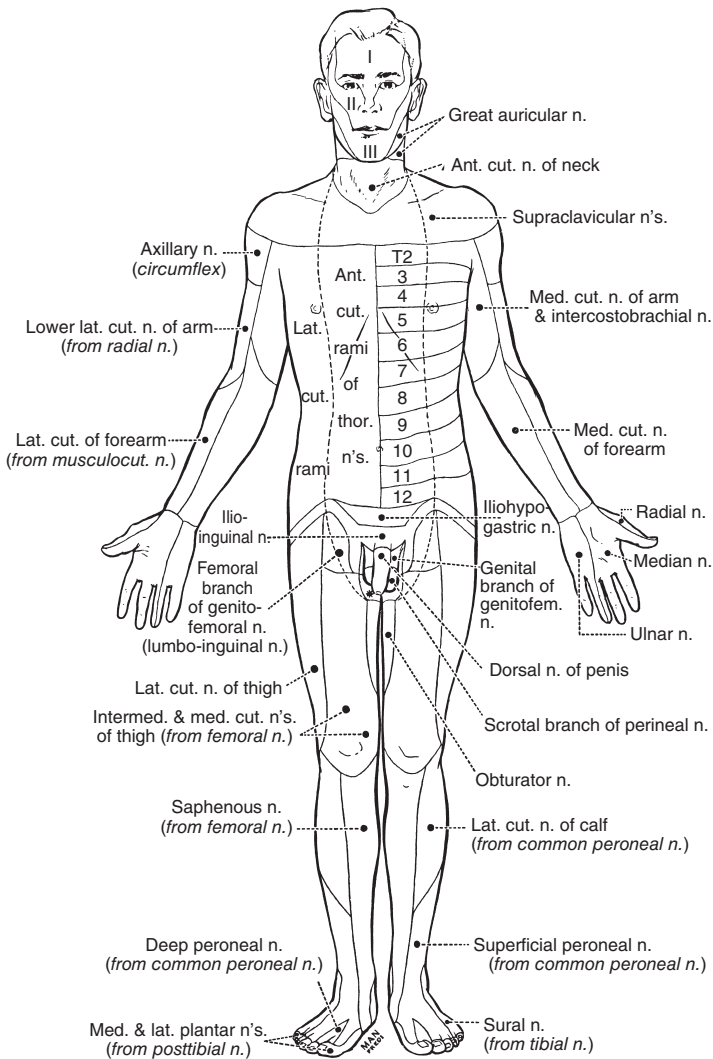


FIGURE 183-1 The cutaneous fields of peripheral nerves. (Reproduced by permission from W Haymaker, B Woodhall: *Peripheral Nerve Injuries*, 2nd ed. Philadelphia, Saunders, 1953.)

down the shin are tests of coordination. Additional tests (drawing objects in the air, following a moving finger, tapping with index finger against thumb or alternately against each individual finger) may also be useful. The ability to walk normally, on a straight line (tandem walk), and to turn should all be observed.

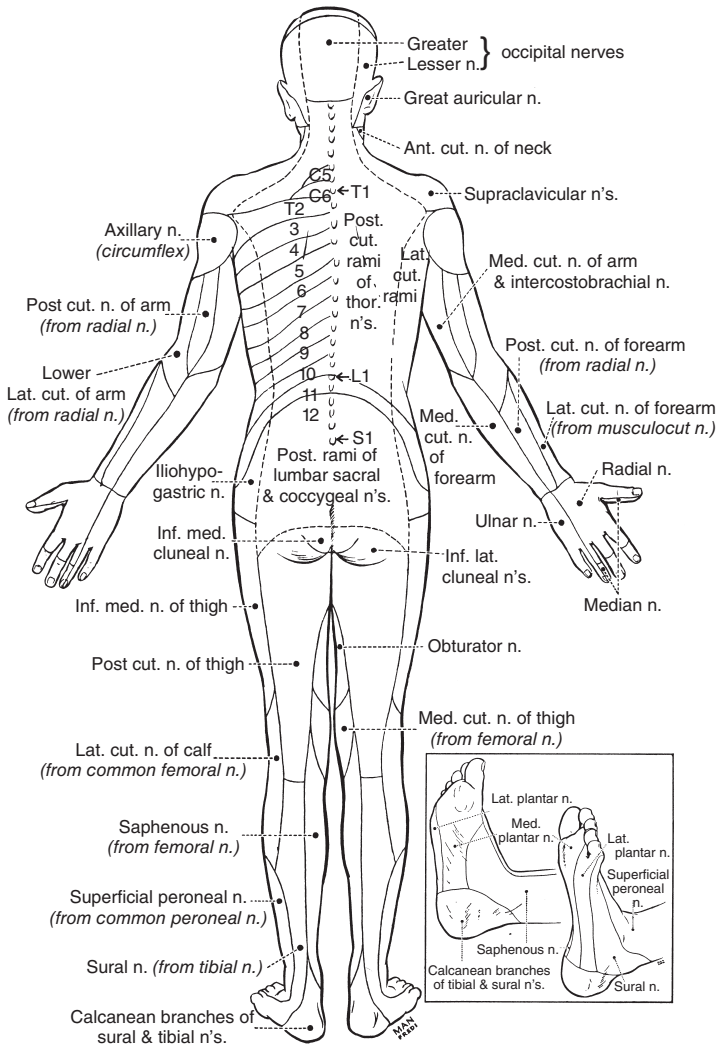


FIGURE 183-1 (Continued)

THE NEUROLOGIC METHOD AND LOCALIZATION

The clinical data obtained from the neurologic examination coupled with a careful history are interpreted to arrive at an anatomic localization that best explains the clinical findings (Table 183-2), to narrow the list of diagnostic possibilities, and to select the diagnostic tests most likely to be informative.

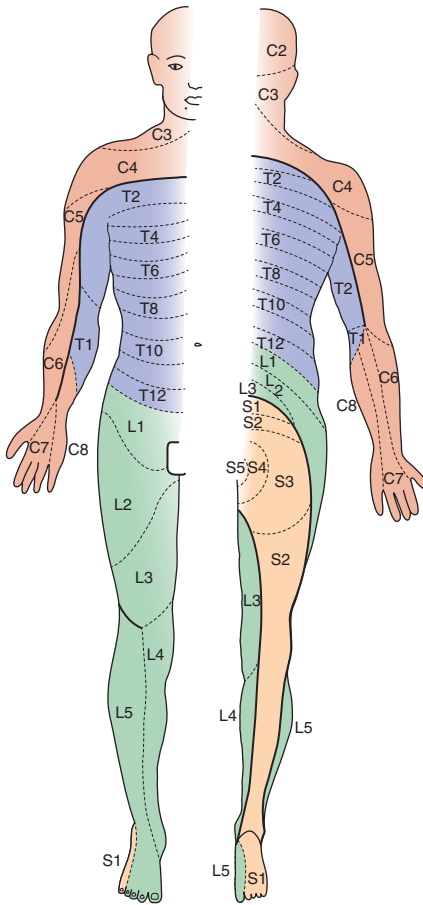


FIGURE 183-2 Distribution of the sensory spinal roots on the surface of the body (dermatomes). (From D Sinclair: *Mechanisms of Cutaneous Sensation*. Oxford, UK, Oxford University Press, 1981; with permission from Dr. David Sinclair.)

TABLE 183-2 Findings Helpful for Localizations within the Nervous System

	SIGNS
Cerebrum	<ul style="list-style-type: none"> Abnormal mental status or cognitive impairment Seizures Unilateral weakness^a and sensory abnormalities including head and limbs Visual field abnormalities Movement abnormalities (e.g., diffuse incoordination, tremor, chorea)

(Continued)

TABLE 183-2 Findings Helpful for Localizations within the Nervous System (Continued)

	SIGNS
Brainstem	Isolated cranial nerve abnormalities (single or multiple) “Crossed” weakness ^a and sensory abnormalities of head and limbs, e.g., weakness of right face and left arm and leg
Spinal cord	Back pain or tenderness Weakness ^a and sensory abnormalities sparing the head Mixed upper and lower motor neuron findings Sensory level Sphincter dysfunction
Spinal roots	Radiating limb pain Weakness ^b or sensory abnormalities following root distribution (see Figs. 183-1 and 183-2) Loss of reflexes
Peripheral nerve	Mid or distal limb pain Weakness ^b or sensory abnormalities following nerve distribution (see Figs. 183-1 and 183-2) “Stocking or glove” distribution of sensory loss Loss of reflexes
Neuromuscular junction	Bilateral weakness including face (ptosis, diplopia, dysphagia) and proximal limbs Increasing weakness with exertion Sparing of sensation
Muscle	Bilateral proximal or distal weakness Sparing of sensation

^aWeakness along with other abnormalities having an “upper motor neuron” pattern, i.e., spasticity, weakness of extensors > flexors in the upper extremity and flexors > extensors in the lower extremity, and hyperreflexia.

^bWeakness along with other abnormalities having a “lower motor neuron” pattern, i.e., flaccidity and hyporeflexia.

184 Seizures and Epilepsy



A *seizure* is a transient occurrence of signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. *Epilepsy* is diagnosed when there is a risk of recurrent seizures due to a chronic, underlying process.

APPROACH TO THE PATIENT

Seizure

Seizure classification: Essential for diagnosis, therapy, and prognosis (Table 184-1). Seizures are focal or generalized: *focal seizures* originate in networks limited to one cerebral hemisphere, and *generalized seizures* rapidly engage networks distributed across both hemispheres. *Focal seizures* are further divided based on presence or absence of cognitive impairment.

TABLE 184-1 Classification of Seizures^a**1. Focal Onset**

(Can be further described as having intact or impaired awareness, motor or nonmotor onset, or evolve from focal to bilateral tonic clonic)

2. Generalized Onset

a. Motor

Tonic-clonic

Other motor (e.g., atonic, myoclonic)

b. Nonmotor (absence)

3. Unknown Onset

(Can be further described as motor or nonmotor, or unclassified)

^aBased on the new 2017 International League Against Epilepsy classification of seizure types (Data from Fisher RS et al: *Epilepsia* 58:522, 2017).

Generalized seizures may occur as a primary disorder or result from secondary generalization of a focal seizure. *Tonic-clonic seizures* (grand mal) cause sudden loss of consciousness, loss of postural control, and tonic muscular contraction producing teeth-clenching and rigidity in extension (tonic phase), followed by rhythmic muscular jerking (clonic phase). Tongue-biting and incontinence may occur during the seizure. Recovery of consciousness is typically gradual over many minutes to hours. Headache and confusion are common postictal phenomena. In *absence seizures* (petit mal) there is sudden, brief impairment of consciousness without loss of postural control. Events rarely last longer than 5–10 s but can recur many times per day. Minor motor symptoms are common, while complex automatisms and clonic activity are not. Other types of generalized seizures include tonic, atonic, and myoclonic seizures.

Etiology: Seizure type and age of pt provide important clues to etiology (Table 184-2).

■ CLINICAL EVALUATION

Careful history is essential since diagnosis of seizures and epilepsy is often based solely on clinical grounds. Differential diagnosis (Table 184-3) includes syncope or psychogenic seizures (“pseudoseizures”). General examination includes search for infection, trauma, toxins, systemic illness, neurocutaneous abnormalities, and vascular disease. A number of drugs lower the seizure threshold (Table 184-4). Asymmetries in neurologic examination suggest brain tumor, stroke, trauma, or other focal lesions. An algorithmic approach is shown in Fig. 184-1.

■ LABORATORY EVALUATION

Routine blood studies are indicated to identify the more common metabolic causes of seizures such as abnormalities in electrolytes, glucose, calcium, or magnesium, and hepatic or renal disease. A screen for toxins in blood and urine should be obtained especially when no clear precipitating factor has been identified. A lumbar puncture is indicated if there is any suspicion of CNS infection such as meningitis or encephalitis; it is mandatory in immunosuppressed pts even in the absence of symptoms or signs suggesting infection. Testing for autoantibodies in the serum and CSF should be considered in pts presenting with an aggressive form of epilepsy associated with cognitive disturbances.

Electroencephalography

All pts should be evaluated as soon as possible with an EEG, which measures electrical activity of the brain by recording from electrodes placed on the scalp. The presence of *electrographic seizure activity* during the clinically evident event

TABLE 184-2 Causes of Seizures

Neonates (<1 month)	<ul style="list-style-type: none"> Perinatal hypoxia and ischemia Intracranial hemorrhage and trauma CNS infection Metabolic disturbances (hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxine deficiency) Drug withdrawal Developmental disorders Genetic disorders
Infants and children (>1 month and <12 years)	<ul style="list-style-type: none"> Febrile seizures Genetic disorders (metabolic, degenerative, primary epilepsy syndromes) CNS infection Developmental disorders Trauma
Adolescents (12–18 years)	<ul style="list-style-type: none"> Trauma Genetic disorders Infection Illicit drug use Brain tumor
Young adults (18–35 years)	<ul style="list-style-type: none"> Trauma Alcohol withdrawal Illicit drug use Brain tumor Autoantibodies
Older adults (>35 years)	<ul style="list-style-type: none"> Cerebrovascular disease Brain tumor Alcohol withdrawal Metabolic disorders (uremia, hepatic failure, electrolyte abnormalities, hypoglycemia, hyperglycemia) Alzheimer's disease and other degenerative CNS diseases Autoantibodies

Abbreviation: CNS, central nervous system.

(i.e., abnormal, repetitive, rhythmic activity having an abrupt onset and termination) clearly establishes the diagnosis. The absence of electrographic seizure activity does not exclude a seizure disorder, however. The EEG is always abnormal during generalized tonic-clonic seizures. Continuous monitoring for prolonged periods may be required to capture the EEG abnormalities. The EEG can, but does not always, show abnormal discharges during the interictal period that support the diagnosis of epilepsy and is useful for classifying seizure disorders, selecting anticonvulsant medications, and determining prognosis.

Brain Imaging

All pts with unexplained new-onset seizures should have a brain imaging study (MRI or CT) to search for an underlying structural abnormality; the only exception may be children who have an unambiguous history and examination

TABLE 184-3 Differential Diagnosis of Seizures

Syncope	Transient ischemic attack (TIA)
Vasovagal syncope	Basilar artery TIA
Cardiac arrhythmia	Sleep disorders
Valvular heart disease	Narcolepsy/cataplexy
Cardiac failure	Benign sleep myoclonus
Orthostatic hypotension	Movement disorders
Psychological disorders	Tics
Psychogenic seizure	Nonepileptic myoclonus
Hyperventilation	Paroxysmal choreoathetosis
Panic attack	Special considerations in children
Metabolic disturbances	Breath-holding spells
Alcoholic blackouts	Migraine with recurrent abdominal pain and cyclic vomiting
Delirium tremens	Benign paroxysmal vertigo
Hypoglycemia	Apnea
Hypoxia	Night terrors
Psychoactive drugs (e.g., hallucinogens)	Sleepwalking
Migraine	
Confusional migraine	
Basilar migraine	

suggestive of a benign, generalized seizure disorder such as absence epilepsy. Newer MRI methods have increased the sensitivity for detection of abnormalities of cortical architecture, including hippocampal atrophy associated with mesial temporal sclerosis, as well as abnormalities of cortical neuronal migration.

TREATMENT

Seizures and Epilepsy

- Acute management of seizures
 - Pt should be placed in semiprone position with head to the side to avoid aspiration.
 - Tongue blades or other objects should not be forced between clenched teeth.
 - Oxygen should be given via face mask.
 - Reversible metabolic disorders (e.g., hypoglycemia, hyponatremia, hypocalcemia, drug or alcohol withdrawal) should be promptly corrected.
 - Treatment of status epilepticus is discussed in [Chap. 24](#).
- Longer-term therapy includes treatment of underlying conditions, avoidance of precipitating factors (e.g., sleep deprivation), prophylactic therapy with antiepileptic medications or surgery, and addressing various psychological and social issues.
- Choice of antiepileptic drug therapy depends on a variety of factors including seizure type, dosing schedule, and potential side effects ([Tables 184-5 and 184-6](#)).
- Therapeutic goal is complete cessation of seizures without side effects using a single drug (monotherapy) and a dosing schedule that is easy for the pt to follow.

TABLE 184-4 Drugs and Other Substances That Can Cause Seizures**Alkylating agents** (e.g., busulfan, chlorambucil)**Antimalarials** (chloroquine, mefloquine)**Antimicrobials/antivirals** β -lactam and related compounds

Quinolones

Acyclovir

Isoniazid

Ganciclovir

Anesthetics and analgesics

Meperidine

Fentanyl

Tramadol

Local anesthetics

Dietary supplements

Ephedra (ma huang)

Gingko

Immunomodulatory drugs

Cyclosporine

OKT3 (monoclonal antibodies to T cells)

Tacrolimus

Interferons

Psychotropics

Antidepressants (e.g., bupropion)

Antipsychotics (e.g., clozapine)

Lithium

Radiographic contrast agents**Drug withdrawal**

Alcohol

Baclofen

Barbiturates (short-acting)

Benzodiazepines (short-acting)

Zolpidem

Drugs of abuse

Amphetamine

Cocaine

Phencyclidine

Methylphenidate

Flumazenil^a^aIn benzodiazepine-dependent pts.

- If ineffective, medication should be increased to maximal tolerated dose based primarily on clinical response rather than serum levels.
- If still unsuccessful, a second drug should be added, and when control is obtained, the first drug can be slowly tapered. Some pts will require polytherapy with two or more drugs, although monotherapy should be the goal.

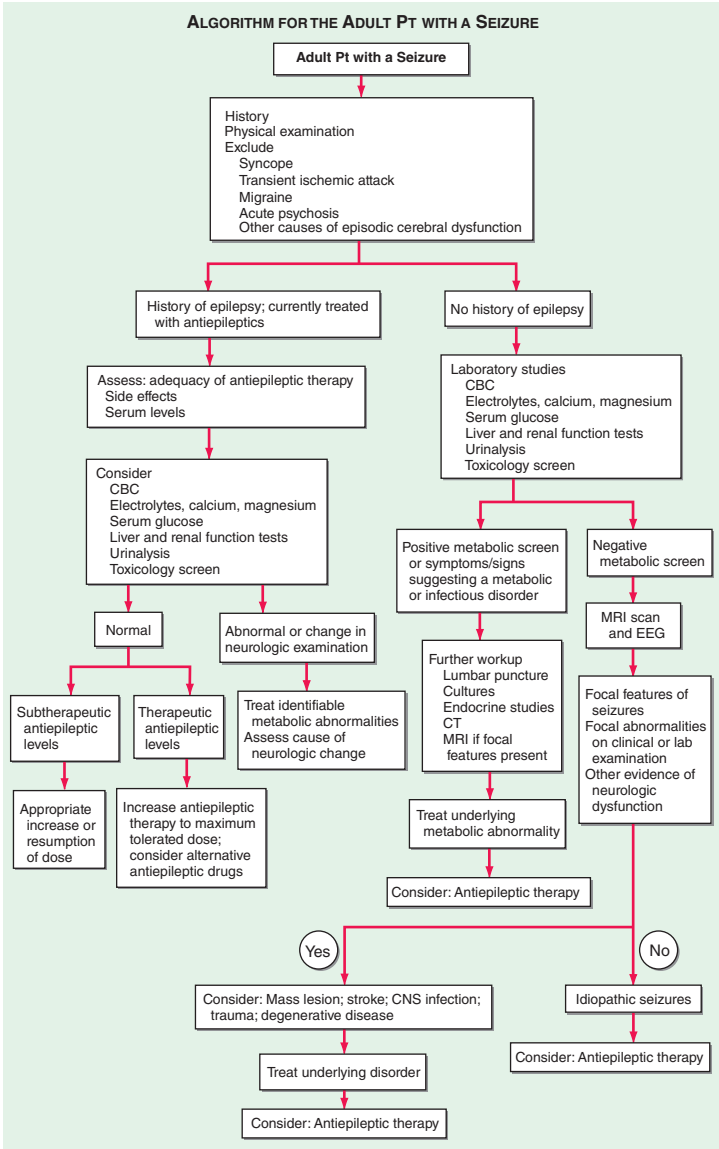


FIGURE 184-1 Evaluation of the adult pt with a seizure. CBC, complete blood count; CNS, central nervous system; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging.

– Pts with certain epilepsy syndromes (e.g., temporal lobe epilepsy) are often refractory to medical therapy and benefit from surgical excision of the seizure focus or various forms of neurostimulation.

TABLE 184-5 Dosage and Adverse Effects of Commonly Used Antiepileptic Drugs

GENERIC NAME	TRADE NAME	PRINCIPAL USES	TYPICAL DOSE; DOSE INTERVAL	HALF-LIFE	THERAPEUTIC RANGE	ADVERSE EFFECTS		DRUG INTERACTIONS ^a
						NEUROLOGIC	SYSTEMIC	
Brivaracetam	Briviact	Focal-onset	100–200 mg/d; bid	7–10 h	Not established	Fatigue Dizziness Weakness Ataxia Mood changes	Gastrointestinal irritation	May increase carbamazepine-epoxide causing decreased tolerability May increase phenytoin
Carbamazepine	Tegreto ^l	Tonic-clonic Focal-onset	600–1800 mg/d (15–35 mg/kg, child); bid (capsules or tablets), tid-qid (oral suspension)	10–17 h (variable due to autoinduction; complete 3–5 wk after initiation)	4–12 µg/mL	Ataxia Dizziness Diplopia Vertigo	Aplastic anemia Leukopenia Gastrointestinal irritation Hepatotoxicity Hyponatremia	Level decreased by enzyme-inducing drugs ^b Level increased by erythromycin, propoxyphene, isoniazid, cimetidine, fluoxetine
Clobazam	Onfi	Lennox-Gastaut syndrome	10–40 mg/d (5–20 mg/d for pts <30 kg body weight); bid	36–42 h (71–82 h for less active metabolite)	Not established	Fatigue Sedation Ataxia Aggression Insomnia	Constipation Anorexia Skin rash	Level increased by CYP2C19 inhibitors

(Continued)

TABLE 184-5 Dosage and Adverse Effects of Commonly Used Antiepileptic Drugs (Continued)

GENERIC NAME	TRADE NAME	PRINCIPAL USES	TYPICAL DOSE; DOSE INTERVAL	HALF-LIFE	THERAPEUTIC RANGE	ADVERSE EFFECTS		DRUG INTERACTIONS ^a
						NEUROLOGIC	SYSTEMIC	
Clonazepam	Klonopin	Absence Atypical absence Myoclonic	1–12 mg/d; qd-tid	24–48 h	10–70 ng/mL	Ataxia Sedation Lethargy	Anorexia	Level decreased by enzyme-inducing drugs ^b
Ethosuximide	Zarontin	Absence	750–1250 mg/d (20–40 mg/kg); qd-bid	60 h, adult 30 h, child	40–100 µg/mL	Ataxia Lethargy Headache	Gastrointestinal irritation Skin rash Bone marrow suppression	Level decreased by enzyme-inducing drugs ^b Level increased by valproic acid
Felbamate	Felbatol	Focal-onset Lennox-Gastaut syndrome Tonic-clonic	2400–3600 mg/d, tid-qid	16–22 h	30–60 µg/mL	Insomnia Dizziness Sedation Headache	Aplastic anemia Hepatic failure Weight loss Gastrointestinal irritation	Increases phenytoin, valproic acid, active carbamazepine metabolite
Gabapentin	Neurontin	Focal-onset	900–2400 mg/d; tid-qid	5–9 h	2–20 µg/mL	Sedation Dizziness Ataxia Fatigue	Gastrointestinal irritation Weight gain Edema	No known significant interactions

Lacosamide	Vimpat	Focal-onset	200–400 mg/d; bid	13 h	Not established	Dizziness Ataxia Diplopia Vertigo	Gastrointestinal irritation Cardiac conduction (PR interval prolongation)	Level decreased by enzyme-inducing drugs ^b
Lamotrigine	Lamictal ^c	Focal-onset Tonic-clonic Atypical absence Myoclonic Lennox-Gastaut syndrome	150–500 mg/d; bid (immediate release), daily (extended release) (lower daily dose for regimens with valproic acid; higher daily dose for regimens with an enzyme inducer)	25 h 14 h (with enzyme-inducers), 59 h (with valproic acid)	2.5–20 µg/mL	Dizziness Diplopia Sedation Ataxia Headache	Skin rash Stevens-Johnson syndrome	Level decreased by enzyme-inducing drugs ^b and oral contraceptives Level increased by valproic acid
Levetiracetam	Keppra ^c	Focal-onset	1000–3000 mg/d; bid (immediate release), daily (extended release)	6–8 h	5–45 µg/mL	Sedation Fatigue Incoordination Mood changes	Anemia Leukopenia	No known significant interactions

(Continued)

TABLE 184-5 Dosage and Adverse Effects of Commonly Used Antiepileptic Drugs (Continued)

GENERIC NAME	TRADE NAME	PRINCIPAL USES	TYPICAL DOSE; DOSE INTERVAL	HALF-LIFE	THERAPEUTIC RANGE	ADVERSE EFFECTS		DRUG INTERACTIONS ^a
						NEUROLOGIC	SYSTEMIC	
Oxcarbazepine ^c	Trileptal	Focal-onset Tonic-clonic	900–2400 mg/d (30–45 mg/kg, child); bid	10–17 h (for active metabolite)	10–35 µg/mL	Fatigue Ataxia Dizziness Diplopia Vertigo Headache	See carbamazepine	Level decreased by enzyme-inducing drugs ^b May increase phenytoin
Phenobarbital	Luminal	Tonic-clonic Focal-onset	60–180 mg/d; qd-tid	90 h	10–40 µg/mL	Sedation Ataxia Confusion Dizziness Decreased libido Depression	Skin rash	Level increased by valproic acid, phenytoin
Phenytoin (diphenylhydantoin)	Dilantin	Tonic-clonic Focal-onset	300–400 mg/d (3–6 mg/kg, adult; 4–8 mg/kg, child); qd-tid	24 h (wide variation, dose-dependent)	10–20 µg/mL	Dizziness Diplopia Ataxia Incoordination Confusion	Gingival hyperplasia Lymphadenopathy Hirsutism Osteomalacia Facial coarsening Skin rash	Level increased by isoniazid, sulfonamides, fluoxetine Level decreased by enzyme-inducing drugs ^b Altered folate metabolism

Primidone	Mysoline	Tonic-clonic Focal-onset	750–1000 mg/d; bid-tid	Primidone, 8–15 h Phenobarbital, 90 h	Primidone, 4–12 µg/mL Phenobarbital, 10–40 µg/mL	Same as phenobarbital		Level increased by valproic acid Level decreased by phenytoin (increased conversion to phenobarbital)
Rufinamide	Banzel	Lennox- Gastaut syndrome	3200 mg/d (45 mg/kg, child); bid	6–10 h	Not established	Sedation Fatigue Dizziness Ataxia Headache Diplopia	Gastrointestinal irritation Leukopenia Cardiac conduction (QT interval shortening)	Level decreased by enzyme- inducing drugs ^b Level increased by valproic acid May increase phenytoin
Tiagabine	Gabitril	Focal-onset	32–56 mg/d; bid-qid (as adjunct to enzyme- inducing antiepileptic drug regimen)	2–5 h (with enzyme inducer), 7–9 h (without enzyme inducer)	Not established	Confusion Sedation Depression Dizziness Speech or language problems Paresthesias Psychosis	Gastrointestinal irritation	Level decreased by enzyme- inducing drugs ^b

(Continued)

TABLE 184-5 Dosage and Adverse Effects of Commonly Used Antiepileptic Drugs (Continued)

GENERIC NAME	TRADE NAME	PRINCIPAL USES	TYPICAL DOSE; DOSE INTERVAL	HALF-LIFE	THERAPEUTIC RANGE	ADVERSE EFFECTS		DRUG INTERACTIONS ^a
						NEUROLOGIC	SYSTEMIC	
Topiramate	Topamax	Focal-onset Tonic-clonic Lennox-Gastaut syndrome	200–400 mg/d; bid (immediate release), daily (extended release)	20 h (immediate release), 30 h (extended release)	2–20 µg/mL	Psychomotor slowing Sedation Speech or language problems Fatigue Paresthesias	Renal stones (avoid use with other carbonic anhydrase inhibitors) Glaucoma Weight loss Hypohidrosis	Level decreased by enzyme-inducing drugs ^b
Valproic acid (valproate sodium, divalproex sodium)	Depakene Depakote ^c	Tonic-clonic Absence Atypical absence Myoclonic Focal-onset Atonic	750–2000 mg/d (20–60 mg/kg); bid-qid (immediate and delayed release), daily (extended release)	15 h	50–125 µg/mL	Ataxia Sedation Tremor	Hepatotoxicity Thrombocytopenia Gastrointestinal irritation Weight gain Transient alopecia Hyperammonemia	Level decreased by enzyme-inducing drugs ^b
Zonisamide	Zonegran	Focal-onset Tonic-clonic	200–400 mg/d; qd-bid	50–68 h	10–40 µg/mL	Sedation Dizziness Confusion Headache Psychosis	Anorexia Renal stones Hypohidrosis	Level decreased by enzyme-inducing drugs ^b

^aExamples only; please refer to other sources for comprehensive listings of all potential drug–drug interactions.

^bPhenytoin, carbamazepine, phenobarbital.

^cExtended-release product available.

TABLE 184-6 Selection of Antiepileptic Drugs

GENERALIZED-ONSET TONIC-CLONIC	FOCAL	TYPICAL ABSENCE	ATYPICAL ABSENCE, MYOCLONIC, ATONIC
First-line			
Lamotrigine	Lamotrigine	Valproic acid	Valproic acid
Valproic acid	Carbamazepine	Ethosuximide	Lamotrigine
	Oxcarbazepine	Lamotrigine	Topiramate
	Phenytoin		
	Levetiracetam		
Alternatives			
Zonisamide ^a	Zonisamide ^a	Lamotrigine	Clonazepam
Phenytoin	Brivaracetam	Clonazepam	Felbamate
Levetiracetam	Topiramate		Clobazam
Carbamazepine	Valproic acid		Rufinamide
Oxcarbazepine	Tiagabine ^a		
Topiramate	Gabapentin ^a		
Phenobarbital	Lacosamide ^a		
Primidone	Phenobarbital		
Felbamate	Primidone		
	Felbamate		

^aAs adjunctive therapy.

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Alzheimer's Disease and Other Dementias



DEMENTIA

Dementia is an acquired deterioration in cognitive ability that impairs the successful performance of activities of daily living. Memory is the most common cognitive ability lost with dementia; 10% of persons age >70 and 20–40% of individuals age >85 have clinically identifiable memory loss. Other mental faculties are also affected in dementia, such as language, visuospatial ability, calculation, judgment, and problem solving. Neuropsychiatric and social deficits develop in many dementia syndromes, resulting in depression, withdrawal, hallucinations, delusions, agitation, insomnia, and disinhibition. Dementia is usually chronic and progressive.

DIAGNOSIS

Brief screening tools such as the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MOCA), and the Cognistat are useful screening tests and can follow progression. The MMSE is a 30-point test of cognitive function, with each correct answer being scored as 1 point. It includes tests in the areas of: orientation (e.g., identify season/date/month/year/floor/hospital/town/state/country); registration (e.g., name and restate 3 objects); recall (e.g., remember the same 3 objects 5 minutes later); and language (e.g., name pencil and watch);

repeat “no ifs ands or buts”; follow a 3-step command; obey a written command; and write a sentence and copy a design). A functional assessment should also be performed to help determine the day-to-day impact of the disorder.

APPROACH TO THE PATIENT

Dementia

Differential Diagnosis: Dementia has many causes (Table 185-1). It is essential to exclude treatable etiologies; the most common potentially reversible diagnoses are depression, hydrocephalus, and alcohol dependence. The major degenerative dementias can usually be distinguished by distinctive symptoms, signs, and neuroimaging features (Table 185-2).

History: A subacute onset of confusion may represent delirium and should trigger the search for intoxication, infection, or metabolic derangement (Chap. 18). An elderly person with slowly progressive memory loss over several years is likely to have Alzheimer’s disease (AD). A change in personality, disinhibition, gain of weight, or compulsive eating suggests frontotemporal dementia (FTD), not AD; apathy, loss of executive function, progressive abnormalities in speech, or relative sparing of memory or visuospatial abilities also suggests FTD. Dementia with Lewy bodies (DLB) is suggested by the early presence of visual hallucinations, parkinsonism, tendency to delirium, sensitivity to psychoactive medications, or a REM behavior disorder (RBD, the loss of skeletal muscle paralysis during dreaming).

A history of stroke suggests vascular dementia, which may also occur with hypertension, atrial fibrillation, peripheral vascular disease, and diabetes. Rapid progression of dementia with myoclonus suggests a prion disease such as Creutzfeldt-Jakob disease (CJD). A rapidly progressive dementia with psychiatric symptoms and seizures suggests paraneoplastic *encephalitis associated with NMDA receptor antibodies*; affected pts are often young women with ovarian teratoma (Chap. 79). Gait disturbance is prominent with vascular dementia, Parkinson’s disease, DLB, or normal-pressure hydrocephalus. Multiple sex partners or IV drug use should trigger search for an infection, especially HIV or syphilis. A history of head trauma could indicate chronic subdural hematoma, chronic traumatic encephalopathy, or normal-pressure hydrocephalus. Alcoholism may suggest malnutrition and thiamine deficiency. A history of gastric surgery may result in loss of intrinsic factor and vitamin B₁₂ deficiency. A careful review of medications, especially of sedatives and tranquilizers, may raise the issue of drug intoxication. A family history of dementia is found in Huntington’s disease and in familial forms of AD, FTD, DLB, or prion disorders. Insomnia or weight loss is often seen with depression-related cognitive impairments, which can also be caused by the recent death of a loved one.

Examination: It is essential to document the dementia, look for other signs of nervous system involvement, and search for clues of a systemic disease that might be responsible for the cognitive disorder. Typical AD does not affect motor systems until late in the course. In contrast, FTD pts often develop axial rigidity, supranuclear gaze palsy, or features of amyotrophic lateral sclerosis. In DLB, initial symptoms may be the new onset of a parkinsonian syndrome (resting tremor, cogwheel rigidity, bradykinesia, and festinating gait). Unexplained falls, axial rigidity, dysphagia, and gaze deficits suggest progressive supranuclear palsy (PSP).

Focal neurologic deficits may occur in vascular dementia or brain tumor. Dementia with a myelopathy and peripheral neuropathy suggests

TABLE 185-1 Differential Diagnosis of Dementia

Most Common Causes of Dementia	
Alzheimer's disease	Alcoholism ^a
Vascular dementia	PDD/LBD spectrum
Multi-infarct	Drug/medication intoxication ^a
Diffuse white matter disease (Binswanger's)	
Less Common Causes of Dementia	
Vitamin deficiencies	Toxic disorders
Thiamine (B ₁): Wernicke's encephalopathy ^a	Drug, medication, and narcotic poisoning ^a
B ₁₂ (subacute combined degeneration) ^a	Heavy metal intoxication ^a
Nicotinic acid (pellagra) ^a	Organic toxins
Endocrine and other organ failure	Psychiatric
Hypothyroidism ^a	Depression (pseudodementia) ^a
Adrenal insufficiency and Cushing's syndrome ^a	Schizophrenia ^a
Hypo- and hyperparathyroidism ^a	Conversion disorder ^a
Renal failure ^a	Degenerative disorders
Liver failure ^a	Huntington's disease
Pulmonary failure ^a	Multisystem atrophy
Chronic infections	Hereditary ataxias (some forms)
HIV	Frontotemporal lobar degeneration spectrum
Neurosyphilis ^a	Multiple sclerosis
Papovavirus (JC virus) (progressive multifocal leukoencephalopathy)	Adult Down's syndrome with Alzheimer's disease
Tuberculosis, fungal, and protozoal ^a	ALS-parkinsonism-dementia complex of Guam
Whipple's disease ^a	Prion (Creutzfeldt-Jakob and Gerstmann-Sträussler-Scheinker diseases)
Head trauma and diffuse brain damage	Miscellaneous
Chronic traumatic encephalopathy	Sarcoidosis ^a
Chronic subdural hematoma ^a	Vasculitis ^a
Postanoxia	CADASIL, etc.
Postencephalitis	Acute intermittent porphyria ^a
Normal-pressure hydrocephalus ^a	Recurrent nonconvulsive seizures ^a
Intracranial hypotension	Additional conditions in children or adolescents
Neoplastic	Pantothenate kinase–associated neurodegeneration
Primary brain tumor ^a	Subacute sclerosing panencephalitis
Metastatic brain tumor ^a	Metabolic disorders (e.g., Wilson's and Leigh's diseases, leukodystrophies, lipid storage diseases, mitochondrial mutations)
Paraneoplastic/autoimmune limbic encephalitis ^a	

^aPotentially reversible dementia.

Abbreviations: ALS, amyotrophic lateral sclerosis; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; LBD, Lewy body disease; PDD, Parkinson's disease dementia.

TABLE 185-2 Clinical Differentiation of the Major Dementias

DISEASE	FIRST SYMPTOM	MENTAL STATUS	NEUROPSYCHIATRY	NEUROLOGY	IMAGING
AD	Memory loss	Episodic memory loss	Irritability, anxiety, depression	Initially normal	Entorhinal cortex and hippocampal atrophy
FTD	Apathy; poor judgment/insight, speech/language; hyperorality	Frontal/executive and/or language; spares drawing	Apathy, disinhibition, overeating, compulsivity	May have vertical gaze palsy, axial rigidity, dystonia, alien hand, or MND	Frontal, insular, and/or temporal atrophy; usually spares posterior parietal lobe
DLB	Visual hallucinations, REM sleep behavior disorder, delirium, Capgras syndrome, parkinsonism	Drawing and frontal/executive; spares memory; delirium-prone	Visual hallucinations, depression, sleep disorder, delusions	Parkinsonism	Posterior parietal atrophy; hippocampi larger than in AD
CJD	Dementia, mood, anxiety, movement disorders	Variable, frontal/executive, focal cortical, memory	Depression, anxiety, psychosis in some	Myoclonus, rigidity, parkinsonism	Cortical ribboning and basal ganglia or thalamus hyperintensity on diffusion/FLAIR MRI
Vascular	Often but not always sudden; variable; apathy, falls, focal weakness	Frontal/executive, cognitive slowing; can spare memory	Apathy, delusions, anxiety	Usually motor slowing, spasticity; can be normal	Cortical and/or subcortical infarctions, confluent white matter disease

Abbreviations: AD, Alzheimer's disease; CBD, cortical basal degeneration; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; FLAIR, fluid-attenuated inversion recovery; FTD, frontotemporal dementia; MND, motor neuron disease; MRI, magnetic resonance imaging; PSP, progressive supranuclear palsy; REM, rapid eye movement.

vitamin B₁₂ deficiency. A peripheral neuropathy could also indicate an underlying vitamin deficiency or heavy metal intoxication. Dry cool skin, hair loss, and bradycardia suggest hypothyroidism. Confusion associated with repetitive stereotyped movements may indicate ongoing seizure activity. Hearing impairment or visual loss may produce confusion and disorientation misinterpreted as dementia. Such sensory deficits are common in the elderly.

Choice of Diagnostic Studies: A reversible or treatable cause must not be missed, yet no single etiology is common; thus a screen must employ multiple tests, each of which has a low yield. **Table 185-3** lists most screening tests for dementia. Guidelines recommend the routine measurement of a complete

TABLE 185-3 Evaluation of the Pt with Dementia

ROUTINE EVALUATION	OPTIONAL FOCUSED TESTS	OCCASIONALLY HELPFUL TESTS
History Physical examination Laboratory tests Thyroid function (TSH) Vitamin B ₁₂ Complete blood count Electrolytes CT/MRI	Psychometric testing Chest x-ray Lumbar puncture Liver function Renal function Urine toxin screen HIV Apolipoprotein E RPR or VDRL	EEG Parathyroid function Adrenal function Urine heavy metals RBC sedimentation rate Angiogram Brain biopsy SPECT PET Lab screen for autoantibodies
Diagnostic categories		
REVERSIBLE CAUSES	IRREVERSIBLE/DEGENERATIVE DEMENTIAS	PSYCHIATRIC DISORDERS
Examples Hypothyroidism Thiamine deficiency Vitamin B ₁₂ deficiency Normal-pressure hydrocephalus Subdural hematoma Chronic infection Brain tumor Drug intoxication Autoimmune encephalopathy	Examples Alzheimer's Frontotemporal dementia Huntington's Dementia with Lewy bodies Vascular Leukoencephalopathies Parkinson's	Depression Schizophrenia Conversion reaction
Associated treatable conditions		
	Depression Seizures Insomnia	Agitation Caregiver "burnout" Drug side effects

Abbreviations: CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; PET, positron emission tomography; RBC, red blood cell; RPR, rapid plasma reagin (test); SPECT, single-photon emission computed tomography; TSH, thyroid-stimulating hormone; VDRL, Venereal Disease Research Laboratory (test for syphilis).

blood count, electrolytes, renal and thyroid function, a vitamin B₁₂ level, and a neuroimaging study (CT or MRI). Lumbar puncture need not be done routinely but is indicated if infection or inflammation is a consideration; CSF levels of tau protein and amyloid β_{42} show differing patterns with the various dementias although their sensitivity and specificity are not yet sufficiently high to warrant routine use. An EEG is rarely helpful except to suggest a prion disease or an underlying nonconvulsive seizure disorder. The role of functional-metabolic imaging in the diagnosis of dementia is still under study; amyloid imaging has shown promise for the diagnosis of AD; currently the main clinical value is to exclude AD as the likely cause of dementia in pts who have negative scans. Brain biopsy may be indicated to diagnose vasculitis, potentially treatable neoplasms, or unusual infections.

ALZHEIMER'S DISEASE

Most common cause of dementia; 10% of all persons age >70 have significant memory loss, and in more than half the cause is AD. Cost is >\$50,000 annually for a pt with advanced AD.

■ CLINICAL MANIFESTATIONS

Cognitive changes follow a characteristic pattern beginning with memory impairment and spreading to language and visuospatial deficits, although 20% present with nonmemory complaints such as word-finding, organizational, or navigational difficulty. Memory loss is often not recognized initially, in part due to preservation of social graces until later phases; impaired activities of daily living (keeping track of finances, appointments) draw attention of friends/family. Once the memory loss becomes noticeable to the pt and spouse and falls 1.5 standard deviations below normal on standardized memory tests, the term *mild cognitive impairment* (MCI) is applied; roughly 50% will progress to AD over 4 years. Increasingly, the MCI construct is being replaced by the notion of "early symptomatic AD" to signify that AD is considered the underlying disease. Recent evidence suggests that partial and sometimes generalized seizures herald AD and can occur even prior to dementia onset, especially in younger pts. Disorientation, poor judgment, poor concentration, aphasia, and apraxia are increasingly evident as the disease progresses. Pts may be frustrated or unaware of deficit. In end-stage AD, pts become rigid, mute, incontinent, and bedridden. Help may be needed with the simplest tasks, such as eating, dressing, and toilet function. Often, death results from malnutrition, secondary infections, pulmonary emboli, heart disease, or, most commonly, aspiration. Typical duration is 8–10 years, but the course can range from 1 to 25 years.

■ PATHOGENESIS

Risk factors for AD: old age, positive family history, and a history of head trauma with concussion. Pathology: neuritic plaques composed in part of A β amyloid, derived from amyloid precursor protein (APP); neurofibrillary tangles composed of abnormally phosphorylated tau protein. The apolipoprotein E (apoE) $\epsilon 4$ allele accelerates age of onset of AD and is associated with sporadic and late-onset familial cases. ApoE testing is not indicated as a predictive test. Rare genetic causes of AD are Down syndrome and mutations in APP, presenilin-1, and presenilin-2 genes; all increase production of A β amyloid. Genetic testing available for presenilin mutations; likely to be revealing only in early-age-of-onset familial AD. Genome-wide association studies have implicated several genes, including *TREM2*, a gene involved with inflammation that increases the likelihood of dementia.

TREATMENT**Alzheimer's Disease**

- AD cannot be cured, and no highly effective drug exists. The focus is on judicious use of cholinesterase inhibitor drugs; symptomatic management of behavioral problems; and building rapport with the pt, family members, and other caregivers.
 - Donepezil (target dose, 10 mg daily), rivastigmine (target dose, 6 mg twice daily or 9.5-mg patch daily), galantamine (target dose 24 mg daily, extended-release), and memantine (target dose, 10 mg twice daily) are approved by the FDA for treatment of AD. Due to hepatotoxicity, tacrine is no longer used. Donepezil (Aricept) has the advantages of few side effects and single daily dosage. With the exception of memantine, action is inhibition of cholinesterase, with a resulting increase in cerebral levels of acetylcholine. Memantine appears to act by blocking overexcited *N*-methyl-D-aspartate (NMDA) channels.
 - These compounds are only modestly effective and offer little or no benefit in the late stages of AD; they are associated with improved caregiver ratings of pts' functioning and with an apparent decreased rate of decline in cognitive test scores over periods of up to 3 years.
- There is no role for hormone replacement therapy in prevention of AD in women, and no benefit has been found in the treatment of established AD with estrogen.
- Randomized trials of *Ginkgo biloba* have found it to be ineffective. Retrospective studies suggest that NSAIDs and statin medications may have a protective effect on dementia if used prior to the onset of the disease but do not benefit established AD.
- Other experimental approaches target amyloid either through diminishing its production or promoting clearance by passive immunization with monoclonal antibodies. New trials have targeted asymptomatic individuals with mild AD, asymptomatic autosomal dominant forms of AD, and cognitively normal elderly who are amyloid positive with PET. Medications that modify tau phosphorylation and aggregation, including tau antibodies, are also under study.
- Depression, common in early stages of AD, may respond to antidepressants or cholinesterase inhibitors. Selective serotonin reuptake inhibitors (SSRIs) are often used due to their low anticholinergic side effects (for example, escitalopram, target dose 5–10 mg daily). Management of behavioral problems in conjunction with family and caregivers is essential. Mild sedation may help insomnia.
- Control of agitation usually involves low doses of atypical antipsychotic medications, but recent trials have shown mild efficacy with significant side effects related to sleep and gait; in addition, all of the antipsychotics carry a black box warning in the elderly, increasing the risk of cardiovascular complications and death, and therefore should be used with caution.
- Notebooks and posted daily reminders can function as memory aids in early stages. Kitchens, bathrooms, and bedrooms need evaluation for safety. Pts must eventually stop driving. Caregiver burnout is common; nursing home placement may be necessary. Local and national support groups (Alzheimer's Disease and Related Disorders Association) are valuable resources.

OTHER CAUSES OF DEMENTIA

■ FRONTOTEMPORAL DEMENTIA

Often begins in the fifth to seventh decades; in this age group it is nearly as prevalent as AD. Unlike AD, behavioral symptoms may predominate in the early stages of FTD. Three main clinical syndromes. In the behavioral variant, the most common FTD syndrome, social and emotional systems dysfunction manifests as apathy, disinhibition, compulsivity, loss of empathy, and overeating, often but not always accompanied by deficits in executive control. Two forms of primary progressive aphasia, the semantic and nonfluent/agrammatic variants, are also commonly due to FTD. In the semantic variant, pts slowly lose the ability to decode word, object, person-specific, and emotion meaning, whereas pts with the nonfluent/agrammatic variant develop profound inability to produce words, often with prominent motor speech impairment. Any of these three clinical syndromes may be accompanied by motor neuron disease (**Chap. 188**). FTD may be sporadic or inherited. The most common autosomal dominant mutations involve the *C9ORF72*, *GRN*, and *MAPT* genes. Treatment is symptomatic; no therapies are known to slow progression or improve cognitive symptoms. Many of the behaviors that accompany FTD such as depression, hyperorality, compulsions, and irritability may be helped with SSRIs.

■ DEMENTIA WITH LEWY BODIES

Characterized by visual hallucinations, parkinsonism, fluctuating alertness, falls, and often RBD. Dementia can precede or follow the appearance of parkinsonism; when it occurs after an established diagnosis of Parkinson's disease (**Chap. 186**), many use the term Parkinson's disease dementia (PDD). Lewy bodies are intraneuronal cytoplasmic inclusions. Anticholinesterase compounds often provide significant benefit due to a severe cholinergic deficit in DLB. Pts with DLB are extremely sensitive to dopaminergic medications, which must be carefully titrated; tolerability may be improved by concomitant use of a cholinesterase inhibitor. Exercise programs to maximize motor function and protect against fall-related injury, and antidepressants to treat depressive syndromes may be helpful. Antipsychotics in low doses to alleviate psychosis may be considered, although DLB pts are also extremely sensitive to these agents and may experience worsening of extrapyramidal symptoms.

■ VASCULAR DEMENTIA

Typically follows a pattern of either multiple stroke-like episodes (multi-infarct dementia) or diffuse white matter disease (leukoaraiosis, subcortical arteriosclerotic encephalopathy, Binswanger's disease) (**Fig. 185-1**). A genetic disorder, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is due to a mutation in the *NOTCH3* gene and presents as small vessel strokes, progressive dementia and extensive white matter disease often beginning in mid-adult life. Unlike AD, in vascular dementia focal neurologic signs (e.g., hemiparesis) are often apparent at presentation. Treatment focuses on underlying causes of atherosclerosis.

■ NORMAL-PRESSURE HYDROCEPHALUS (NPH)

Uncommon; presents as a gait disorder (ataxic or apraxic), dementia, and urinary incontinence. Gait improves in some pts following ventricular shunting; dementia and incontinence do not improve. The diagnosis is difficult to make, and the clinical picture may overlap with several other causes of dementia including AD; historically many individuals treated for NPH have suffered from other dementias.

■ HUNTINGTON'S DISEASE

Chorea, behavioral disturbance, and a frontal/executive disorder (**Chap. 56**). Typical onset fourth to fifth decade but can present at almost any age. Autosomal

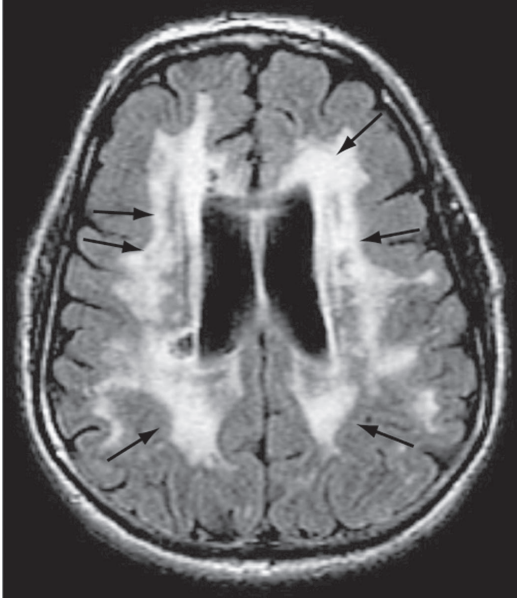


FIGURE 185-1 Diffuse white matter disease. Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance image through the lateral ventricles reveals multiple areas of hyperintensity (arrows) involving the periventricular white matter as well as the corona radiata and striatum. Although seen in some individuals with normal cognition, this appearance is more pronounced in pts with dementia of a vascular etiology.

dominant inheritance due to expanded trinucleotide repeat in gene encoding the protein huntingtin. Diagnosis confirmed with genetic testing coupled with genetic counseling. Symptomatic treatment of movements and behaviors; SSRIs may help depression.

■ CREUTZFELDT-JAKOB DISEASE

Prion disorders such as CJD are rare (~1 per million). CJD is a rapidly progressive disorder with dementia, focal cortical signs, rigidity, and myoclonus; death in <1 year from first symptom. The markedly abnormal periodic discharges on EEG and cortical ribboning and basal ganglia hyperintensities on diffusion-weighted and fluid-attenuated inversion recovery MRI are diagnostic features. No proven treatments exist.

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Parkinson's Disease



■ CLINICAL FEATURES

Parkinsonism is a general term used to define a syndrome of bradykinesia (slowness of voluntary movements) with rigidity and/or tremor (Table 186-1); it has a wide differential diagnosis (Table 186-2). *Parkinson's disease* (PD) is idiopathic

TABLE 186-1 Clinical Features of Parkinson's Disease

CARDINAL MOTOR FEATURES	OTHER MOTOR FEATURES	NONMOTOR FEATURES
Bradykinesia	Micrographia	Anosmia
Rest tremor	Masked facies (hypomimia)	Sensory disturbances (e.g., pain)
Rigidity	Reduced eye blinking	Mood disorders (e.g., depression)
Postural instability	Drooling	Sleep disturbances (e.g., RBD)
	Soft voice (hypophonia)	Autonomic disturbances
	Dysphagia	Orthostatic hypotension
	Freezing	Gastrointestinal disturbances
		Genitourinal disturbances
		Sexual dysfunction
		Cognitive impairment/ Dementia

Abbreviation: RBD, rapid eye movement behavior disorder.

parkinsonism without evidence of more widespread neurologic involvement. PD afflicts >1 million individuals in the United States. Mean age of onset is about 60 years; course progressive over 10–25 years. Tremor (“pill rolling” of hands) at rest (4–6 Hz). Presentation with tremor confined to one limb or one side of body is common. Other findings: rigidity (“cogwheeling”—increased ratchet-like resistance to passive limb movements), bradykinesia, fixed expressionless face (facial masking) with reduced frequency of blinking, hypophonic voice, drooling, impaired rapid alternating movements, micrographia (small handwriting), reduced arm swing, and flexed “stooped” posture with walking, shuffling gait, difficulty initiating or stopping walking, en-bloc turning (multiple small steps required to turn), retropulsion (tendency to fall backwards). Nonmotor aspects of PD include depression and anxiety, cognitive impairment, sleep disturbances, sensation of inner restlessness, loss of smell (*anosmia*), and disturbances of autonomic function. Normal muscular strength, deep tendon reflexes, and sensory examination. Diagnosis based on history and examination; neuroimaging, EEG, and CSF studies usually normal for age.

■ PATHOPHYSIOLOGY

Most PD cases occur sporadically. Degeneration of pigmented pars compacta neurons of the substantia nigra in the midbrain resulting in lack of dopaminergic input to striatum; accumulation of cytoplasmic intraneuronal inclusion granules (Lewy bodies). Cause of cell death is unknown, but may result from generation of free radicals and oxidative stress, inflammation, or mitochondrial dysfunction; no environmental factor has yet been conclusively determined to cause typical PD. Genetic forms of parkinsonism exist (5–15% of cases); most common are mutations in glucocerebrosidase, *LRRK2*, *α-synuclein* or *parkin* genes. Early age of onset suggests a possible genetic cause of PD, although *LLRK2* mutations cause PD in the same age range as sporadic.

■ DIFFERENTIAL DIAGNOSIS

Atypical parkinsonism refers to a group of neurodegenerative conditions usually associated with more widespread neurodegeneration than is found in PD

TABLE 186-2 Differential Diagnosis of Parkinsonism

Parkinson's disease	Atypical parkinsonism	Secondary parkinsonism	Neurodegenerative disorders and other forms of parkinsonism
Sporadic	Multiple-system atrophy (MSA)	Drug-induced	Wilson's disease
Genetic	Cerebellar type (MSA-c)	Tumor	Huntington's disease
Dementia with Lewy bodies	Parkinson type (MSA-p)	Infection	Neurodegeneration with brain iron accumulation
	Progressive supranuclear palsy	Vascular	SCA 3 (spinocerebellar ataxia)
	Parkinsonism	Normal-pressure hydrocephalus	Fragile X–associated ataxia-tremor-parkinsonism
	Richardson variant	Trauma	Prion disease
	Corticobasal syndrome	Liver failure	X-linked dystonia-parkinsonism
	Frontotemporal dementia	Toxins (e.g., carbon monoxide, manganese, MPTP, cyanide, hexane, methanol, carbon disulfide)	Alzheimer's disease with parkinsonism
			Dopa-responsive dystonia

Abbreviation: MPTP, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine.

TABLE 186-3 Features Suggesting an Atypical or Secondary Cause of Parkinsonism

SYMPTOMS/SIGNS	ALTERNATIVE DIAGNOSIS TO CONSIDER
History	
Early speech and gait impairment (Lack of tremor, lack of motor asymmetry)	Atypical parkinsonism
Exposure to neuroleptics	Drug-induced parkinsonism
Onset prior to age 40	Genetic form of PD
Liver disease	Wilson's disease, non-Wilsonian hepatolenticular degeneration
Early hallucinations and dementia with later development of PD features	Dementia with Lewy bodies
Diplopia, impaired down gaze	PSP
Poor or no response to an adequate trial of levodopa	Atypical or secondary parkinsonism
Physical Examination	
Dementia as first or early feature	Dementia with Lewy bodies
Prominent orthostatic hypotension	MSA-p
Prominent cerebellar signs	MSA-c
Slow saccades with impaired down gaze	PSP
High-frequency (6–10 Hz) symmetric postural tremor with a prominent kinetic component	Essential tremor

Abbreviations: MSA-c, multiple-system atrophy–cerebellar type; MSA-p, multiple-system atrophy–Parkinson's type; PD, Parkinson's disease; PSP, progressive supranuclear palsy.

including multiple-system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal ganglionic degeneration (CBGD), and frontotemporal dementia (FTD). Secondary parkinsonism can be associated with drugs (neuroleptics as well as GI medications such as metoclopramide, all of which block dopamine), infection, or exposure to toxins such as carbon monoxide or manganese. Some features to suggest that parkinsonism might be due to a condition other than PD are shown in [Table 186-3](#).

TREATMENT

Parkinson's Disease (See [Fig. 186-1](#), [Table 186-4](#))

Goals are to maintain function and avoid drug-induced complications; start therapy when symptoms interfere with quality of life. Bradykinesia, tremor, rigidity, and abnormal posture respond early in illness; cognitive symptoms, hypophonia, autonomic dysfunction, and balance difficulties respond poorly.

LEVODOPA

- Routinely administered in combination with a decarboxylase inhibitor to prevent its peripheral metabolism to dopamine and the development of nausea and vomiting. In the United States, levodopa is combined with carbidopa (Sinemet).
- Levodopa is also available in controlled-release formulations and in those with a catechol-O-methyl transferase (COMT) inhibitor (see below).

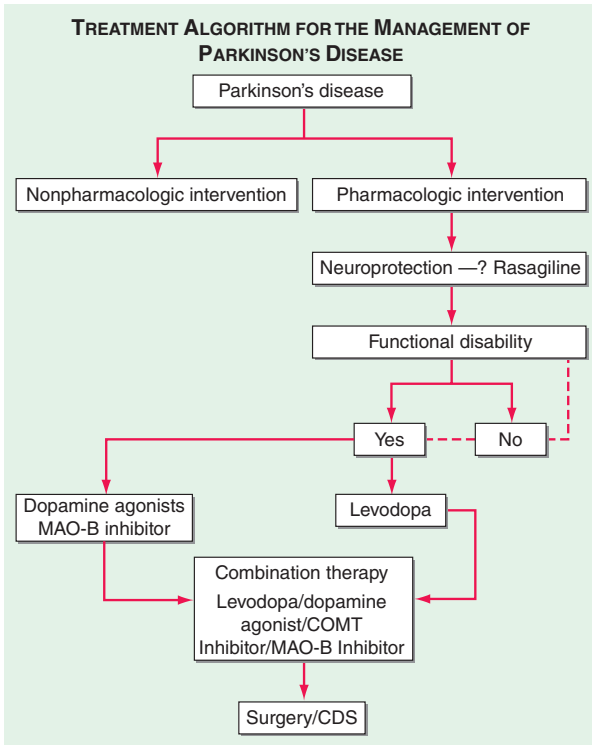


FIGURE 186-1 Treatment options for the management of Parkinson's disease (PD). Decision points include: (1) Introduction of a neuroprotective therapy: no drug has been established to have or is currently approved for neuroprotection or disease modification, but there are several agents that have this potential based on laboratory and preliminary clinical studies (e.g., rasagiline 1 mg/d, coenzyme Q10 1200 mg/d, the dopamine agonists ropinirole, and pramipexole). (2) When to initiate symptomatic therapy: There is a trend toward initiating therapy at the time of diagnosis or early in the course of the disease because pts may have some disability even at an early stage, and there is the possibility that early treatment may preserve beneficial compensatory mechanisms; however, some experts recommend waiting until there is functional disability before initiating therapy. (3) What therapy to initiate: many experts favor starting with a monoamine oxidase type B (MAO-B) inhibitor in mildly affected pts because of the good safety profile of the drug and the potential for a disease-modifying effect; dopamine agonists for younger pts with functionally significant disability to reduce the risk of motor complications; and levodopa for pts with more advanced disease, the elderly, or those with cognitive impairment. Recent studies suggest the early employment of polypharmacy using low doses of multiple drugs to avoid side effects associated with high doses of any one agent. (4) Management of motor complications: motor complications are typically approached with combination therapy to try and reduce dyskinesia and enhance the "on" time. When medical therapies cannot provide satisfactory control, surgical therapies such as DBS or continuous infusion of levodopa/carbidopa intestinal gel can be considered. (5) Nonpharmacologic approaches: interventions such as exercise, education, and support should be considered throughout the course of the disease. CDS, continuous dopaminergic stimulation; COMT, catechol-O-methyltransferase. (Adapted from Olanow CW et al: *The scientific and clinical basis for the treatment of Parkinson disease* (2009). *Neurology* 72:S1, 2009.)

TABLE 186-4 Drugs Commonly Used for Treatment of Parkinson's Disease^a

AGENT	AVAILABLE DOSAGES	TYPICAL DOSING
Levodopa ^a		
Carbidopa/levodopa	10/100, 25/100, 25/250 mg	200–1000 mg levodopa/day
Benserazide/levodopa	25/100, 50/200 mg	
Carbidopa/levodopa CR	25/100, 50/200 mg	
Benserazide/levodopa MDS	25/200, 25/250 mg	
Parcopa	10/100, 25/100, 25/250	
Rytary (carbidopa/levodopa)	23.75/95, 36.25/145, 48.75/195, 61.25/245	See conversion tables
Carbidopa/levodopa/entacapone	12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200 mg	
Dopamine agonists		
Pramipexole	0.125, 0.25, 0.5, 1.0, 1.5 mg	0.25–1.0 mg tid
Pramipexole ER	0.375, 0.75, 1.5, 3.0, 4.5 mg	1–3 mg/d
Ropinirole	0.25, 0.5, 1.0, 3.0 mg	6–24 mg/d
Ropinirole XL	2, 4, 6, 8 mg	6–24 mg/d
Rotigotine patch	2-, 4-, 6-, 8-mg patches	4–24 mg/d
Apomorphine SC	2–8 mg	2–8 mg
COMT inhibitors		
Entacapone	200 mg	200 mg with each levodopa dose
Tolcapone	100, 200 mg	100–200 mg tid
Opicapone	50 mg	50 mg HS
MAO-B inhibitors		
Selegiline	5 mg	5 mg bid
Rasagiline	0.5, 1.0 mg	mg QAM
Safinamide	100 mg	100 mg QAM

^aTreatment should be individualized. Generally, drugs should be started in low doses and titrated to optimal dose.

Note: Drugs should not be withdrawn abruptly but should be gradually lowered or removed as appropriate.

Abbreviations: COMT, catechol-O-methyltransferase; MAO-B, monoamine oxidase type B; QAM, every morning.

- Levodopa remains the most effective symptomatic treatment for PD, and lack of response to the medication despite an adequate trial should cause the diagnosis to be questioned.
- Side effects include nausea, vomiting, and orthostatic hypotension that can be avoided by gradual titration.
- Levodopa-induced motor complications consist of fluctuations in motor response and involuntary movements known as dyskinesias.
- When pts initially take the drug, the benefits are long-lasting; with continued treatment, the duration of benefit following an individual dose becomes progressively shorter (“wearing-off effect”).

DOPAMINE AGONISTS

- A diverse group of drugs that act directly on dopamine receptors. Second-generation non-ergot dopamine agonists are commonly used (e.g., pramipexole, ropinirole, rotigotine).
- Compared with levodopa, dopamine agonists are longer acting and thus provide a more uniform stimulation of dopamine receptors; less prone to induce dyskinesias compared with levodopa.
- They are effective as monotherapeutic agents and as adjuncts to carbidopa/levodopa therapy.
- Side effects include nausea, vomiting, and postural hypotension. Hallucinations and cognitive impairment are more common than with levodopa, so caution is urged in those older than 70.
- Sedation with sudden episodes of falling asleep while driving have been reported.
- Associated with impulse-control disorders including pathologic gambling, hypersexuality, and compulsive eating and shopping.

MAO-B INHIBITORS

- Block central dopamine metabolism and increase synaptic concentrations of the neurotransmitter; generally safe and well tolerated.
- Provide modest antiparkinson benefits when used as monotherapy in early disease.
- Recent work has examined whether these drugs could have a disease-modifying effect; however, long-term significance is uncertain.

COMT INHIBITORS

- When levodopa is administered with a decarboxylase inhibitor, it is primarily metabolized by COMT; inhibitors of COMT increase the elimination half-life of levodopa and enhance its brain availability.
- Combining levodopa with a COMT inhibitor reduces wearing-off time.

OTHER MEDICAL THERAPIES

- Anticholinergics (trihexyphenidyl, benztrapine) have their major clinical effect on tremor. Use in the elderly is limited due to propensity for inducing urinary dysfunction, glaucoma, and particularly cognitive impairment.
- The mechanism of action of amantadine is unknown; it has *N*-methyl-D-aspartate (NMDA) antagonist properties; it is most commonly used as an antidyskinesia agent in pts with advanced PD. Side effects include livedo reticularis, weight gain, and impaired cognitive function; discontinue slowly as pts can experience withdrawal symptoms.

SURGICAL TREATMENTS

- In refractory cases, surgical treatment of PD should be considered.
- Deep-brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus interna (GPi) has largely replaced ablation surgery (e.g., pallidotomy or thalamotomy).
- DBS is primarily indicated for pts who suffer disability resulting from severe tremor or levodopa-induced motor complications; the procedure is profoundly beneficial to many pts.

- Contraindications to surgery include atypical PD, advanced cognitive impairment, major psychiatric illness, substantial medical comorbidities, and advanced age (a relative factor).
- Experimental surgical procedures including cell-based therapies, gene therapies, and trophic factors are under investigation.

187 Ataxic Disorders



■ CLINICAL PRESENTATION

Symptoms and signs may include gait impairment, visual blurring due to nystagmus, unclear (“scanning”) speech, hand incoordination, and tremor with movement. *Differential diagnosis:* Unsteady gait associated with vertigo from vestibular nerve or labyrinthine disease can resemble gait instability of cerebellar disease but produces a perception of movement, dizziness, or light-headedness. Sensory disturbances also can simulate cerebellar disease; with sensory ataxia, imbalance dramatically worsens when visual input is removed (Romberg sign). Bilateral proximal leg weakness also can rarely mimic cerebellar ataxia.

APPROACH TO THE PATIENT

Ataxia

Causes are best grouped by determining whether ataxia is symmetric or focal and by the time course (Table 187-1). Also important to distinguish whether ataxia is present in isolation or is part of a multisystem neurologic disorder. Acute symmetric ataxia is usually due to medications, toxins including alcohol, viral infection, or a postinfectious syndrome (especially varicella). Subacute or chronic symmetric ataxia can result from hypothyroidism, vitamin deficiencies, infections (Lyme disease, *tabes dorsalis* from syphilis, prions), alcohol, other toxins, or an inherited condition (see below). An immune-mediated progressive ataxia is associated with antigliadin antibodies; biopsy of the small intestine may reveal villous atrophy of gluten enteropathy. Elevated serum anti-glutamic acid decarboxylase (GAD) antibodies have been associated with a progressive ataxic syndrome affecting speech and gait. Progressive nonfamilial cerebellar ataxia after age 45 suggests a paraneoplastic syndrome, either subacute cortical cerebellar degeneration (ovarian, breast, lung, Hodgkin’s) or opsoclonus-myoclonus (neuroblastoma, breast, lung).

Unilateral ataxia suggests a focal lesion in the ipsilateral cerebellar hemisphere or its connections. An important cause of acute unilateral ataxia is stroke. Mass effect from cerebellar hemorrhage or swelling from cerebellar infarction can compress brainstem structures, producing altered consciousness and ipsilateral pontine signs (small pupils, sixth or seventh nerve palsies) sometime without prominent limb ataxia; prompt surgical decompression of the posterior fossa can be lifesaving. Other diseases producing asymmetric or unilateral ataxia include tumors, multiple sclerosis, progressive multifocal leukoencephalopathy (in immunodeficiency states), and congenital malformations.

TABLE 187-1 Etiology of Cerebellar Ataxia

SYMMETRIC AND PROGRESSIVE SIGNS			FOCAL AND IPSILATERAL CEREBELLAR SIGNS		
ACUTE (HOURS TO DAYS)	SUBACUTE (DAYS TO WEEKS)	CHRONIC (MONTHS TO YEARS)	ACUTE (HOURS TO DAYS)	SUBACUTE (DAYS TO WEEKS)	CHRONIC (MONTHS TO YEARS)
Intoxication: alcohol, lithium, phenytoin, barbiturates (positive history and toxicology screen) Acute viral cerebellitis (CSF supportive of acute viral infection) Postinfection syndrome	Intoxication: mercury, solvents, gasoline, glue Cytotoxic chemotherapeutic drugs Alcoholic-nutritional (vitamin B ₁ and B ₁₂ deficiency) Lyme disease	Paraneoplastic syndrome Antigliadin antibody syndrome Hypothyroidism Inherited diseases Tabes dorsalis (tertiary syphilis) Phenytoin toxicity Amiodarone	Vascular: cerebellar infarction, hemorrhage, or subdural hematoma Infectious: cerebellar abscess (mass lesion on MRI/CT, history in support of lesion)	Neoplastic: cerebellar glioma or metastatic tumor (positive for neoplasm on MRI/CT) Demyelinating: multiple sclerosis (history, CSF, and MRI are consistent) AIDS-related multifocal leukoencephalopathy (positive HIV test and CD4+ cell count for AIDS)	Stable gliosis secondary to vascular lesion or demyelinating plaque (stable lesion on MRI/CT older than several months) Congenital lesion: Chiari or Dandy-Walker malformations (malformation noted on MRI/CT)

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging.

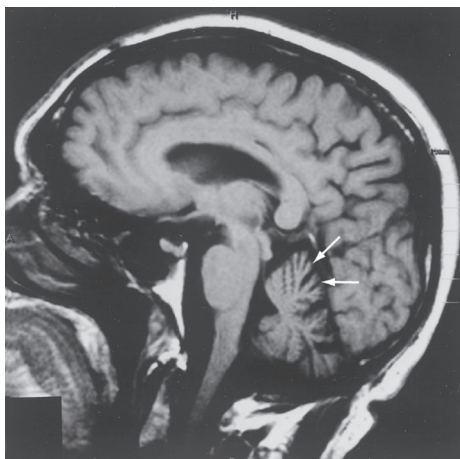


FIGURE 187-1 Sagittal magnetic resonance imaging (MRI) of the brain of a 60-year-old man with gait ataxia and dysarthria due to spinocerebellar ataxia type 1 (SCA1), illustrating cerebellar atrophy (arrows). (Reproduced with permission from RN Rosenberg, P Khemani, in RN Rosenberg, JM Pascual [eds]: *Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease*, 5th ed. London, Elsevier, 2015.)

■ INHERITED ATAXIAS

May be autosomal dominant, autosomal recessive, or mitochondrial (maternal inheritance); >30 disorders recognized. Friedreich's ataxia is most common; autosomal recessive, onset before age 25; ataxia with areflexia, upgoing toes, vibration and position sense deficits, cardiomyopathy, hammer toes, scoliosis; linked to expanded trinucleotide repeat in the intron of gene encoding frataxin; a second form is associated with genetically determined vitamin E deficiency syndrome. Most common dominantly inherited ataxias are spinocerebellar ataxia (SCA)1 (olivopontocerebellar atrophy; "ataxin-1" gene) ([Fig. 187-1](#)), SCA2 (ataxin-2; pts from Cuba and India), and SCA3 (Machado-Joseph disease); all may manifest as ataxia with brainstem and/or extrapyramidal signs; SCA3 may also have dystonia and amyotrophy; genes for each disorder contain unstable trinucleotide repeats in coding region.

■ EVALUATION

Diagnostic approach is determined by the nature of the ataxia (Table 187-1). For symmetric ataxias, drug and toxicology screens; vitamin B₁, B₁₂, and E levels; thyroid function tests; antibody tests for syphilis, Lyme, and *Legionella* infection; antigliadin and anti-GAD antibodies; paraneoplastic antibodies ([Chap. 79](#)); and CSF studies often indicated. Genetic testing is available for many inherited ataxias. For unilateral or asymmetric ataxias, brain MRI or CT scan is the initial test of choice; CT is insensitive for nonhemorrhagic lesions of the cerebellum.

TREATMENT

Ataxia

- The most important goal is to identify treatable entities including hypothyroidism, vitamin deficiency, and infectious causes.
- Ataxia with antigliadin antibodies and gluten enteropathy may improve with a gluten-free diet.

- Paraneoplastic disorders are often refractory to therapy, but some pts improve following removal of the tumor or immunotherapy (Chap. 79).
- Vitamins B₁, B₁₂, and E should be administered to pts with deficient levels.
- The deleterious effects of phenytoin and alcohol on the cerebellum are well known, and these exposures should be avoided in pts with ataxia of any cause.
- There is no proven therapy for any of the autosomal dominant ataxias; family and genetic counseling are important.
- There is evidence that idebenone, a free-radical scavenger, can improve myocardial hypertrophy in Friedreich's ataxia; there is no evidence that it improves neurologic function.
- Cerebellar hemorrhage and other mass lesions of the posterior fossa may require emergent surgical treatment to prevent fatal brainstem compression.

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ALS and Other Motor Neuron Diseases



Amyotrophic lateral sclerosis (ALS) is the most common form of progressive motor neuron disease (Table 188-1). ALS is caused by degeneration of motor neurons at all levels of the CNS, including anterior horns of the spinal cord, brainstem motor nuclei, and motor cortex. Familial ALS (FALS) represents 5–10% of the total and is inherited usually as an autosomal dominant disorder.

TABLE 188-1 Sporadic Motor Neuron Diseases

CHRONIC	ENTITY
Upper and lower motor neuron	Amyotrophic lateral sclerosis
Predominantly upper motor neuron	Primary lateral sclerosis
Predominantly lower motor neuron	Multifocal motor neuropathy with conduction block
	Motor neuropathy with paraproteinemia or cancer
	Motor predominant peripheral neuropathies
Other	
Associated with other neurodegenerative disorders	
Secondary motor neuron disorders (see Table 188-2)	
Acute	
Poliomyelitis	
Herpes zoster	
Coxsackie virus	
West Nile virus	

■ CLINICAL FEATURES

Onset is usually midlife, with most cases progressing to death in 3–5 years. In most societies there is an incidence of 1–3 per 100,000 and a prevalence of 3–5 per 100,000. Presentation is variable depending on whether upper motor or lower motor neurons are more prominently involved initially.

Common initial symptoms are weakness, muscle wasting, stiffness and cramping, and twitching in muscles of hands and arms, often first in the intrinsic hand muscles. Legs are less severely involved than arms, with complaints of leg stiffness, cramping, and weakness common. Symptoms of brainstem involvement include dysphagia, which may lead to aspiration pneumonia and compromised energy intake; there may be prominent wasting of the tongue leading to difficulty in articulation (dysarthria), phonation, and deglutition. Weakness of ventilatory muscles leads to respiratory insufficiency. Additional features that characterize ALS are lack of sensory abnormalities, pseudobulbar palsy (e.g., involuntary laughter, crying), and absence of bowel or bladder dysfunction. Dementia is not a component of sporadic ALS; in some families ALS is co-inherited with frontotemporal dementia characterized by behavioral abnormalities due to frontal lobe dysfunction ([Chap. 185](#)).

■ PATHOPHYSIOLOGY

Pathologic hallmark is death of lower motor neurons (consisting of anterior horn cells in the spinal cord and their brainstem homologues innervating bulbar muscles) and upper, or corticospinal, motor neurons (originating in layer five of the motor cortex and descending via the pyramidal tract to synapse with lower motor neurons). Although at onset ALS may involve selective loss of only upper or lower motor neurons, it ultimately causes progressive loss of both; the absence of clear involvement of both motor neuron types should call into question the diagnosis of ALS.

The cause of sporadic ALS is not well defined. Genetic causes of ALS can be grouped into three general categories. In one, the primary problem is inherent instability of mutant proteins, with perturbations in protein degradation (SOD1, ubiquilin-1 and 2, p62). In the second category, the mutant genes perturb RNA processing, transport, and metabolism (C9orf73, TDP43, FUS); for C9orf72, there is expansion of an intronic hexanucleotide repeat. In the third group of ALS genes, the primary problem is defective axonal cytoskeleton and transport (dynactin, profilin-1).

■ LABORATORY EVALUATION

EMG provides objective evidence of extensive muscle denervation not confined to the territory of individual peripheral nerves and nerve roots. CSF is usually normal. Muscle enzymes (e.g., CK) may be elevated.

Several types of secondary motor neuron disorders that resemble ALS are treatable ([Table 188-2](#)); therefore, all pts should have a careful search for these disorders.

MRI or CT myelography is often required to exclude compressive lesions of the foramen magnum or cervical spine. When involvement is restricted to lower motor neurons only, another important entity is multifocal motor neuropathy with conduction block (MMN). A diffuse, lower motor axonal neuropathy mimicking ALS sometimes evolves in association with hematopoietic disorders such as lymphoma or multiple myeloma; an M-component in serum should prompt consideration of a bone marrow biopsy. Lyme disease may also cause an axonal, lower motor neuropathy, typically with intense proximal limb pain and a CSF pleocytosis. Other treatable disorders that occasionally mimic ALS are chronic lead poisoning and thyrotoxicosis.

TABLE 188-2 Etiology of Motor Neuron Disorders

DIAGNOSTIC CATEGORY	INVESTIGATION
Structural lesions Parasagittal or foramen magnum tumors Cervical spondylosis Chiari malformation of syrinx Spinal cord arteriovenous malformation	MRI scan of head (including foramen magnum and cervical spine)
Infections Bacterial—tetanus, Lyme Viral—poliomyelitis, herpes zoster Retroviral—myelopathy	CSF exam, culture Lyme titer Anti-viral antibody HTLV-1 titers
Intoxications, physical agents Toxins—lead, aluminum, others Drugs—strychnine, phenytoin Electric short, x-irradiation	24-h urine for heavy metals Serum lead level
Immunologic mechanisms Plasma cell dyscrasias Autoimmune polyradiculopathy Motor neuropathy with conduction block Paraneoplastic Paracarcinomatous	Complete blood count ^a Sedimentation rate ^a Total protein ^a Anti-GM1 antibodies ^a Anti-Hu antibody MRI scan, bone marrow biopsy
Metabolic Hypoglycemia Hyperparathyroidism Hyperthyroidism Deficiency of folate, vitamin B ₁₂ , vitamin E Malabsorption Deficiency of copper, zinc Mitochondrial dysfunction	Fasting blood sugar ^a Routine chemistries including calcium ^a PTH Thyroid function ^a Vitamin B ₁₂ , vitamin E, folate ^a Serum zinc, copper ^a 24-h stool fat, carotene, prothrombin time Fasting lactate, pyruvate, ammonia Consider mtDNA
Hyperlipidemia	Lipid electrophoresis
Hyperglycinuria	Urine and serum amino acids CSF amino acids
Hereditary disorders C9orf72 Superoxide dismutase TDP43 FUS/TLS Androgen receptor defect (Kennedy's disease)	WBC DNA for mutational analysis

^aShould be obtained in all cases.

Abbreviations: CSF, cerebrospinal fluid; FUS/TLS, fused in sarcoma/translocated in liposarcoma; HTLV-1, human T-cell lymphotropic virus; MRI, magnetic resonance imaging; PTH, parathyroid; WBC, white blood cell.

Pulmonary function studies may aid in management of ventilation. Swallowing evaluation identifies those at risk for aspiration. Genetic testing is available for superoxide dismutase 1 (SOD1) (20% of FALS) and for rare mutations in other genes.

TREATMENT

Amyotrophic Lateral Sclerosis

- There is no treatment that arrests the underlying pathologic process in ALS.
- The drug riluzole produces modest lengthening of survival; in one trial the survival rate at 18 months with riluzole (100 mg/d) was similar to placebo at 15 months. It may act by diminishing glutamate release and thereby decreasing excitotoxic neuronal cell death. Side effects of riluzole include nausea, dizziness, weight loss, and elevation of liver enzymes.
- A second drug, edaravone, has also been approved by the Food and Drug Administration based on a single 6 month study in a highly selected ALS population that demonstrated a modest reduction in the trajectory of worsening on an ALS disability scale; survival was not included as an endpoint. This drug, which is believed to act as an anti-oxidant, is administered via recurring monthly 10-day series of daily intravenous infusions.
- Multiple therapies are presently in clinical trials for ALS including small molecules, mesenchymal stem cells, and immunosuppression; interventions such as antisense oligonucleotides that diminish expression of mutant SOD1 protein are in clinical trials for SOD1-mediated ALS.
- A variety of rehabilitative aids may substantially assist ALS pts. Foot-drop splints facilitate ambulation, and finger extension splints can potentiate grip.
- Respiratory support may be life-sustaining. For pts who decide against long-term ventilation by tracheostomy, positive-pressure ventilation by mouth or nose provides transient (weeks to months) relief from hypercarbia and hypoxia. Also beneficial are respiratory devices that produce an artificial cough; these help to clear airways and prevent aspiration pneumonia.
- When bulbar disease prevents normal chewing and swallowing, gastrostomy is helpful in restoring normal nutrition and hydration.
- Speech synthesizers can augment speech when there is advanced bulbar palsy.
- Web-based information on ALS is offered by the Amyotrophic Lateral Sclerosis Association (www.alsa.org).

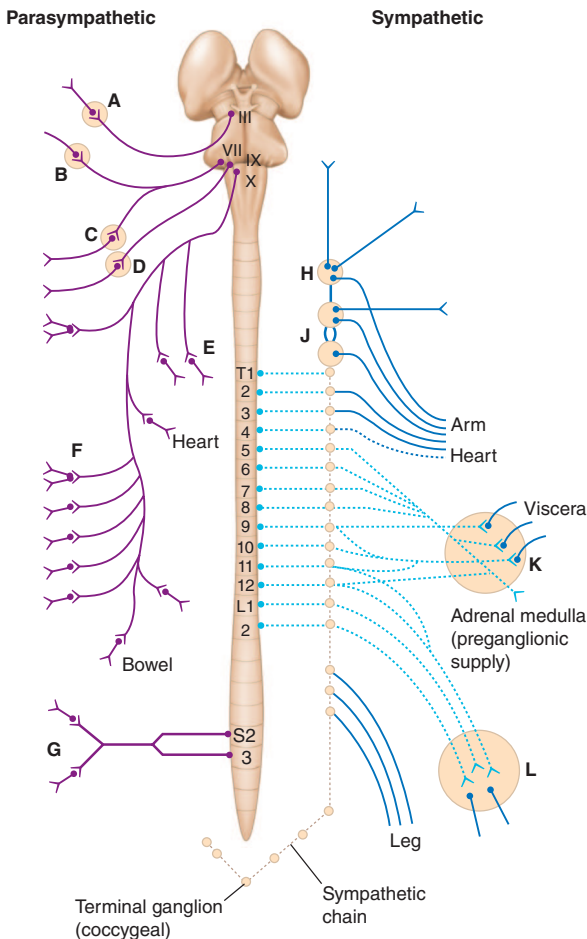
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Autonomic Nervous System Disorders



The autonomic nervous system (ANS) (Fig. 189-1) innervates the entire neuraxis and permeates all organ systems. It regulates bp, heart rate, sleep, glandular, pupillary, and bladder and bowel function. It maintains organ homeostasis and operates automatically, its full importance becomes recognized only when ANS function is compromised, resulting in dysautonomia.

Key features of the ANS are summarized in Table 189-1. Responses to sympathetic or parasympathetic activation are frequently antagonistic; partial



Parasympathetic system
from cranial nerves III, VII, IX, X
and from sacral nerves 2 and 3

- A Ciliary ganglion
- B Sphenopalatine (pterygopalatine) ganglion
- C Submandibular ganglion
- D Otic ganglion
- E Vagal ganglion cells in the heart wall
- F Vagal ganglion cells in bowel wall
- G Pelvic ganglia

Sympathetic system
from T1-L2

- Preganglionic fibers (dotted line)
- Postganglionic fibers ——— (solid line)
- H Superior cervical ganglion
- J Middle cervical ganglion and inferior cervical (stellate) ganglion including T1 ganglion
- K Coeliac and other abdominal ganglia
- L Lower abdominal sympathetic ganglia

FIGURE 189-1 Schematic representation of the autonomic nervous system. (From Moskowitz MA: 9—Diseases of the autonomic nervous system. *Clin Endocrinol Metab* 6:745, 1977.)

TABLE 189-1 Functional Consequences of Normal ANS Activation

	SYMPATHETIC	PARASYMPATHETIC
Heart rate	Increased	Decreased
Blood pressure	Increased	Mildly decreased
Bladder	Increased sphincter tone	Voiding (decreased tone)
Bowel motility	Decreased motility	Increased
Lung	Bronchodilation	Bronchoconstriction
Sweat glands	Sweating	—
Pupils	Dilation	Constriction
Adrenal glands	Catecholamine release	—
Sexual function	Ejaculation, orgasm	Erection
Lacrimal glands	—	Tearing
Parotid glands	—	Salivation

activation of both systems allows for simultaneous integration of multiple body functions.

Consider disorders of autonomic function in the differential diagnosis of pts with unexplained orthostatic hypotension (OH), sleep dysfunction, impotence, bladder dysfunction (urinary frequency, hesitancy, or incontinence), diarrhea, constipation, upper gastrointestinal symptoms (bloating, nausea, vomiting of old food), impaired lacrimation, or altered sweating (hyperhidrosis or hypohidrosis).

OH is often the most disabling feature of autonomic dysfunction. Syncope results when the drop in bp impairs cerebral perfusion (**Chap. 52**). Other manifestations of impaired baroreflexes are supine hypertension, a fixed heart rate regardless of posture, postprandial hypotension, and a high nocturnal bp. Many pts with OH have a preceding diagnosis of hypertension. Most causes of OH are not neurologic in origin; these must be distinguished from neurogenic causes.

APPROACH TO THE PATIENT

Autonomic Nervous System Disorders

The first step in the evaluation of OH is to exclude treatable causes. History should include a review of medications that may cause OH (e.g., diuretics, antihypertensives, antidepressants, ethanol, opioids, insulin, dopamine agonists, and barbiturates); precipitation of OH by medications may also be the first sign of an underlying autonomic disorder. History may reveal an underlying cause for symptoms (e.g., diabetes, Parkinson's disease) or identify causative mechanisms (e.g., cardiac pump failure, reduced intravascular volume). Any relationship of symptoms to meals (splanchnic pooling), standing on awakening in the morning (intravascular volume depletion), ambient warming (vasodilatation), or exercise (muscle arteriolar vasodilatation) should be sought.

Physical examination includes measurement of supine and standing pulse and bp. OH is defined as a sustained drop in systolic (≥ 20 mmHg) or diastolic (≥ 10 mmHg) bp within 2–3 min of standing. In nonneurogenic causes of OH (such as hypovolemia), the bp drop is accompanied by a compensatory increase in heart rate of >15 beats/min. A clue to neurogenic OH is aggravation or precipitation of OH by autonomic stressors (such as a meal, hot tub/hot bath, and exercise). Neurologic evaluation should include a mental status examination (to exclude neurodegenerative disorders such as Lewy body

dementia), cranial nerve examination (impaired downgaze in progressive supranuclear palsy, abnormal pupils with Horner's or Adie's syndrome), motor tone (Parkinsonian syndromes), motor strength and sensory examination (polyneuropathies). In pts without a clear initial diagnosis, follow-up evaluations every few months or whenever symptoms worsen may reveal the underlying cause.

Autonomic testing: Autonomic function tests are helpful when history and physical examination findings are inconclusive, to detect subclinical involvement, or to follow the course of an autonomic disorder. Heart rate variation with deep breathing is a measure of vagal function. The Valsalva maneuver measures changes in heart rate and bp while a constant expiratory pressure of 40 mmHg is maintained for 15 s. The Valsalva ratio is the maximum heart rate during the maneuver divided by the minimum heart rate following the maneuver; the ratio reflects cardiovagal function. Tilt-table beat-to-beat bp measurements in the supine, 70° tilt, and tilt-back positions can be used to evaluate orthostatic failure in bp control in pts with unexplained syncope. Most pts with syncope do not have autonomic failure; the tilt-table test can be used to diagnose vasovagal syncope with high sensitivity, specificity, and reproducibility.

Other tests of autonomic function include the quantitative sudomotor axon reflex test (QSART) and the thermoregulatory sweat test (TST). The QSART provides quantitative measure of regional autonomic function mediated by acetylcholine (ACh)-induced sweating. The TST provides a qualitative measure of sweating in response to a standardized elevation of body temperature.

■ DISORDERS OF THE AUTONOMIC NERVOUS SYSTEM

Autonomic disorders may occur with many disorders of the central and/or peripheral nervous systems (Table 189-2). Diseases of the CNS may cause ANS dysfunction at many levels, including hypothalamus, brainstem, or spinal cord.

Multiple system atrophy (MSA) is a progressive neurodegenerative disorder comprising autonomic failure (OH and/or a neurogenic bladder) combined with either parkinsonism (MSA-p) or cerebellar signs (MSA-c), often with progressive cognitive dysfunction. Dysautonomia is also common in advanced Parkinson's disease and in dementia with Lewy bodies.

Spinal cord injury may produce autonomic hyperreflexia affecting bowel, bladder, sexual, temperature-regulation, or cardiovascular functions. With spinal cord lesions above T6, increased autonomic discharges (autonomic dysreflexia) can be elicited by irritation of bladder, skin, or muscles. Bladder distention from palpation, catheter insertion, catheter obstruction, or urinary infection is a common and correctable trigger of autonomic dysreflexia. Dangerous increases or decreases in body temperature can result from an inability to experience the sensory accompaniments of heat or cold exposure below the level of injury.

Peripheral neuropathies affecting small myelinated and unmyelinated fibers of the sympathetic and parasympathetic nerves are the most common cause of chronic autonomic insufficiency (Chap. 196). Autonomic involvement in *diabetes mellitus* typically begins ~10 years after onset of diabetes and slowly progresses. Diabetic enteric neuropathy produces gastroparesis, nausea and vomiting, malnutrition, achlorhydria, and bowel incontinence. Impotence, urinary incontinence, pupillary abnormalities, and OH may occur as well. Prolongation of the QT interval increases risk of sudden death. Autonomic neuropathy occurs in sporadic and familial forms of *amyloidosis*. Pts typically present with distal, painful polyneuropathy. *Alcoholic polyneuropathy* produces symptoms of autonomic

TABLE 189-2 Classification of Clinical Autonomic Disorders**I. Autonomic Disorders with Brain Involvement**

- A. Associated with multisystem degeneration
 - 1. Multisystem degeneration: autonomic failure clinically prominent
 - a. Multiple system atrophy (MSA)
 - b. Parkinson's disease with autonomic failure
 - c. Diffuse Lewy body disease with autonomic failure
 - 2. Multisystem degeneration: autonomic failure clinically not usually prominent
 - a. Parkinson's disease without autonomic failure
 - b. Other extrapyramidal disorders (inherited spinocerebellar atrophies, progressive supranuclear palsy, corticobasal degeneration, Machado-Joseph disease, fragile X syndrome [FXTAS])
- B. Unassociated with multisystem degeneration (focal CNS disorders)
 - 1. Disorders mainly due to cerebral cortex involvement
 - a. Frontal cortex lesions causing urinary/bowel incontinence
 - b. Focal seizures (temporal lobe or anterior cingulate)
 - c. Cerebral infarction of the insula
 - 2. Disorders of the limbic and paralimbic circuits
 - a. Shapiro's syndrome (agenesis of corpus callosum, hyperhidrosis, hypothermia)
 - b. Autonomic seizures
 - c. Limbic encephalitis
 - 3. Disorders of the hypothalamus
 - a. Thiamine deficiency (Wernicke-Korsakoff syndrome)
 - b. Diencephalic syndrome
 - c. Neuroleptic malignant syndrome
 - d. Serotonin syndrome
 - e. Fatal familial insomnia
 - f. Antidiuretic hormone (ADH) syndromes (diabetes insipidus, inappropriate ADH secretion)
 - g. Disturbances of temperature regulation (hyperthermia, hypothermia)
 - h. Disturbances of sexual function
 - i. Disturbances of appetite
 - j. Disturbances of BP/HR and gastric function
 - k. Horner's syndrome
 - 4. Disorders of the brainstem and cerebellum
 - a. Posterior fossa tumors
 - b. Syringobulbia and Arnold-Chiari malformation
 - c. Disorders of BP control (hypertension, hypotension)
 - d. Cardiac arrhythmias
 - e. Central sleep apnea
 - f. Baroreflex failure
 - g. Horner's syndrome
 - h. Vertebrobasilar and lateral medullary (Wallenberg's) syndromes
 - i. Brainstem encephalitis

(Continued)

TABLE 189-2 Classification of Clinical Autonomic Disorders (Continued)**II. Autonomic Disorders with Spinal Cord Involvement**

- A. Traumatic quadriplegia
- B. Syringomyelia
- C. Subacute combined degeneration
- D. Multiple sclerosis and neuromyelitis optica
- E. Amyotrophic lateral sclerosis
- F. Tetanus
- G. Stiff-person syndrome
- H. Spinal cord tumors

III. Autonomic Neuropathies

- A. Acute/subacute autonomic neuropathies
 - a. Subacute autoimmune autonomic ganglionopathy (AAG)
 - b. Subacute paraneoplastic autonomic neuropathy
 - c. Guillain-Barré syndrome
 - d. Botulism
 - e. Porphyria
 - f. Drug induced autonomic neuropathies-stimulants, drug withdrawal, vasoconstrictor, vasodilators, beta-receptor antagonists, beta-agonists
 - g. Toxin-induced autonomic neuropathies
 - h. Subacute cholinergic neuropathy
- B. Chronic peripheral autonomic neuropathies
 - 1. Distal small fiber neuropathy
 - 2. Combined sympathetic and parasympathetic failure
 - a. Amyloid
 - b. Diabetic autonomic neuropathy
 - c. AAG (paraneoplastic and idiopathic)
 - d. Sensory neuronopathy with autonomic failure
 - e. Familial dysautonomia (Riley-Day syndrome)
 - f. Diabetic, uremic, or nutritional deficiency
 - g. Geriatric dysautonomia (age >80 years)
 - 3. Disorders of orthostatic intolerance: reflex syncope; POTS; prolonged bed rest; space flight; chronic fatigue

Abbreviations: BP, blood pressure; CNS, central nervous system; HR, heart rate; POTS, postural orthostatic tachycardia syndrome.

failure when the neuropathy is severe, and autonomic involvement contributes to the high mortality rates associated with alcoholism. Attacks of *acute intermittent porphyria* (AIP) are associated with tachycardia, sweating, urinary retention, and hypertension; other prominent symptoms include anxiety, abdominal pain, nausea, and vomiting. BP fluctuation and cardiac arrhythmias can be severe in *Guillain-Barré syndrome*. *Autoimmune autonomic ganglionopathy* presents as the subacute development of autonomic failure with OH, enteric neuropathy (gastroparesis, ileus, constipation/diarrhea), flaccid bladder, loss of sweating, sicca complex, and a tonic pupil. Onset may follow a viral infection; serum antibodies to the $\alpha 3$ subunit of the ganglionic ACh receptor ($\alpha 3$ AChR) are diagnostic, and some pts appear to respond to immunotherapy. Rare pts develop *dysautonomia*

as a paraneoplastic disorder (**Chap. 79**). There are five known hereditary sensory and autonomic neuropathies (*HSAN I–V*).

Botulism is associated with blurred vision, dry mouth, nausea, unreactive or sluggishly reactive pupils, urinary retention, and constipation. *Postural orthostatic tachycardia syndrome* (POTS) presents with symptoms of orthostatic intolerance (not OH), including shortness of breath, light-headedness, and exercise intolerance accompanied by an increase in heart rate but no drop in bp. *Primary hyperhidrosis* affects 0.6–1.0% of the population; the usual symptoms are excessive sweating of the palms and soles. Onset is in adolescence, and symptoms tend to improve with age. Although not dangerous, this condition is socially embarrassing; treatment with sympathectomy or local injection of botulinum toxin is often effective.

■ COMPLEX REGIONAL PAIN SYNDROMES

Complex regional pain syndrome (CRPS) type I is a regional pain syndrome that usually develops after tissue trauma. *Allodynia* (the perception of a nonpainful stimulus as painful), *hyperpathia* (an exaggerated pain response to a painful stimulus), and spontaneous pain occur. Symptoms are unrelated to the severity of the initial trauma and are not confined to the distribution of a single peripheral nerve. CRPS type II is a regional pain syndrome that develops after injury to a peripheral nerve, usually a major nerve trunk. Spontaneous pain initially develops within the territory of the affected nerve but eventually may spread outside the nerve distribution.

- Early mobilization with physical therapy or a brief course of glucocorticoids may be helpful for CRPS type I or II. Chronic glucocorticoid treatment is not recommended.
- Current treatment paradigms are multidisciplinary with a focus on early mobilization, physical therapy, pain management, pt education, and psychological support.

TREATMENT

Autonomic Nervous System Disorders

- Of particular importance is the removal of drugs or amelioration of underlying conditions that cause or aggravate symptoms. For example, OH can be related to antihypertensive agents, antidepressants, levodopa or dopaminergic agonists, ethanol, opioids, insulin, and barbiturates.
- Nonpharmacologic approaches are summarized in **Table 189-3**. Adequate intake of salt and fluids to produce a voiding volume between 1.5 and 2.5 L of urine (containing >170 meq of Na⁺) each 24 h is essential. Sleeping with

TABLE 189-3 Initial Treatment of Orthostatic Hypotension (OH)

Pt education: mechanisms and stressors of OH
High-salt diet (10–20 g/d)
High-fluid intake (2 L/d)
Elevate head of bed 10 cm (4 in.) to minimize supine hypertension
Maintain postural stimuli
Learn physical counter-maneuvers
Compression garments
Correct anemia

the head of the bed elevated will minimize the effects of supine nocturnal hypertension.

- Prolonged recumbency should be avoided. Pts are advised to sit with legs dangling over the edge of the bed for several minutes before attempting to stand in the morning. Compressive garments such as compression stockings and abdominal binders may be helpful if they can be tolerated. Anemia should be corrected, if necessary, with erythropoietin; the increased intravascular volume that accompanies the rise in hematocrit can exacerbate supine hypertension. Postprandial OH may respond to frequent, small, low-carbohydrate meals.
- If these measures are not sufficient, drug treatment might be necessary.
- Midodrine is a directly acting α_1 -agonist that does not cross the blood-brain barrier. The dose is 5–10 mg orally three times a day, but some pts respond best to a decremental dose (e.g., 15 mg on awakening, 10 mg at noon, and 5 mg in the afternoon). Midodrine should not be taken after 6 P.M. Side effects include pruritus, uncomfortable piloerection, and supine hypertension.
- Droxidopa is approved for treatment of neurogenic OH associated with autonomic failure, Parkinson's disease, or MSA.
- Pyridostigmine appears to improve OH without aggravating supine hypertension by enhancing ganglionic transmission (maximal when orthostatic, minimal supine) with only modest clinical effects on bp.
- Fludrocortisone (0.1–0.3 mg PO twice daily) will reduce OH, but it aggravates supine hypertension. Susceptible pts may develop fluid overload, congestive heart failure, supine hypertension, or hypokalemia.

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Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders



Disorders of vision and ocular movement are discussed in [Chap. 54](#) and dizziness and vertigo in [Chap. 53](#).

■ FACIAL PAIN OR NUMBNESS (TRIGEMINAL NERVE [V])

See [Fig. 190-1](#).

Trigeminal Neuralgia (Tic Douloureux)

Frequent, excruciating paroxysms of pain in lips, gums, cheek, or chin (rarely in ophthalmic division of fifth nerve) lasting seconds to minutes. Typically presents in middle or old age. Pain is often stimulated at trigger points. Sensory deficit cannot be demonstrated. Must be distinguished from other forms of facial pain arising from diseases of jaw, teeth, or sinuses. Pain from migraine or cluster headache tends to be deep-seated and steady, unlike the superficial stabbing quality of trigeminal neuralgia. In temporal arteritis, superficial facial pain is not shock-like, pt frequently complains of myalgias and other systemic symptoms, and an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) is usually present. Rare causes are herpes zoster or a tumor. An onset in young adulthood or if bilateral raises the possibility of multiple sclerosis (MS) ([Chap. 192](#)).

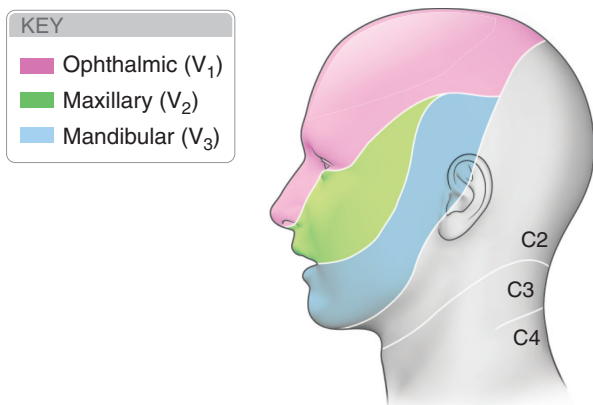


FIGURE 190-1 The three major sensory divisions of the trigeminal nerve consist of the ophthalmic, maxillary, and mandibular nerves. (Adapted from Waxman SG: *Clinical Neuroanatomy*, 26th ed. New York, McGraw-Hill, 2009.)

TREATMENT

Trigeminal Neuralgia

- Carbamazepine is effective in 50–75% of cases. Begin at 100-mg single daily dose taken with food and advance by 100 mg every 1–2 days until substantial (>50%) pain relief occurs. Most pts require 200 mg four times a day; doses >1200 mg daily usually provide no additional benefit.
- Oxcarbazepine (300–1200 mg bid) is an alternative with less bone marrow toxicity and probably similar efficacy.
- For nonresponders, lamotrigine (400 mg daily), phenytoin (300–400 mg/d), or baclofen (initially 5–10 mg three times a day) can be tried.
- When medications fail, surgical microvascular decompression to relieve pressure on the trigeminal nerve can be offered.
- Other options include gamma knife radiosurgery and radiofrequency thermal rhizotomy.

Trigeminal Neuropathy

Usually presents as facial sensory loss or weakness of jaw muscles. Causes are varied (Table 190-1), including tumors of middle cranial fossa or trigeminal nerve, metastases to base of skull, or lesions in cavernous sinus (affecting first and second divisions of fifth nerve) or superior orbital fissure (affecting first division of fifth nerve).

■ FACIAL WEAKNESS (FACIAL NERVE [VII]) (SEE FIG. 190-2)

Look for hemifacial weakness that includes muscles of forehead and orbicularis oculi. If lesion is in middle ear portion, taste is lost over the anterior two-thirds of tongue and there may be hyperacusis; if lesion is at internal auditory meatus, there may be involvement of auditory and vestibular nerves; pontine lesions usually affect abducens (sixth cranial) nerve and often corticospinal tract. Peripheral nerve lesions with incomplete recovery may produce continuous contractions

TABLE 190-1 Trigeminal Nerve Disorders

Nuclear (brainstem) lesions	Peripheral nerve lesions
Multiple sclerosis	Nasopharyngeal carcinoma
Stroke	Trauma
Syringobulbia	Guillain-Barré syndrome
Glioma	Sjögren's syndrome
Lymphoma	Collagen-vascular diseases
Preganglionic lesions	Sarcoidosis
Acoustic neuroma	Leprosy
Meningioma	Drugs (stilbamidine, trichloroethylene)
Metastasis	Idiopathic trigeminal neuropathy
Chronic meningitis	
Cavernous carotid aneurysm	
Gasserian ganglion lesions	
Trigeminal neuroma	
Herpes zoster	
Infection (spread from otitis media or mastoiditis)	

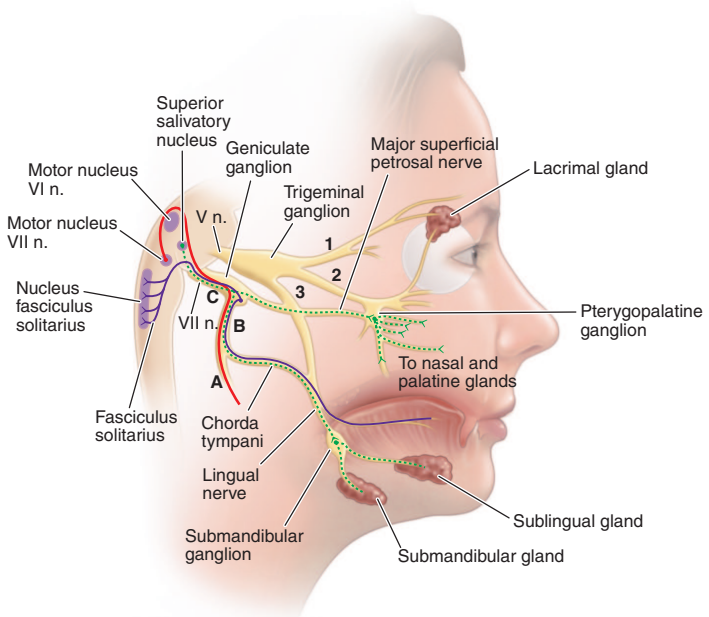


FIGURE 190-2 The facial nerve. A, B, and C denote lesions of the facial nerve at the stylomastoid foramen, distal and proximal to the geniculate ganglion, respectively. Green lines indicate the parasympathetic fibers, red line indicates motor fibers, and purple lines indicate visceral afferent fibers (taste). (Reprinted with permission from Carpenter MB: *Core Text of Neuroanatomy*, 2nd ed. Baltimore, Williams & Wilkins, 1978.)

of affected musculature (*facial myokymia*); contraction of all facial muscles on attempts to move one group selectively (*synkinesis*); hemifacial spasms; or anomalous tears when facial muscles activated as in eating (*crocodile tears*).

Bell's Palsy

Most common form of idiopathic facial paralysis; affects 1 in 60 persons over a lifetime. Association with herpes simplex virus type 1. Risk factors include pregnancy and diabetes mellitus. Weakness evolves gradually with maximal weakness by 48 h, sometimes preceded by retroaural pain. Hyperacusis may be present. Full recovery within several weeks or months in 80%; incomplete paralysis in first week is the most favorable prognostic sign.

Diagnosis can be made clinically in pts with (1) a typical presentation, (2) no risk factors or preexisting symptoms for other causes of facial paralysis, (3) no lesions of herpes zoster in the external ear canal, and (4) a normal neurologic examination with the exception of the facial nerve. In uncertain cases, an ESR or CRP, testing for diabetes mellitus, a Lyme titer, angiotensin-converting enzyme level and chest imaging study for possible sarcoidosis, a lumbar puncture for possible Guillain-Barré syndrome, or MRI scanning may be indicated.

TREATMENT

Bell's Palsy

- Protect the eye with paper tape to depress the upper eyelid during sleep and prevent corneal drying.
- Artificial tears.
- Massage of the weakened muscle may help symptomatically as well.
- Prednisone (60–80 mg/d over 5 days, tapered off over the next 5 days) modestly shortens the recovery period and improves functional outcome.
- Large randomized trials found no added benefit for valacyclovir or acyclovir compared with glucocorticoids alone.
- For pts with permanent paralysis, cosmetic surgical procedures can restore a relatively symmetric appearance to the face.

Other Facial Nerve Disorders

Ramsay Hunt syndrome is caused by herpes zoster infection of geniculate ganglion; distinguished from Bell's palsy by a vesicular eruption in pharynx and external auditory canal, and by frequent involvement of eighth cranial nerve. *Acoustic neuromas* often compress the seventh nerve. *Infarcts*, *demyelinating lesions of multiple sclerosis*, and *tumors* are common pontine causes. *Bilateral facial weakness* may occur in Guillain-Barré syndrome, sarcoidosis, Lyme disease, and leprosy. *Hemifacial spasm* may occur with Bell's palsy, compression and/or demyelination of the nerve by tumor, infection or MS, or as an idiopathic disorder. *Blepharospasm* consists of involuntary recurrent spasms of both eyelids, usually occurring in the elderly and sometimes with associated facial spasm; may subside spontaneously. Hemifacial spasm or blepharospasm can be treated by injection of botulinum toxin into the orbicularis oculi.

■ OTHER CRANIAL NERVE DISORDERS

Disorders of the Sense of Smell

Olfactory nerve (I) disorders are due to interference with access of the odorant to the olfactory neuroepithelium (transport loss), injury to receptor region (sensory loss), or damage to central olfactory pathways (neural loss). The causes of olfactory disorders are summarized in [Table 190-2](#); most common other than

TABLE 190-2 Disorders and Conditions Associated with Compromised Olfactory Function, as Measured by Olfactory Testing

22q11 deletion syndrome	Korsakoff's psychosis
AIDS/HIV infection	Laryngopharyngeal reflux disease
Adenoid hypertrophy	Legionnaires' disease
Adrenal cortical insufficiency	Leprosy
Age	Liver disease
Alcoholism	Lubag disease
Allergies	Medications
Alzheimer's disease	Migraine
Amyotrophic lateral sclerosis (ALS)	Multiple sclerosis
Anorexia nervosa	Multi-infarct dementia
Asperger's syndrome	Myasthenia gravis
Ataxias	Narcolepsy with cataplexy
Attention deficit/hyperactivity disorder	Neoplasms, cranial/nasal
Behcet's disease	Nutritional deficiencies
Bardet-Biedl syndrome	Obstructive pulmonary disease
Chagas' disease	Obesity
Chemical exposure	Obsessive compulsive disorder
Chronic obstructive pulmonary disease	Orthostatic tremor
Congenital	Panic disorder
Cushing's syndrome	Parkinson's disease (PD)
Cystic fibrosis	Pick's disease
Degenerative ataxias	Posttraumatic stress disorder
Depression	Pregnancy
Diabetes	Pseudohypoparathyroidism
Down's syndrome	Psychopathy
Epilepsy	Radiation (therapeutic, cranial)
Facial paralysis	REM behavior disorder
Fibromyalgia	Refsum's disease
Frontotemporal lobe degeneration	Renal failure/end-stage kidney disease
Gonadal dysgenesis (Turner's syndrome)	Restless leg syndrome
Granulomatosis with Polyangiitis (Wegener's)	Rhinosinusitis/polyposis
Guamanian ALS/PD/dementia syndrome	Schizophrenia
Head trauma	Seasonal affective disorder
Herpes simplex encephalitis	Sjögren's syndrome
Hypothyroidism	Stroke
Huntington's disease	Systemic sclerosis
latrogenesis	Tobacco smoking
Idiopathic inflammatory myopathies	Toxic chemical exposure
Kallmann's syndrome	Upper respiratory infections
	Usher syndrome
	Vitamin B ₁₂ deficiency

aging are severe upper respiratory infections, head trauma, and chronic rhinosinusitis. Although more than half of people between 65 and 80 years of age suffer from olfactory dysfunction that is idiopathic (*presbyosmia*), it is increasingly recognized that a number of neurodegenerative disorders are accompanied by olfactory impairment. Pts often present with a complaint of loss of the sense of taste even though their taste thresholds may be within normal limits.

TREATMENT

Disorders of the Sense of Smell

- Therapy for allergic rhinitis, bacterial rhinitis and sinusitis, polyps, neoplasms, and structural abnormalities of the nasal cavities is usually successful in restoring the sense of smell.
- There is no proven treatment for sensorineural olfactory losses; fortunately, spontaneous recovery can occur.
- Cases due to exposure to cigarette smoke and other airborne toxic chemicals can recover if the insult is discontinued.
- Preliminary data suggests that pts with hyposmia may benefit from repeated smelling of odors (such as eucalyptol, citronella, eugenol, and phenyl ethyl alcohol) over weeks or months; the usual paradigm is to smell odors before going to bed and again upon awakening each day.
- The use of zinc and vitamin A is controversial, and there does not appear to be much benefit beyond replenishing established deficiencies.

Glossopharyngeal Neuralgia

This neuralgia involves the ninth (glossopharyngeal) and sometimes portions of the tenth (vagus) cranial nerves. Presents with paroxysmal, intense pain in tonsillar fossa of throat that may be precipitated by swallowing. There is no objective sensory or motor deficit. Other diseases affecting this nerve include herpes zoster, MS, or compressive neuropathy due to tumor or aneurysm in region of jugular foramen (when associated with vagus and accessory nerve palsies).

TREATMENT

Glossopharyngeal Neuralgia

- Medical therapy is similar to that for trigeminal neuralgia, and carbamazepine is generally the first choice.
- If drug therapy is unsuccessful, surgical procedures (including microvascular decompression if vascular compression is evident, or rhizotomy of glossopharyngeal and vagal fibers in the jugular bulb) are frequently successful.

Dysphagia and Dysphonia

Lesions of the vagus nerve (X) may be responsible. Unilateral lesions produce drooping of soft palate, loss of gag reflex, and "curtain movement" of lateral wall of pharynx with hoarse, nasal voice. Etiologies include neoplastic and infectious processes of the meninges, tumors and vascular lesions in the medulla, motor neuron disease (e.g., ALS), or compression of the recurrent laryngeal nerve by intrathoracic processes. Aneurysm of the aortic arch, an enlarged left atrium, and tumors of the mediastinum and bronchi are much more frequent causes of an isolated vocal cord palsy than are intracranial disorders. A substantial number of cases of recurrent laryngeal palsy remain idiopathic.

With laryngeal palsy, first determine the site of the lesion. If intramedullary, there are usually other brainstem or cerebellar signs. If extramedullary, the glossopharyngeal (IX) and spinal accessory (XI) nerves are frequently involved (jugular foramen syndrome). If extracranial in the posterior laterocondylar or retroparotid space, there may be combinations of ninth, tenth, eleventh, and twelfth cranial nerve palsies and a Horner's syndrome. If there is no sensory loss over the palate and pharynx and no palatal weakness or dysphagia, lesion is below the origin of the pharyngeal branches, which leave the vagus nerve high in the cervical region; the usual site of disease is then the mediastinum.

Neck Weakness

Isolated involvement of the accessory (XI) nerve can occur anywhere along its route, resulting in paralysis of the sternocleidomastoid and trapezius muscles. More commonly, involvement occurs in combination with deficits of the ninth and tenth cranial nerves in the jugular foramen or after exit from the skull. An idiopathic form of accessory neuropathy, similar to Bell's palsy, has been described; most pts recover but it may recur.

Tongue Paralysis

The hypoglossal (XII) nerve supplies the ipsilateral muscles of the tongue. The nucleus of the nerve or its fibers of exit may be involved by intramedullary lesions such as tumor, poliomyelitis, or most often motor neuron disease. Lesions of the basal meninges and the occipital bones (platybasia, invagination of occipital condyles, Paget's disease) may compress the nerve in its extramedullary course or in the hypoglossal canal. Isolated lesions of unknown cause can occur. Atrophy and fasciculation of the tongue develop weeks to months after interruption of the nerve.

■ MULTIPLE CRANIAL NERVE PALSIES

APPROACH TO THE PATIENT

Multiple Cranial Nerve Palsies

First determine whether the process is within the brainstem or outside it. Lesions on the surface of the brainstem tend to involve adjacent cranial nerves in succession with only late and slight involvement of long sensory and motor pathways. The opposite is true of processes within the brainstem. Involvement of multiple cranial nerves outside the brainstem may be due to trauma, localized infections including varicella zoster virus, infectious and noninfectious (especially carcinomatous) causes of meningitis; granulomatous diseases such as granulomatosis with polyangiitis, Behçet's disease, vascular disorders including those associated with diabetes, enlarging aneurysms, or locally infiltrating tumors. A purely motor disorder without atrophy raises the question of myasthenia gravis. *Facial diplegia* is common in Guillain-Barré syndrome. *Ophthalmoplegia* may occur with Guillain-Barré syndrome (Fisher variant) or Wernicke's encephalopathy.

The *cavernous sinus syndrome* (Fig. 190-3) is frequently life threatening. It often presents as orbital or facial pain; orbital swelling and chemosis; fever; oculomotor neuropathy; and trigeminal neuropathy affecting the ophthalmic (V_1) and occasionally maxillary (V_2) divisions. Cavernous sinus thrombosis, often secondary to infection from orbital cellulitis, a cutaneous source on the face, or sinusitis, is the most frequent cause; other etiologies include aneurysm of the carotid artery, a carotid-cavernous fistula (orbital bruit may be present), meningioma, nasopharyngeal carcinoma, other tumors, or an idiopathic granulomatous disorder (Tolosa-Hunt syndrome). In infectious

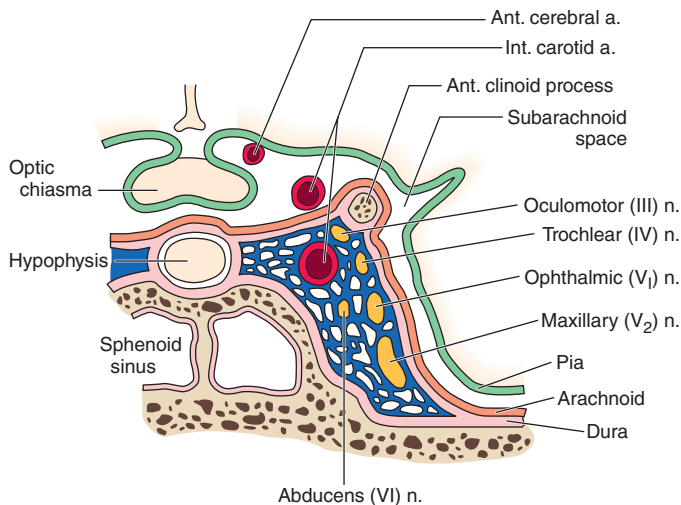


FIGURE 190-3 Anatomy of the cavernous sinus in coronal section, illustrating the location of the cranial nerves in relation to the vascular sinus, internal carotid artery (which loops anteriorly to the section), and surrounding structures.

cases, prompt administration of broad-spectrum antibiotics, drainage of any abscess cavities, and identification of the offending organism are essential. Anticoagulant therapy may benefit cases of primary thrombosis. Repair or occlusion of the carotid artery may be required for treatment of fistulas or aneurysms. Tolosa-Hunt syndrome generally responds to glucocorticoids.

191 Spinal Cord Diseases

Spinal cord disorders can be devastating, but many are treatable if recognized early ([Table 191-1](#)). Knowledge of relevant spinal cord anatomy is often the key to correct diagnosis ([Fig. 191-1](#)).

■ SYMPTOMS AND SIGNS

Sensory symptoms often include paresthesias; may begin in one or both feet and ascend. Sensory level to pin sensation or vibration often correlates well with location of transverse lesions. May have isolated pain/temperature sensation loss over the shoulders (“cape” or “syringomyelic” pattern) or loss of sensation to vibration/position sense on one side of the body and pain/temperature loss on the other (Brown-Séquard hemisection syndrome).

Motor symptoms are caused by disruption of corticospinal tracts that leads to quadriplegia or paraplegia with increased muscle tone, hyperactive deep tendon reflexes, and extensor plantar responses. With acute severe lesions, there may be initial flaccidity and areflexia (spinal shock).

TABLE 191-1 Treatable Spinal Cord Disorders**Compressive**

Epidural, intradural, or intramedullary neoplasm
 Epidural abscess
 Epidural hemorrhage
 Cervical spondylosis
 Herniated disk
 Posttraumatic compression by fractured or displaced vertebra or hemorrhage

Vascular

Arteriovenous malformation and dural fistula
 Antiphospholipid syndrome and other hypercoagulable states

Inflammatory

Multiple sclerosis
 Neuromyelitis optica
 Transverse myelitis
 Sarcoidosis
 Sjögren-related myelopathy
 Systemic lupus erythematosus-related myelopathy
 Vasculitis

Infectious

Viral: VZV, HSV-1 and 2, CMV, HIV, HTLV-1, others
 Bacterial and mycobacterial: *Borrelia*, *Listeria*, syphilis, others
Mycoplasma pneumoniae
 Parasitic: schistosomiasis, toxoplasmosis, cystercercosis

Developmental

Syringomyelia
 Meningomyelocele
 Tethered cord syndrome

Metabolic

Vitamin B₁₂ deficiency (subacute combined degeneration)
 Copper deficiency

Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; HTLV, human T cell lymphotropic virus; VZV, varicella-zoster virus.

Autonomic dysfunction includes primarily urinary retention; should raise suspicion of spinal cord disease when associated with back or neck pain, weakness, and/or a sensory level.

Interscapular pain may be first sign of midthoracic cord compression; radicular pain may mark site of more laterally placed spinal lesion; pain from lower cord (conus medullaris) lesion may be referred to low back.

■ SPECIFIC SIGNS BY SPINAL CORD LEVEL

Approximate indicators of level of lesion include the location of a sensory level, a band of hyperalgesia/hyperpathia at the upper end of the sensory disturbance, isolated atrophy or fasciculations, or lost tendon reflex at a specific spinal cord segment.

Lesions Near the Foramen Magnum

Weakness of the ipsilateral shoulder and arm, followed by weakness of ipsilateral leg, then contralateral leg, then contralateral arm, often with respiratory paralysis. There is often suboccipital pain spreading to the neck and shoulders.

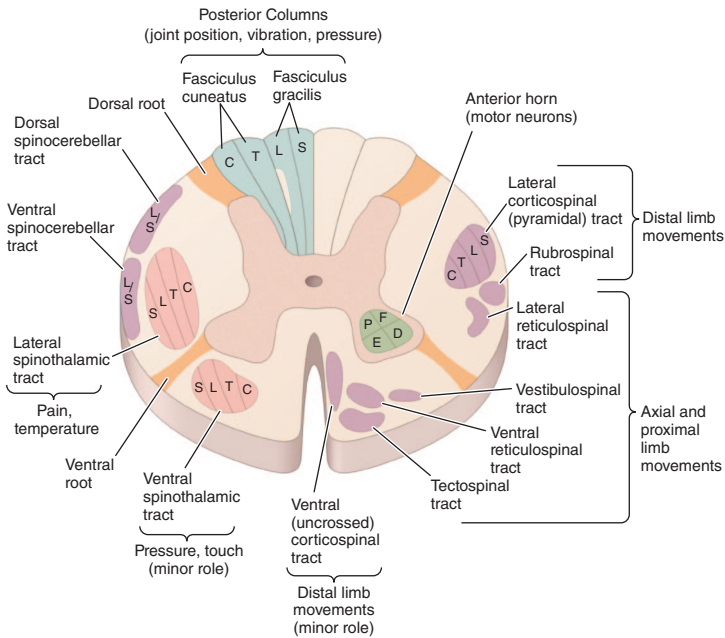


FIGURE 191-1 Transverse section through the spinal cord, composite representation, illustrating the principal ascending (*left*) and descending (*right*) pathways. The lateral and ventral spinothalamic tracts ascend contralateral to the side of the body that is innervated. C, cervical; D, distal; E, extensors; F, flexors; L, lumbar; P, proximal; S, sacral; T, thoracic.

Cervical Cord

Best localized by noting pattern of motor weakness and areflexia; shoulder (C5), biceps (C5–6), brachioradialis (C6), triceps/finger and wrist extensors (C7), finger and wrist flexors (C8).

Thoracic Cord

Localized by identification of a sensory level on the trunk. Useful markers are the nipples (T4) and umbilicus (T10).

Lumbar Cord

Upper lumbar cord lesions paralyze hip flexion and knee extension and abolish the patella reflex, whereas lower lumbar lesions affect foot and ankle movements, knee flexion, and thigh extension, while abolishing the ankle jerks.

Sacral Cord (Conus Medullaris)

Saddle anesthesia, early bladder/bowel dysfunction, impotence; muscle strength is largely preserved.

Cauda Equina (Cluster of Nerve Roots Derived from Lower Cord)

Lesions below spinal cord termination at the L1 vertebral level produce a flaccid, areflexic, asymmetric paraparesis with possible bladder/bowel dysfunction and sensory loss below L1; pain is common and projected to perineum or thighs.

■ INTRAMEDULLARY AND EXTRAMEDULLARY SYNDROMES

Spinal cord disorders may be intramedullary (arising from within the substance of the cord) or extramedullary (compressing the cord or its blood supply).

Extramedullary lesions often produce radicular pain, early motor signs, and sacral sensory loss. Intramedullary lesions produce poorly localized burning pain, less prominent motor signs, and often spare perineal/sacral sensation.

■ **ACUTE AND SUBACUTE SPINAL CORD DISEASES (SEE CHAP. 22)**

Neoplastic spinal cord compression (Chap. 22): Most are epidural in origin, resulting from metastases to the adjacent spinal bones (Fig. 191-2). Almost any tumor can be responsible: breast, lung, prostate, kidney, lymphoma, and myeloma most frequent. Thoracic cord most commonly involved. Initial symptom is usually back pain, worse when recumbent, with local tenderness preceding other symptoms by many weeks. Spinal cord compression due to metastases is a medical emergency; in general, therapy will not reverse paralysis of >48 h duration.

Spinal epidural abscess: Triad of fever, localized midline dorsal spine or neck pain, and progressive limb weakness; once neurologic signs appear, cord compression rapidly progresses.

Spinal epidural hematoma: Presents as acute focal or radicular pain followed by variable signs of a spinal cord or conus medullaris disorder.

Acute disk herniation: Cervical and thoracic disk herniations are less common than lumbar.

Spinal cord infarction: Anterior spinal artery infarction produces paraplegia or quadriplegia, sensory loss affecting pain/temperature but sparing vibration/position sensation (supplied by posterior spinal arteries), and loss of sphincter control. Onset sudden or progressive, evolving over minutes or a few hours. Associated conditions: aortic atherosclerosis, dissecting aortic aneurysm, vertebral artery occlusion or dissection in the neck, aortic surgery, or profound hypotension. Therapy is directed at the predisposing condition. When due to thromboembolism, acute anticoagulation is not indicated, with the possible

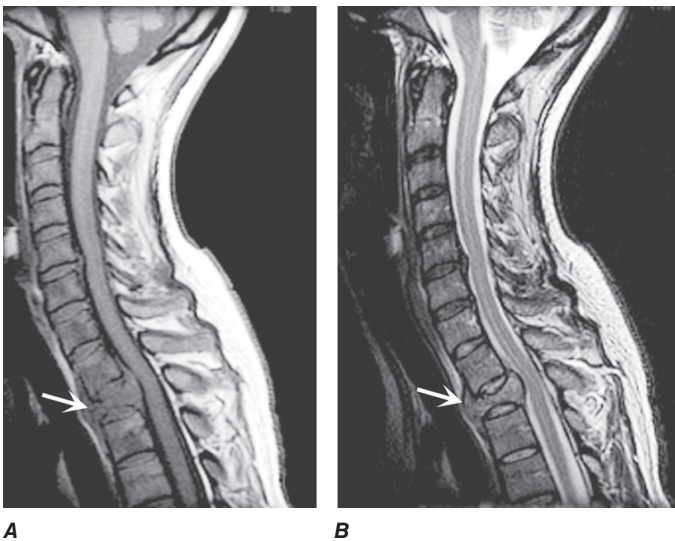


FIGURE 191-2 Epidural spinal cord compression due to breast carcinoma. Sagittal T1-weighted (**A**) and T2-weighted (**B**) MRI scans through the cervicothoracic junction reveal an infiltrated and collapsed second thoracic vertebral body with posterior displacement and compression of the upper thoracic spinal cord. The low-intensity bone marrow signal in A signifies replacement by tumor.

exception of the unusual transient ischemic attack or incomplete infarction with a stuttering or progressive course.

Immune-mediated myelopathies: Acute transverse myelopathy (ATM) occurs in 1% of pts with SLE; associated with antiphospholipid antibodies. Sjögren's and Behçet's syndromes, mixed connective tissue disease, and p-ANCA vasculitis are other causes. Sarcoid can produce ATM with large edematous swelling of the spinal cord. Demyelinating diseases, either neuromyelitis optica (NMO) or multiple sclerosis (MS), also can present as ATM; glucocorticoids, consisting of IV methylprednisolone followed by oral prednisone, are indicated for moderate to severe symptoms and refractory cases may respond to plasma exchange (**Chaps. 192 and 193**). Treatment with mycophenolate mofetil or rituximab may protect against relapses in NMO. Other cases of ATM are idiopathic.

Infectious myelopathies: Herpes zoster is the most common viral agent, but herpes simplex virus types 1 and 2, EBV, CMV, rabies virus, and Zika virus are also well described; in cases of suspected viral myelitis, antivirals may be appropriately started pending laboratory confirmation. A number of enteroviruses and flaviviruses (e.g., Japanese encephalitis and West Nile virus) can cause a polio-like syndrome. Bacterial and mycobacterial causes are less common. Schistosomiasis is an important cause worldwide.

■ CHRONIC MYELOPATHIES

Spondylitic myelopathies: One of the most common causes of gait difficulty in the elderly. Presents as neck and shoulder pain with stiffness, radicular arm pain, and progressive spastic paraparesis with paresthesias and loss of vibration sense; in advanced cases, urinary incontinence may occur. A tendon reflex in the arms is often diminished at some level. Diagnosis is best made by MRI. Treatment is surgical (**Chap. 50**).

Vascular malformations: An important treatable cause of progressive or episodic myelopathy. May occur at any level; diagnosis is often suggested by contrast-enhanced MRI (**Fig. 191-3**), but is confirmed by selective spinal angiography. Treatment generally consists of microsurgical resection, endovascular embolization of the major feeding vessels, or a combination of the two approaches.

Retrovirus-associated myelopathies: Infection with human T-cell lymphotropic virus I (HTLV-I) may produce a slowly progressive spastic paraparesis with variable pain, sensory loss, and bladder disturbance; diagnosis is made by demonstration of specific serum antibody. Treatment is symptomatic. A progressive vacuolar myelopathy may also result from HIV infection.

Syringomyelia: Cavitory expansion of the spinal cord resulting in progressive myelopathy; may be an isolated finding or associated with protrusion of cerebellar tonsils into cervical spinal canal (Chiari type 1). Classic presentation is loss of pain/temperature sensation in the neck, shoulders, forearms, or hands with areflexic weakness in the upper limbs and progressive spastic paraparesis; cough headache, facial numbness, or thoracic kyphoscoliosis may occur. Diagnosis is by MRI; treatment is surgical and often unsatisfactory.

Multiple sclerosis: Spinal cord involvement is common and is a major cause of disability especially in progressive forms of MS (**Chap. 192**).

Subacute combined degeneration (vitamin B₁₂ deficiency): Paresthesias in hands and feet, early loss of vibration/position sense, progressive spastic/ataxic weakness, and areflexia due to associated peripheral neuropathy; mental changes and optic atrophy may be present along with a serum macrocytic anemia. Causes include dietary deficiency especially in vegans, and gastric malabsorption syndromes including pernicious anemia. Diagnosis is confirmed by a low serum B₁₂ level, elevated levels of homocysteine and methylmalonic acid. Treatment is

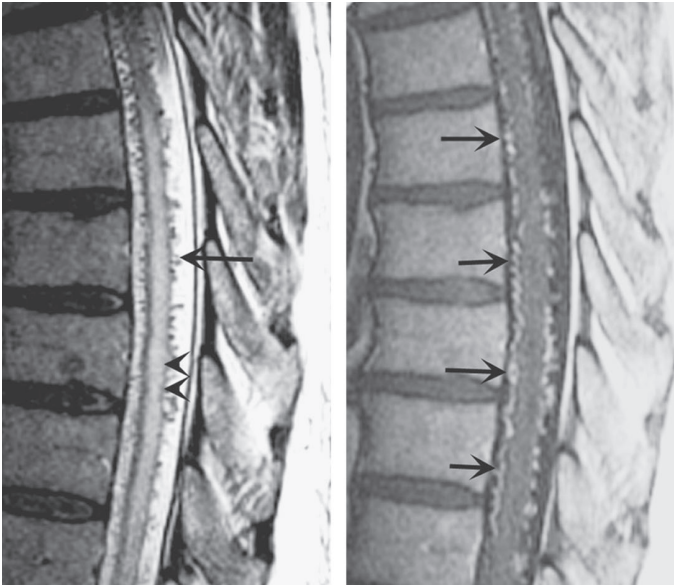


FIGURE 191-3 Arteriovenous malformation. Sagittal MR scans of the thoracic spinal cord: T2 fast spin-echo technique (left) and T1 postcontrast image (right). On the T2-weighted image (left), abnormally high signal intensity is noted in the central aspect of the spinal cord (arrowheads). Numerous punctate flow voids indent the dorsal and ventral spinal cord (arrow). These represent the abnormally dilated venous plexus supplied by the dural arteriovenous fistula. After contrast administration (right), multiple, serpentine, enhancing veins (arrows) on the ventral and dorsal aspect of the thoracic spinal cord are visualized, diagnostic of arteriovenous malformation. This pt was a 54-year-old man with a 4-year history of progressive paraparesis.

vitamin replacement beginning with 1 mg of IM vitamin B₁₂ repeated at regular intervals or by subsequent oral treatment.

Hypocupric myelopathy: Clinically nearly identical to subacute combined degeneration (above) except there is no neuropathy. Low levels of serum copper and usually ceruloplasmin make the diagnosis. Some cases are idiopathic and others follow GI procedures that hinder absorption; excess zinc ingestion is another cause. Treatment is oral copper supplementation.

Tabes dorsalis (tertiary syphilis): May present as lancinating pains, gait ataxia, bladder disturbances, and visceral crises. Cardinal signs are areflexia in the legs, impaired vibration/position sense, Romberg sign, and Argyll Robertson pupils which fail to constrict to light but accommodate.

Hereditary spastic paraplegia: Progressive spasticity and weakness in the legs occurring on a familial basis; may be autosomal dominant, recessive, or X-linked. More than 60 different loci identified.

Adrenomyeloneuropathy: X-linked disorder that is a variant of adrenoleukodystrophy. Usually, affected males have a history of adrenal insufficiency and then develop a progressive spastic paraparesis. Female heterozygotes may develop a slower progressive myelopathy without adrenal insufficiency. Diagnosis made by elevated very long chain fatty acids in plasma and in cultured fibroblasts. Allogeneic bone marrow transplantation has been successful in slowing

progression of cognitive decline in ALD, but appears to be ineffective for the myelopathy. Nutritional supplements (Lorenzo's oil) have also been attempted without evidence of efficacy.

■ COMPLICATIONS

Bladder dysfunction with risk of urinary tract infection; bowel dysmotility; pressure sores; in high cervical cord lesions, mechanical respiratory failure; paroxysmal hypertension or hypotension with volume changes; severe hypertension and bradycardia in response to noxious stimuli or bladder or bowel distention; venous thrombosis and pulmonary embolism.

192 Multiple Sclerosis



Characterized by inflammation, selective destruction of CNS myelin, and neurodegeneration; peripheral nervous system is spared. Pathologically, the multifocal scarred lesions of multiple sclerosis (MS) are termed *plaques*. Etiology is autoimmune, with susceptibility determined by genetic and environmental factors. MS affects >900,000 in the United States and 3 million worldwide; onset is often in early to middle adulthood, and women are affected three times as often as men.

■ CLINICAL FEATURES

Onset may be abrupt or insidious. Some pts have symptoms that are so trivial that they may not seek medical attention for months or years. Recurrent attacks of focal neurologic dysfunction lasting weeks or months and followed by variable recovery are typical; some pts initially present with slowly progressive deterioration. Symptoms often transiently worsen with fatigue, stress, exercise, or heat. Manifestations include weakness and/or sensory symptoms, visual difficulties, abnormalities of gait and coordination, urinary urgency or frequency, and fatigue. Motor involvement can present as a heavy, stiff, weak, or clumsy limb. Localized tingling, "pins and needles," and "dead" sensations are common. Optic neuritis produces monocular blurring of vision, especially in the central visual field, often with associated retro-orbital pain accentuated by eye movement. Involvement of the brainstem may result in diplopia, nystagmus, vertigo, or facial pain, numbness, weakness, hemispasm, or myokymia (rippling muscular contractions). Ataxia, tremor, and dysarthria may reflect disease of cerebellar pathways. Lhermitte's symptom, a momentary electric shock-like sensation evoked by neck flexion, indicates disease in the cervical spinal cord. Diagnostic criteria are listed in [Table 192-1](#); MS mimics are summarized in [Table 192-2](#).

■ PHYSICAL EXAMINATION

Abnormal signs usually more widespread than expected from the history. Check for abnormalities in visual fields, loss of visual acuity, disturbed color perception, optic pallor or papillitis, afferent pupillary defect (paradoxical dilation to direct light following constriction to consensual light), nystagmus, internuclear ophthalmoplegia (slowness or loss of adduction in one eye with nystagmus in the abducting eye on lateral gaze), facial numbness or weakness, dysarthria, weakness and spasticity, hyperreflexia, ankle clonus, upgoing toes, ataxia, sensory abnormalities.

TABLE 192-1 Diagnostic Criteria for Multiple Sclerosis (MS)

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED FOR MS DIAGNOSIS
2 or more attacks; objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None
2 or more attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by <ul style="list-style-type: none"> • ≥ 1 T2 lesion on MRI in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) OR <ul style="list-style-type: none"> • Await a further clinical attack implicating a different CNS site
1 attack; objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by <ul style="list-style-type: none"> • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time OR <ul style="list-style-type: none"> • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan OR <ul style="list-style-type: none"> • Await a second clinical attack
1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: <p>For dissemination in space</p> <ul style="list-style-type: none"> • ≥ 1 T2 lesion in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) OR <ul style="list-style-type: none"> • Await a second clinical attack implicating a different CNS site AND <p>For dissemination in time</p> <ul style="list-style-type: none"> • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time OR <ul style="list-style-type: none"> • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan OR <ul style="list-style-type: none"> • Await a second clinical attack

(Continued)

TABLE 192-1 Diagnostic Criteria for Multiple Sclerosis (MS) (Continued)

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED FOR MS DIAGNOSIS
Insidious neurologic progression suggestive of MS (PPMS)	<p>1 year of disease progression (retrospectively or prospectively determined)</p> <p>PLUS</p> <p>2 out of the 3 following criteria:</p> <p>Evidence for dissemination in space in the brain based on ≥ 1 T2+ lesions in the MS-characteristic periventricular, juxtacortical, or infratentorial regions</p> <p>Evidence for dissemination in space in the spinal cord based on ≥ 2 T2+ lesions in the cord</p> <p>Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)</p>

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PPMS, primary progressive multiple sclerosis.

Source: From Polman CH et al: Diagnostic criteria for multiple sclerosis: 2010 Revisions to the "McDonald Criteria." *Ann Neurol* 69:292, 2011. Reprinted with permission from John Wiley & Sons, Inc.

TABLE 192-2 Disorders That Can Mimic Multiple Sclerosis (MS)

Acute disseminated encephalomyelitis (ADEM)
Antiphospholipid antibody syndrome
Behçet's disease
Cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy (CADASIL)
Congenital leukodystrophies (e.g., adrenoleukodystrophy, metachromatic leukodystrophy)
Human immunodeficiency virus (HIV) infection
Ischemic optic neuropathy (arteritic and nonarteritic)
Lyme disease
Mitochondrial encephalopathy with lactic acidosis and stroke (MELAS)
Neoplasms (e.g., lymphoma, glioma, meningioma)
Sarcoid
Sjögren's syndrome
Stroke and ischemic cerebrovascular disease
Syphilis
Systemic lupus erythematosus and related collagen vascular disorders
Tropical spastic paraparesis (HTLV-1/2 infection)
Vascular malformations (especially spinal dural AV fistulas)
Vasculitis (primary CNS or other)
Vitamin B ₁₂ deficiency

Abbreviations: AV, arteriovenous; CNS, central nervous system; HTLV, human T cell lymphotropic virus.

■ DISEASE COURSE

Three major subtypes:

- *Relapsing MS (RMS)* is characterized by discrete attacks of neurologic dysfunction over days to weeks with or without recovery; between attacks, no progression of neurologic impairment is noted. Accounts for 90% of new-onset MS cases.
- *Secondary progressive MS (SPMS)* always begins as RMS. At some point, however, the clinical course changes so that the pt experiences deterioration in function unassociated with acute attacks. SPMS produces more fixed neurologic disability than RMS. For a pt with RMS, risk of developing SPMS is ~1–2% each year.
- *Primary progressive MS (PPMS)* accounts for ~10% of cases. These pts experience a steady decline in function from disease onset. Compared to RMS, the sex distribution is more even, the disease begins later in life (mean age ~40 years), and disability develops faster. Despite these differences, PPMS appears to represent the same underlying illness as RMS.

Progressive MS and Disease Activity. Pts with SPMS or even PPMS will occasionally experience relapses, albeit less often than in RMS. Progressive MS pts experiencing relapses or who are found to have acute new lesions on MRI are considered to have “active” MS. In contrast, the term “progression” is reserved to describe neurological worsening that accumulates independently from disease activity.

Most pts ultimately develop progressive neurologic disability. In older studies, 15 years after onset, only 20% of pts had no functional limitation, and between one-third and one-half of RMS pts progressed to SPMS and required assistance with ambulation. The long-term prognosis for MS has improved greatly in recent years due, at least in part, to widespread use of therapies for RMS.

■ LABORATORY EVALUATION

MRI reveals multifocal bright areas on T2-weighted sequences in >95% of pts, often in periventricular location; gadolinium enhancement indicates acute lesions with disruption of blood-brain barrier (Fig. 192-1). MRI is also useful to exclude MS mimics, although findings in MS are not completely specific for the disorder. CSF findings include mild lymphocytic pleocytosis (5–75 cells in 25%), oligoclonal bands (>75% have two or more), elevated IgG (80%), and normal total protein level. Visual, auditory, and somatosensory evoked response tests can identify lesions that are clinically silent; one or more evoked response tests are prolonged in 80–90% of pts. Urodynamic studies aid in management of bladder symptoms.

TREATMENT

Multiple Sclerosis (See Fig. 192-2)

■ THERAPIES FOR RELAPSING FORMS OF MS (RMS, SPMS WITH EXACERBATIONS)

More than a dozen are available.

Frequently Used

OCRELIZUMAB (OCR) (HIGHLY EFFECTIVE; ANTI-CD20 [B-CELL] MONOCLONAL ANTIBODY)
Dose 600 mg IV every 24 weeks (first dose split as two 300-mg infusions spaced 2 weeks apart); IV methylprednisolone 100 mg prior to each infusion and

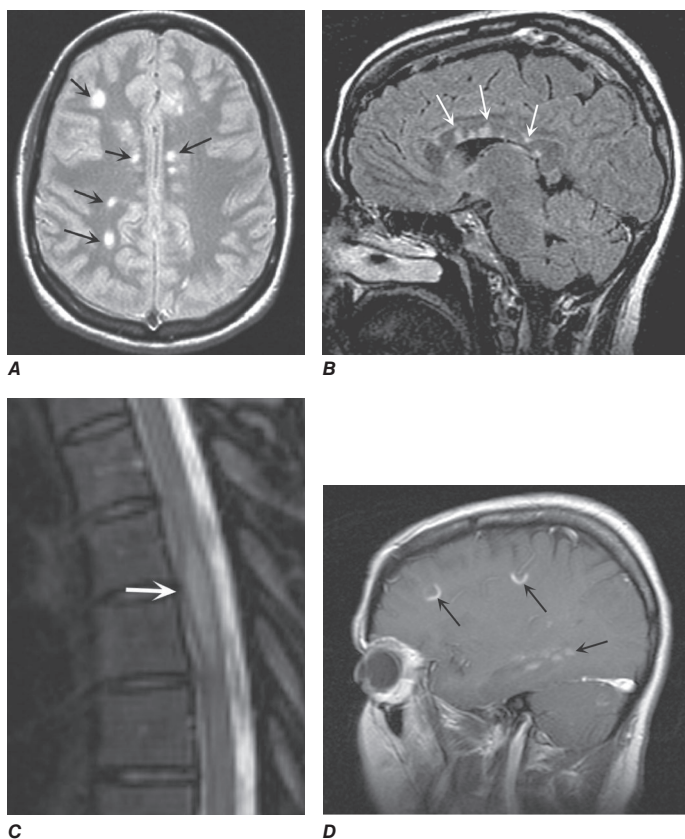


FIGURE 192-1 MRI findings in MS. **A.** Axial first-echo image from T2-weighted sequence demonstrates multiple bright signal abnormalities in white matter, typical for MS. **B.** Sagittal T2-weighted fluid-attenuated inversion recovery image (FLAIR) in which the high signal of CSF has been suppressed. CSF appears dark, while areas of brain edema or demyelination appear high in signal as shown here in the corpus callosum (arrows). Lesions in the anterior corpus callosum are frequent in MS and rare in vascular disease. **C.** Sagittal T2-weighted fast spin-echo image of the thoracic spine demonstrates a fusiform high-signal-intensity lesion in the midthoracic spinal cord. **D.** Sagittal T1-weighted image obtained after the IV administration of gadolinium reveals focal areas of blood-brain barrier disruption, identified as high-signal-intensity regions (arrows).

prophylaxis with analgesics/antipyretics and antihistamines recommended. Generally well tolerated; infusion-related reactions in a minority of pts, most with first infusion and mild in degree. OCR trials showed a small imbalance of malignancies including breast cancer, but no excess cancer risk has been found in the postmarketing setting. Another anti-CD20 antibody, **rituximab**, was tested against MS in preliminary trials and is also used in some settings despite lack of pivotal trial data.

NATALIZUMAB (NTZ) (HIGHLY EFFECTIVE; ANTI-INTEGRIN MONOCLONAL ANTIBODY)
Dose 300 mg IV each month. Well tolerated; a small percentage of pts experience hypersensitivity reactions (including anaphylaxis) or develop neutralizing

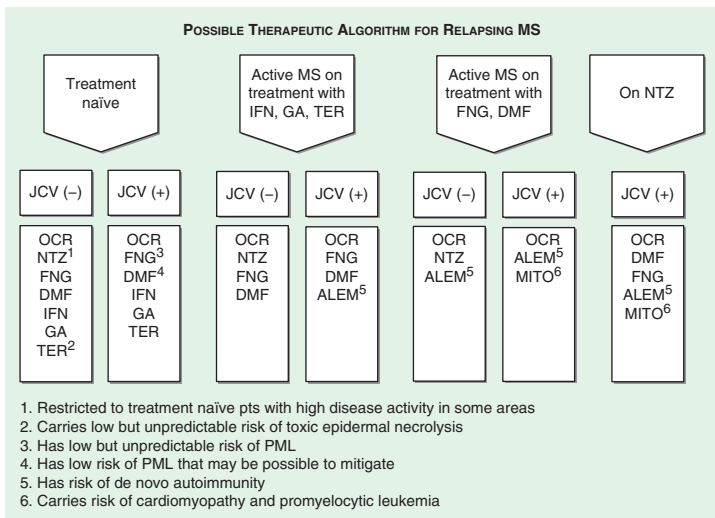


FIGURE 192-2 Therapeutic decision-making for relapsing MS. Options are shown for different clinical scenarios and based on JCV status. Active MS is defined by clinical relapses or the development of new focal MRI white matter lesions. Treatment options can also include trials of different preparations of interferon β (IFN- β), particularly advancing from once-weekly (Avonex) to a more frequent (e.g., Rebif, Betaseron/Extavia) dosing regimen, as well as use of natalizumab in JC virus–positive pts.

antibodies. Major concern is risk of life-threatening progressive multifocal leukoencephalopathy (PML). Measure serum antibodies against JC virus (JCV) to stratify risk, as pts who test negative have minimal risk; with treatment repeat testing at 6 month intervals, as seroconversion can occur.

FINGOLIMOD (FGL) (MODERATELY EFFECTIVE; INHIBITS LYMPHOCYTE TRAFFICKING)

Dose 0.5 mg, oral each day. Lab abnormalities (e.g., elevated liver function tests or lymphopenia) usually mild but may require discontinuation. Heart block and bradycardia can occur when therapy is initiated; a 6-h period of first dose observation (including ECG monitoring) recommended. Other side effects: macular edema and, rarely, disseminated varicella-zoster virus (VZV) and cryptococcal infection.

DIMETHYL FUMARATE (DMF) (MODERATELY EFFECTIVE; IMMUNOMODULATOR)

Dose 240 mg oral twice each day. GI side effects common at the start of therapy but often subside with continued use. Other adverse events include flushing, mild decrease in neutrophil and lymphocyte counts, and elevation in liver enzymes. In lymphopenic pts, consider alternate treatments due to PML risk.

INTERFERON (IFN)- β (MODESTLY EFFECTIVE; IMMUNOMODULATOR)

IFN- β -1a, 30 μ g, IM once per week; IFN- β -1a, 44 μ g, SQ three times per week. IFN- β -1b, 250 μ g, SQ every other day. Pegylated IFN- β -1a, 125 μ g, SQ every 14 days. Side effects: mild lab abnormalities (e.g., elevated liver function tests or lymphopenia), SQ injection site reactions. Some pts develop neutralizing antibodies to IFN- β which can degrade effectiveness.

GLATIRAMER ACETATE (GA) (MODESTLY EFFECTIVE; IMMUNOMODULATOR) 20 mg SQ every day or 40 mg three times weekly. Side effects: injection-site reactions, lipatrophy; ~15% of pts experience one or more brief episodes of flushing, chest tightness, dyspnea, palpitations, and anxiety after injection.

Less Commonly Used

SIPONIMOD (MODERATELY EFFECTIVE; INHIBITS LYMPHOCYTE TRAFFICKING) Maintenance dose 1 or 2 mg oral each day, initiated by gradual escalation to final dose. Possible side effects include lab abnormalities (e.g., elevated liver function tests or lymphopenia); bradycardia; macular edema; possibly teratogenic. Siponimod is a selective inhibitor of the sphingosine-1-phosphate (S1P) receptor, thus it works in a fashion similar to FGL.

TERIFLUNOMIDE (MODESTLY EFFECTIVE; BLOCKS PYRIMIDINE SYNTHESIS) Dose either 7 or 14 mg PO each day. Side effects: mild hair thinning and gastrointestinal; rarely causes toxic epidermal necrolysis or Stevens-Johnson syndrome. A major limitation, especially in women of childbearing age, is possible teratogenicity.

ALEMTUZUMAB (HIGHLY EFFECTIVE; ANTI-CD52 [PAN-LYMPHOCYTE] MONOCLONAL ANTIBODY) The toxicities of concern are (1) autoimmune diseases including thyroiditis, Graves' disease, thrombocytopenia; (2) malignancies; (3) serious infections; and (4) infusion reactions. Because of its toxicity profile, the US FDA indicated alemtuzumab only in pts who have tried and failed at least two other DMTs.

INITIATING AND CHANGING TREATMENT Previously, most pts with RMS received injectable agents (IFN- β or GA) as first-line therapy. However, with the introduction of more effective agents administered by infusion including OCR (irrespective of JCV status) and NTL (in JCV negative pts), and the oral agents FGL and DMF, this has begun to change. OCR can be used first-line, supported by the combination of high efficacy, infrequently administered infusions, and a favorable safety profile. NTL, which is highly effective, well tolerated, and apparently safe in JCV antibody-negative pts, provides another attractive option.

MILD INITIAL COURSE In pts with recent onset, normal examination or minimal impairment (EDSS \leq 2.5 or less), or low disease activity, either an injectable (IFN- β or GA) or an oral agent (FGL, DMF) is reasonable. High efficacy therapy such as OCR (irrespective of JCV status) or NTL (in JCV negative pts) can also be considered even in minimally affected pts. The injectable agents (IFN- β and glatiramer acetate) have a superb track record for safety but a high nuisance factor due to need for frequent injections, as well as bothersome side effects that contribute to noncompliance.

MODERATE OR SEVERE INITIAL COURSE Either OCR or, if the pt is JCV seronegative, NTZ, or an oral agent (FGL or DMF) is recommended.

Regardless of which agent is chosen first, treatment should probably be changed in pts who continue to have relapses, progressive neurologic impairment or, arguably, ongoing evidence of subclinical MRI activity.

- In addition, vitamin D deficiency should be corrected in all pts with MS, usually by oral supplementation with vitamin D₃, 4000–5000 IU daily.

■ THERAPIES FOR ACUTE RELAPSES

- Acute relapses that produce functional impairment may be treated with a short course of IV methylprednisolone (500–1000 mg IV q A.M. \times 3–5 days) followed often by oral prednisone (60 mg q A.M. \times 4, 40 mg q A.M. \times 4, 20 mg q A.M. \times 3).

This regimen modestly reduces the severity and shortens the duration of attacks.

- Plasma exchange (seven exchanges: 40–60 mL/kg, every other day for 14 days) may benefit pts with fulminant attacks of demyelination (not only MS) that are unresponsive to glucocorticoids; cost is high and conclusive evidence of efficacy is lacking.

■ THERAPIES FOR PROGRESSIVE MS

SPMS

Pts with SPMS who have continuing relapses or active disease by MRI should be treated as in RMS; siponimod has been recently approved specifically for this population. IFN- β is probably ineffective in pts with SPMS who do not have active disease. Other agents have not yet been studied in this population.

PPMS

OCR was shown to reduce progression of clinical disability in PPMS by 24% compared with placebo, and also to improve other clinical and MRI markers of inflammatory and degenerative disease activity. The dose for PPMS is identical as for RMS (above).

■ SYMPTOMATIC THERAPY

- Spasticity may respond to physical therapy, baclofen (20–120 mg/d), diazepam (2–40 mg/d), tizanidine (8–32 mg/d), dantrolene (25–400 mg/d), and cyclobenzaprine hydrochloride (10–60 mg/d).
- *Weakness* can sometimes be improved with the use of potassium channel blockers such as extended release 4-aminopyridine (10 mg twice daily), particularly when lower extremity weakness interferes with the pt's ability to ambulate.
- *Dysesthesia* may respond to carbamazepine (100–1000 mg/d in divided doses), phenytoin (300–600 mg/d), gabapentin (300–3600 mg/d), pregabalin (50–300 mg/d), or amitriptyline (25–150 mg/d).
- Treatment of bladder symptoms is based on the underlying pathophysiology investigated with urodynamic testing: bladder hyperreflexia is treated with evening fluid restriction and frequent voiding; if this fails, anticholinergics such as oxybutynin (5–15 mg/d) may be tried; hyporeflexia is treated with the cholinergic drug bethanechol (30–150 mg a day), and dyssynergia due to loss of coordination between bladder wall and sphincter muscles is treated with anticholinergics and intermittent catheterization.
- Depression should be treated aggressively.

■ VARIANTS OF MS

Acute Disseminated Encephalomyelitis (ADEM)

A fulminant, often devastating, demyelinating disease that has a monophasic course and may be associated with antecedent immunization or infection. Postinfectious encephalomyelitis is most frequently associated with measles, varicella, as well as numerous other virus infections and *Mycoplasma pneumoniae*. Signs of disseminated neurologic disease are consistently present (e.g., hemiparesis or quadriplegia, extensor plantar responses, lost or hyperactive tendon reflexes, sensory loss, and brainstem involvement). Fever, headache, meningismus, lethargy progressing to coma, and seizures may occur. CSF pleocytosis, generally 200 cells/ μ L, is common. MRI may reveal extensive gadolinium enhancement of white matter in brain and spinal cord. Initial treatment is with high-dose glucocorticoids. Pts who fail to respond may benefit from a course of plasma exchange or IVIg.

193 Neuromyelitis Optica



Neuromyelitis optica (NMO; Devic's disease) is an aggressive inflammatory disorder characterized by recurrent attacks of optic neuritis (ON) and myelitis; the more inclusive term *NMO Spectrum Disorders* (NMOSD) incorporates pts with partial forms, and with involvement of additional CNS structures (**Table 193-1**). NMO is more frequent in women than men (>3:1), and typically begins in adulthood but can arise at any age. An important consideration is distinguishing between NMO and multiple sclerosis (MS; **Chap. 192**). In NMO, attacks of ON can be bilateral and produce severe visual loss (uncommon in MS); myelitis can be severe and transverse (rare in MS) and is typically longitudinally extensive (**Fig. 193-1**) involving three or more contiguous vertebral segments. Also in contrast to MS, progressive symptoms typically do not occur in NMO.

Brain MRI may be normal or show areas of nonspecific signal change as well as lesions associated with specific syndromes such as the hypothalamus causing an endocrinopathy; the lower medulla presenting as intractable hiccoughs or vomiting; or cerebral hemispheres producing focal symptoms, encephalopathy, or seizures. Large MRI lesions in the cerebral hemispheres may have a "cloud-like" appearance and, unlike MS lesions, are often not destructive and can

TABLE 193-1 Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorder

Diagnostic Criteria for NMOSD with AQP4-IgG

1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses

Diagnostic Criteria for NMOSD without AQP4-IgG or NMOSD with Unknown AQP4-IgG Status

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
 - a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
 - b. Dissemination in space (2 or more different clinical characteristics)
 - c. Fulfillment of additional MRI requirements, as applicable
2. Negative test for AQP4-IgG using best available detection method or testing unavailable
3. Exclusion of alternative diagnoses

Core Clinical Characteristics

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea or vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

(Continued)

TABLE 193-1 Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorder (Continued)**Additional MRI Requirements for NMOSD without AQP4-IgG and NMOSD with Unknown AQP4-IgG Status**

1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion of T1-weighted gadolinium-enhancing lesion extending over $>1/2$ optic nerve length or involving optic chiasm
2. Acute myelitis: requires associated intramedullary MRI lesion extending ≥ 3 contiguous segments (LETM) OR ≥ 3 contiguous segments of focal spinal cord atrophy in pts with history compatible with acute myelitis
3. Area postrema syndrome requires associated dorsal medulla/area postrema lesions
4. Acute brainstem syndrome requires periependymal brainstem lesions

Abbreviations: AQP-4, aquaporin-4; LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder.

Source: Adapted from Wingerchuk DM et al: International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 85:177–189, 2015. Used with permission.

resolve completely. Spinal cord MRI lesions typically consist of focal enhancing areas of swelling and tissue destruction, extending over three or more spinal cord segments, and on axial sequences, these are centered on the gray matter of the cord. CSF findings include pleocytosis greater than in MS, with neutrophils and eosinophils in many acute cases; oligoclonal bands are uncommon.

NMO is an autoimmune disease associated with a highly specific autoantibody directed against the water channel protein aquaporin-4 (AQP4) that is present in the sera of approximately 70% of pts with a clinical diagnosis of NMO. AQP4 is localized to the foot processes of astrocytes. Pathology reveals inflammation, loss of astrocytes, and an absence of staining of AQP4 by immunohistochemistry, plus thickened blood vessel walls, demyelination, and deposition of antibody and complement.

Clinical Course

NMO is typically a recurrent disease; the course is monophasic in fewer than 10% of pts. Individuals who test negative for AQP-4 antibodies are somewhat more likely to have a monophasic course. Untreated NMO is usually disabling over time; in one series, respiratory failure from cervical myelitis was present in one-third of pts, and 8 years after onset, 60% of pts were blind and more than half had permanent paralysis of one or more limbs. NMO can occur in people of any ethnic background, but individuals of Asian and African origin are disproportionately affected.

Up to 40% of NMO pts have a systemic autoimmune disorder, such as systemic lupus erythematosus, Sjögren's syndrome, perinuclear antineutrophil cytoplasmic antibody (p-ANCA)-associated vasculitis, myasthenia gravis, Hashimoto's thyroiditis, or mixed connective tissue disease. In others, onset may be associated with acute infection with VZV, EBV, HIV, or tuberculosis. Rare cases appear to be paraneoplastic.

TREATMENT

Neuromyelitis Optica

Acute attacks are usually treated with high-dose glucocorticoids (e.g., methylprednisolone 1 g/d for 5–10 days followed by a prednisone taper). Plasma exchange (typically 5–7 exchanges of 1.5 plasma volumes/exchange) is used

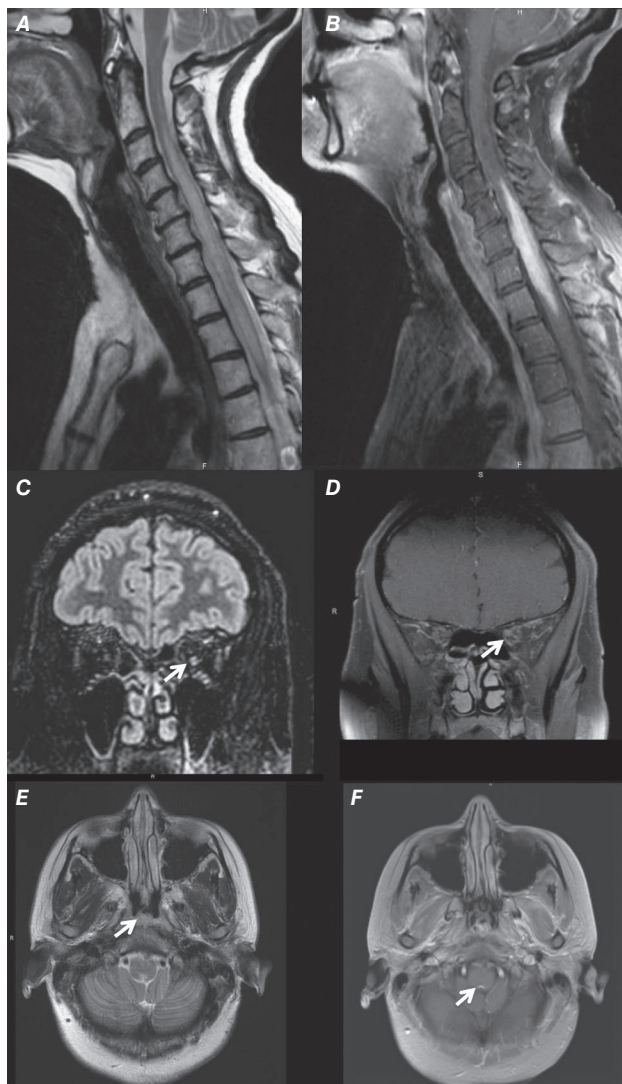


FIGURE 193-1 Imaging findings in neuromyelitis optica: longitudinally extensive transverse myelitis, optic neuritis and brainstem involvement. (A) Sagittal fluid attenuation inversion recovery (FLAIR) cervical-spine magnetic resonance image (MRI) showing an area of increased signal change on T2-weighted imaging spanning more than 3 vertebral segments in length. (B) Sagittal T1-weighted cervical-spine MRI following gadolinium-DPTA infusion showing enhancement. (C) Coronal brain MRI shows hyperintense signal on FLAIR imaging within the left optic nerve. (D) Coronal T1-weighted brain MRI following gadolinium-DPTA infusion shows enhancement of the left optic nerve. (E) Axial brain MRI shows an area of hyperintense signal on T2-weighted imaging within the area postrema (arrows). (F) Axial T1-weighted brain MRI following gadolinium-diethylene triamine pentaacetic acid (DPTA) infusion shows punctate enhancement of the area postrema (arrows).

empirically for acute episodes that do not respond to glucocorticoids. Given the unfavorable natural history of untreated NMO, prophylaxis against relapses is recommended for most pts using one of the following regimens: mycophenolate mofetil (1000 mg bid); rituximab a B-cell depleting anti-CD20 monoclonal antibody (2 g IV Q 6 months); or a combination of glucocorticoids (500 mg IV methylprednisolone daily for 5 days; then oral prednisone 1 mg/kg per day for 2 months, followed by slow taper) plus azathioprine (2 mg/kg per day started on week 3). Some therapies with proven efficacy in MS do not appear to be useful for NMO. Clinical trials with the B-cell depleting anti-CD19 monoclonal antibody (inebilizumab), the terminal complement inhibitor (eculizumab), and an IL-6 receptor blocking antibody (SA-237) are ongoing.

■ DEMYELINATION ASSOCIATED WITH ANTI-MOG ANTIBODIES

Antibodies against myelin oligodendrocyte glycoprotein (MOG) are present in some pts with AQP4 seronegative NMO. Pts who are seropositive for anti-MOG antibodies are at risk for bilateral, synchronous ON and myelitis. A clinical feature of ON associated with anti-MOG antibodies is the presence of papillitis seen by funduscopy or orbital MRI. ON associated with anti-MOG antibodies is typically longitudinally extensive on MRI, and brain MRI can be normal or show fluffy areas of increased signal change in white or gray matter structures, similar to NMO. Spinal cord lesions can be longitudinally extensive or short. Demyelination associated with anti-MOG antibodies is sometimes monophasic, as in acute disseminated encephalomyelitis (ADEM), but can also be recurrent. Acute episodes are managed with high dose glucocorticoids followed by a prednisone taper and sometimes by PLEX, as with NMO. Brain lesions associated with anti-MOG antibodies often respond rapidly to treatment with glucocorticoids and may resolve entirely. Some pts experience disease recurrence following discontinuation of prednisone and can become glucocorticoid dependent. There is limited data on use of other immunosuppressant medications typically used in NMO.

194

Acute Meningitis and Encephalitis



Acute infections of the nervous system include bacterial meningitis, viral meningitis, encephalitis, focal infections such as brain abscess and subdural empyema, and infectious thrombophlebitis. Key goals: emergently distinguish between these conditions, identify the pathogen, and initiate appropriate antimicrobial therapy.

APPROACH TO THE PATIENT

Acute Infection of the Nervous System

(Fig. 194-1) First identify whether infection predominantly involves the subarachnoid space (*meningitis*) or brain tissue (termed *encephalitis* when viral, *cerebritis* or *abscess* if bacterial, fungal, or parasitic). Nuchal rigidity is the pathognomonic sign of meningeal irritation and is present when the neck resists passive flexion.

Principles of management:

- Initiate empirical therapy whenever bacterial meningitis is considered.
- All pts with head trauma, immunocompromised states, known malignancies, or focal neurologic findings (including papilledema or stupor/coma)

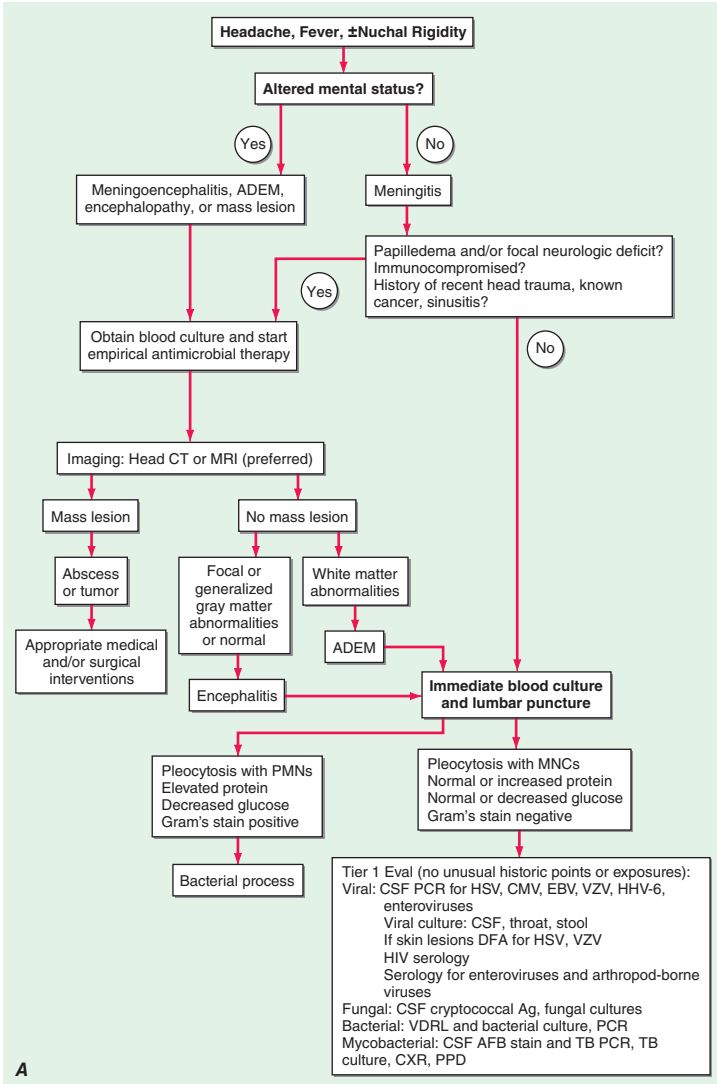


FIGURE 194-1 The management of pts with suspected CNS infection. ADEM, acute disseminated encephalomyelitis; AFB, acid-fast bacillus; Ag, antigen; CTFV, Colorado tick fever virus; DFA, direct fluorescent antibody; HHV, human herpesvirus; LCMV, lymphocytic choriomeningitis virus; MNCs, mononuclear cells; TB, tuberculosis; WNV, West Nile virus.

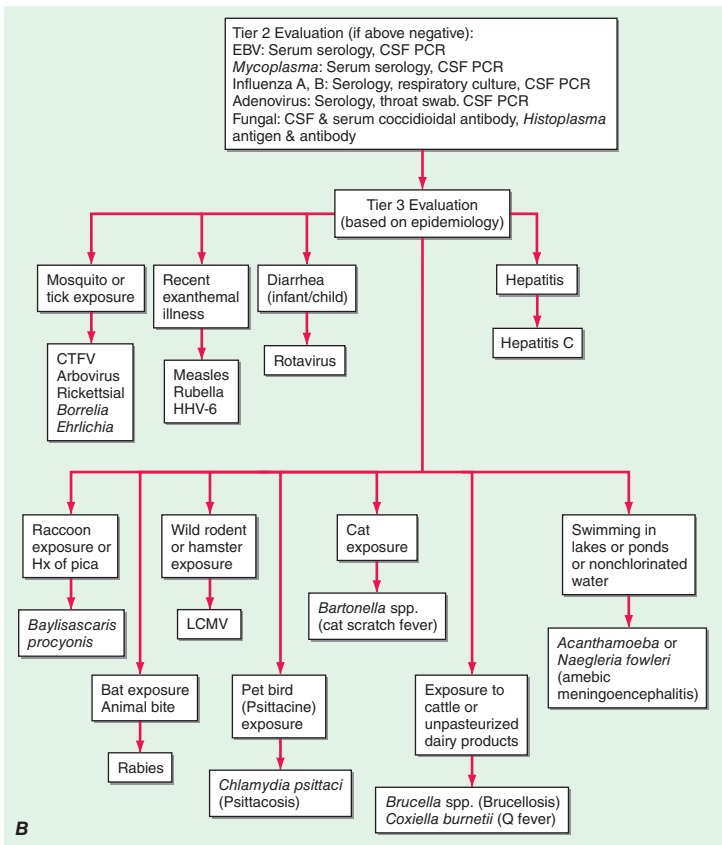


FIGURE 194-1 (Continued)

should undergo a neuroimaging study of the brain prior to LP. If bacterial meningitis is suspected, begin empirical antibiotic therapy prior to neuroimaging and LP.

- Stupor/coma, seizures, or focal neurologic deficits do not occur in viral meningitis; pts with these symptoms should be hospitalized and treated empirically for bacterial and viral meningoencephalitis.
- Immunocompetent pts with a normal level of consciousness, no prior antimicrobial treatment, and a CSF profile consistent with viral meningitis (lymphocytic pleocytosis and a normal glucose concentration) can often be treated as outpatients. Failure of a pt with suspected viral meningitis to improve within 48 h should prompt reevaluation including follow-up examination, repeat imaging, and laboratory studies, often including a second LP.

ACUTE BACTERIAL MENINGITIS

Pathogens most frequently involved in immunocompetent adults are *Streptococcus pneumoniae* ("pneumococcus," ~50%) and *Neisseria meningitidis* ("meningococcus," ~25%). Predisposing factors for pneumococcal

meningitis include infection (pneumonia, otitis, sinusitis), asplenia, hypogammaglobulinemia, complement deficiency, alcoholism, diabetes, and head trauma with cerebrospinal fluid (CSF) leak. *Listeria monocytogenes* is a consideration in pregnant women, individuals >60 years, alcoholics, and immunocompromised individuals of all ages. Enteric gram-negative bacilli and group B *Streptococcus* are increasingly common causes of meningitis in individuals with chronic medical conditions. *Staphylococcus aureus* and coagulase-negative staphylococci are causes following neurosurgical procedures, especially shunting procedures for hydrocephalus.

■ CLINICAL FEATURES

Presents as an acute fulminant illness that progresses rapidly in a few hours or as a subacute infection that progressively worsens over several days. The classic clinical triad of meningitis is fever, headache, and nuchal rigidity (“stiff neck”). Mental status changes occur in >75% of pts and vary from lethargy to coma. Nausea, vomiting, and photophobia are also common. Seizures occur in 20–40% of pts. Raised intracranial pressure (ICP) is the major cause of obtundation and coma. The rash of meningococemia begins as a diffuse maculopapular rash resembling a viral exanthem but rapidly becomes petechial on trunk and lower extremities, mucous membranes and conjunctiva, and occasionally palms and soles.

■ LABORATORY EVALUATION

The CSF profile is shown in [Table 194-1](#). CSF bacterial cultures are positive in >80% of pts, and CSF Gram’s stain demonstrates organisms in >60%. There are a number of “CSF pathogen panels” available that use specific bacterial primers to detect the nucleic acid of *S. pneumoniae*, *N. meningitidis*, *Escherichia coli*, *L. monocytogenes*, *Haemophilus influenzae*, and *Streptococcus agalactiae* (Group B streptococci). The latex agglutination (LA) test for detection of bacterial antigens of *S. pneumoniae*, *N. meningitidis*, *H. influenzae* type b, group B streptococcus, and *E. coli* K1 strains in the CSF is being replaced by the CSF bacterial polymerase chain reaction (PCR) assay. The Limulus amoebocyte lysate assay rapidly detects gram-negative endotoxin in CSF and thus is useful in diagnosis of gram-negative bacterial meningitis; false-positives may occur but sensitivity approaches 100%.

TABLE 194-1 Cerebrospinal Fluid (CSF) Abnormalities in Bacterial Meningitis

Opening pressure	>180 mmH ₂ O
White blood cells	10/μL to 10,000/μL; neutrophils predominate
Red blood cells	Absent in nontraumatic tap
Glucose	<2.2 mmol/L (<40 mg/dL)
CSF/serum glucose	<0.4
Protein	>0.45 g/L (>45 mg/dL)
Gram’s stain	Positive in >60%
Culture	Positive in >80%
PCR	Detects bacterial DNA
Latex agglutination	May be positive in pts with meningitis due to <i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , <i>Haemophilus influenzae</i> type b, <i>Escherichia coli</i> , group B streptococci
Limulus lysate	Positive in cases of gram-negative meningitis

Abbreviation: PCR, polymerase chain reaction.

Petechial skin lesions, if present, should be biopsied. Blood cultures should always be obtained.

■ DIFFERENTIAL DIAGNOSIS

Includes viral meningoencephalitis, especially herpes simplex virus (HSV) encephalitis (see next); rickettsial diseases such as Rocky Mountain spotted fever (immunofluorescent staining of skin lesions); focal suppurative CNS infections including subdural and epidural empyema and brain abscess (see next); subarachnoid hemorrhage (Chap. 20); and the demyelinating disease acute disseminated encephalomyelitis (ADEM, Chap. 192).

TREATMENT

Acute Bacterial Meningitis

- Recommendations for empirical therapy are summarized in Table 194-2. Therapy is then modified based on results of CSF culture (Table 194-3).

TABLE 194-2 Antibiotics Used in Empirical Therapy of Bacterial Meningitis and Focal Central Nervous System Infections^a

INDICATION	ANTIBIOTIC	
Preterm infants to infants <1 month	Ampicillin + cefotaxime	
Infants 1–3 months	Ampicillin + cefotaxime or ceftriaxone	
Immunocompetent children >3 months and adults <55	Cefotaxime, ceftriaxone, or cefepime + vancomycin	
Adults >55 and adults of any age with alcoholism or other debilitating illnesses	Ampicillin + cefotaxime, ceftriaxone or cefepime + vancomycin	
Hospital-acquired meningitis, posttraumatic or postneurosurgery meningitis, neutropenic pts, or pts with impaired cell-mediated immunity	Ampicillin + ceftazidime or meropenem + vancomycin	
ANTIMICROBIAL AGENT	TOTAL DAILY DOSE AND DOSING INTERVAL	
	CHILD (>1 MONTH)	ADULT
Ampicillin	300 (mg/kg)/d, q6h	12 g/d, q4h
Cefepime	150 (mg/kg)/d, q8h	6 g/d, q8h
Cefotaxime	225–300 (mg/kg)/d, q6h	12 g/d, q4h
Ceftriaxone	100 (mg/kg)/d, q12h	4 g/d, q12h
Ceftazidime	150 (mg/kg)/d, q8h	6 g/d, q8h
Gentamicin	7.5 (mg/kg)/d, q8h ^b	7.5 (mg/kg)/d, q8h
Meropenem	120 (mg/kg)/d, q8h	6 g/d, q8h
Metronidazole	30 (mg/kg)/d, q6h	1500–2000 mg/d, q6h
Nafcillin	100–200 (mg/kg)/d, q6h	9–12 g/d, q4h
Penicillin G	400,000 (U/kg)/d, q4h	20–24 million U/d, q4h
Vancomycin	45–60 (mg/kg)/d, q6h	45–60 (mg/kg)/d, q6–12h ^b

^aAll antibiotics are administered intravenously; doses indicated assume normal renal and hepatic function.

^bDoses should be adjusted based on serum peak and trough levels: gentamicin therapeutic level: peak: 5–8 µg/mL; trough: <2 µg/mL; vancomycin therapeutic level: peak: 25–40 µg/mL; trough: 5–15 µg/mL.

TABLE 194-3 Antimicrobial Therapy of Central Nervous System Bacterial Infections Based on Pathogen^a

ORGANISM	ANTIBIOTIC
<i>Neisseria meningitidis</i>	
Penicillin-sensitive	Penicillin G or ampicillin
Penicillin-resistant	Ceftriaxone or cefotaxime
<i>Streptococcus pneumoniae</i>	
Penicillin-sensitive	Penicillin G
Penicillin-intermediate	Ceftriaxone or cefotaxime or cefepime
Penicillin-resistant	Ceftriaxone (or cefotaxime or cefepime) + vancomycin
Gram-negative bacilli (except <i>Pseudomonas</i> spp.)	
<i>Pseudomonas aeruginosa</i>	Ceftazidime or meropenem
<i>Staphylococci</i> spp.	
Methicillin-sensitive	Nafcillin
Methicillin-resistant	Vancomycin
<i>Listeria monocytogenes</i>	Ampicillin + gentamicin
<i>Haemophilus influenzae</i>	Ceftriaxone or cefotaxime or cefepime
<i>Streptococcus agalactiae</i>	Penicillin G or ampicillin
<i>Bacteroides fragilis</i>	Metronidazole
<i>Fusobacterium</i> spp.	Metronidazole

^aDoses are as indicated in Table 194-2.

- In general, the treatment course is 7 days for meningococcus, 14 days for pneumococcus, 21 days for gram-negative meningitis, and at least 21 days for *L. monocytogenes*.
- Adjunctive therapy with dexamethasone (10 mg IV), administered 15–20 min before the first dose of an antimicrobial agent and repeated every 6 h for 4 days, improves outcome from bacterial meningitis; benefits most striking in pneumococcal meningitis. Dexamethasone may decrease the penetration of vancomycin into CSF, and thus higher vancomycin doses may be needed.
- In meningococcal meningitis, all close contacts should receive prophylaxis with rifampin (600 mg in adults [10 mg/kg in children >1 year]) every 12 h for 2 days; rifampin is not recommended in pregnant women. Alternatively, adults can be treated with one dose of azithromycin (500 mg), or one IM dose of ceftriaxone (250 mg).

■ PROGNOSIS

Moderate or severe sequelae occur in ~25% of survivors; outcome varies with the infecting organism and can include decreased intellectual function, memory impairment, seizures, hearing loss and dizziness, and gait disturbances.

VIRAL MENINGITIS

Presents as fever, headache, and meningeal irritation associated with a CSF lymphocytic pleocytosis. Fever may be accompanied by malaise, myalgia, anorexia, nausea and vomiting, abdominal pain, and/or diarrhea. A mild degree of lethargy or drowsiness may occur; however, a more profound alteration in

TABLE 194-4 Viruses Causing Acute Meningitis in North America

COMMON	LESS COMMON
Enteroviruses (coxsackieviruses, echoviruses, and human enteroviruses 68–71)	Herpes simplex virus 1
Varicella-zoster virus	Human herpesvirus 6
Herpes simplex virus 2	Cytomegalovirus
Epstein-Barr virus	Lymphocytic choriomeningitis virus
Arthropod-borne viruses	Mumps
HIV	Zika

consciousness should prompt consideration of alternative diagnoses, including encephalitis.

■ ETIOLOGY

Using a variety of diagnostic techniques, including CSF PCR, culture, and serology, a specific viral cause can be found in 60–90% of cases. The most important agents are enteroviruses, VZV, HSV type 2, arboviruses, and HIV (Table 194-4). The incidence of enteroviral and arboviral infections is greatly increased during the summer.

■ DIAGNOSIS

Most important test is examination of the CSF. The typical profile is a lymphocytic pleocytosis (25–500 cells/ μ L), a normal or slightly elevated protein concentration (0.2–0.8 g/L [20–80 mg/dL]), a normal glucose concentration, and a normal or mildly elevated opening pressure (100–350 mmH₂O). Organisms are *not* seen on Gram or acid-fast stained smears or india ink preparations of CSF. Rarely, polymorphonuclear leukocytes (PMN) predominate in the first 48 h of illness, especially with echovirus 9, West Nile virus (WNV), eastern equine encephalitis virus, or mumps. The total CSF cell count in viral meningitis is typically 25–500/ μ L. As a general rule, a lymphocytic pleocytosis with a low glucose concentration should suggest fungal, listerial, or tuberculous meningitis or noninfectious disorders (e.g., sarcoid, neoplastic meningitis).

CSF PCR testing is the procedure of choice for rapid, sensitive, and specific identification of enteroviruses, HSV, EBV, varicella zoster virus (VZV), human herpes virus 6 (HHV-6), and CMV. Attempts should also be made to culture virus from CSF and other sites and body fluids including blood, throat swabs, stool, and urine, although sensitivity of cultures is generally poor. CSF PCR for WNV is not as sensitive as detection of WNV-specific CSF IgM. PCR is also useful in the diagnosis of CNS infection caused by *Mycoplasma pneumoniae*. PCR of throat washings may assist in diagnosis of enteroviral and mycoplasmal CNS infections and PCR of stool specimens for enteroviral infections. Serologic studies are important for diagnosis of arboviruses such as WNV; however, these are less useful for viruses such as HSV, VZV, CMV, and EBV that have a high seroprevalence in the general population.

■ DIFFERENTIAL DIAGNOSIS

Consider bacterial, fungal, tuberculous, spirochetal, and other infectious causes of meningitis; parameningeal infections; partially treated bacterial meningitis; neoplastic meningitis; noninfectious inflammatory diseases including sarcoid and Behçet's disease.

TREATMENT**Viral Meningitis**

- Supportive or symptomatic therapy is usually sufficient, and hospitalization is not required.
- The elderly and immunocompromised pts should be hospitalized, as should individuals in whom the diagnosis is uncertain or those with significant alterations in consciousness, seizures, or focal neurologic signs or symptoms.
- Severe cases of meningitis due to HSV, EBV, and VZV can be treated with IV acyclovir (5–10 mg/kg every 8 h), followed by an oral drug (acyclovir 800 mg, five times daily; famciclovir 500 mg tid; or valacyclovir 1000 mg tid) for a total course of 7–14 days; for mildly affected pts, an oral course of antivirals alone may be appropriate.
- Additional supportive therapy can include analgesics and antipyretics.
- Prognosis for full recovery is excellent.
- Vaccination is an effective method of preventing meningitis and other neurologic complications associated with poliovirus, mumps, rubella, measles, and VZV infection.

VIRAL ENCEPHALITIS

An infection of the brain parenchyma commonly associated with meningitis (“meningoencephalitis”). Clinical features are those of viral meningitis plus evidence of brain tissue involvement, commonly including altered consciousness such as behavioral changes and hallucinations; seizures; and focal neurologic findings such as aphasia, hemiparesis, involuntary movements, and cranial nerve deficits.

■ ETIOLOGY

The same organisms responsible for viral meningitis are also responsible for encephalitis, although relative frequencies differ. The most common causes of sporadic encephalitis in immunocompetent adults are herpesviruses (HSV, VZV, EBV) (Table 194-5). HSV encephalitis should be considered when focal findings are present and when involvement of the inferomedial frontotemporal regions of the brain is likely (olfactory hallucinations, anosmia, bizarre behavior, or memory disturbance). Epidemics of encephalitis are usually caused by arboviruses. WNV has been responsible for the majority of arbovirus meningitis and encephalitis cases in the United States since 2002. Prominent motor manifestations, including acute poliomyelitis-like paralysis, may occur with WNV.

■ DIAGNOSIS

CSF studies are essential; typical CSF profile is similar to viral meningitis. CSF PCR tests allow for rapid and reliable diagnosis of HSV, EBV, CMV, HHV-6, and enteroviruses. In VZV CNS infection, CSF PCR and detection of virus-specific IgM or intrathecal antibody synthesis both provide important aids to diagnosis. Unbiased rapid parallel sequencing technologies capable of identifying infectious genomes in CSF, brain, and other tissues have recently shown great promise for rapid diagnosis of obscure cases. CSF virus cultures are generally negative. For viruses with low seroprevalence rates, diagnosis of acute viral infection can be made by documenting seroconversion between acute-phase and convalescent sera (typically obtained after 2–4 weeks) or by demonstrating the presence of

TABLE 194-5 Viruses Causing Acute Encephalitis in North America

COMMON	LESS COMMON
Herpesviruses	Rabies
Cytomegalovirus ^a	Eastern equine encephalitis virus
Herpes simplex virus 1 ^b	Powassan virus
Herpes simplex virus 2	Cytomegalovirus ^a
Human herpesvirus 6	Colorado tick fever virus
Varicella-zoster virus	Mumps
Epstein-Barr virus	
Arthropod-borne viruses	
La Crosse virus	
West Nile virus ^c	
St. Louis encephalitis virus	
Zika	
Enteroviruses	

^aImmunocompromised host.

^bThe most common cause of sporadic encephalitis.

^cThe most common cause of epidemic encephalitis.

virus-specific IgM antibodies. Demonstration of WNV IgM antibodies in the CSF is diagnostic of WNV encephalitis.

MRI is the neuroimaging procedure of choice and demonstrates areas of increased T2 signal. Bitemporal and orbitofrontal areas of increased signal are seen in HSV encephalitis, but are not diagnostic (Fig. 194-2). The EEG may

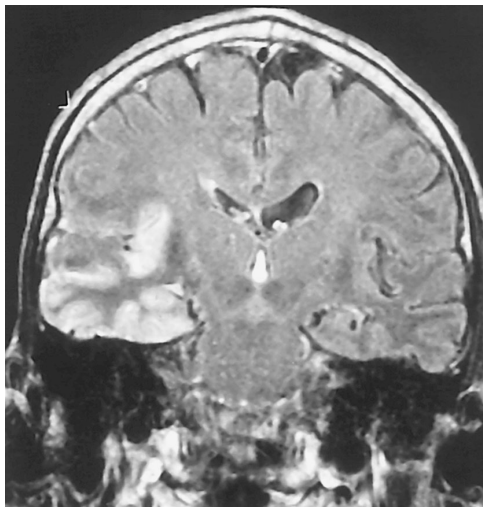


FIGURE 194-2 Coronal FLAIR magnetic resonance image from a pt with herpes simplex encephalitis. Note the area of increased signal in the right temporal lobe (left side of image) confined predominantly to the gray matter. This pt had predominantly unilateral disease; bilateral lesions are more common, but may be quite asymmetric in their intensity.

suggest seizures or show temporally predominant periodic spikes on a slow, low-amplitude background suggestive of HSV encephalitis.

Brain biopsy is now used only when CSF PCR studies fail to identify the cause, focal abnormalities on MRI are present, and progressive clinical deterioration occurs despite treatment with acyclovir and supportive therapy.

■ DIFFERENTIAL DIAGNOSIS

Includes both infectious and noninfectious causes of encephalitis, including vascular diseases; abscess and empyema; fungal (*Cryptococcus* and *Mucor*), spirochetal (*Leptospira*), rickettsial, bacterial (*Listeria*), tuberculous, and mycoplasmal infections; tumors; toxic encephalopathy; SLE; and ADEM; as well as an increasing number of antibodies that cause paraneoplastic autoimmune encephalitis (Chap. 79).

TREATMENT

Viral Encephalitis

- All pts with suspected HSV encephalitis should be treated with IV acyclovir (10 mg/kg every 8 h) while awaiting diagnostic studies.
- Pts with a PCR-confirmed diagnosis of HSV encephalitis should receive a 21-day course of therapy.
- Acyclovir treatment may also be of benefit in severe encephalitis due to EBV and VZV. No therapy currently available for enteroviral, mumps, or measles encephalitis.
- IV ribavirin (15–25 mg/kg per day given in three divided doses) may benefit severe encephalitis due to California encephalitis (LaCrosse) virus.
- CMV encephalitis can be treated with ganciclovir (5 mg/kg every 12 h IV over 1 h, followed by maintenance therapy of 5 mg/kg every day), foscarnet (60 mg/kg every 8 h IV over 1 h, followed by maintenance therapy 60–120 mg/kg per day), or a combination of the two drugs; cidofovir (5 mg/kg IV once weekly for 2 weeks, then biweekly for two or more additional doses, depending on response; prehydrate with normal saline and pretreat with probenecid) may provide an alternative for nonresponders.
- No proven therapy is available for WNV encephalitis; small groups of pts have been treated with interferon, ribavirin, WNV-specific antisense oligonucleotides, DNA plasmid vaccines, IV immunoglobulin preparations of Israeli origin containing high-titer anti-WNV antibody, and humanized monoclonal antibodies directed against the viral envelope glycoprotein.

■ PROGNOSIS

Considerable variation exists in the incidence and severity of sequelae in pts surviving viral encephalitis. In HSV encephalitis treated with acyclovir, 81% survival in one series; neurologic sequelae were mild or absent in 46%, moderate in 12%, and severe in 42%.

BRAIN ABSCESS

A focal, suppurative infection within the brain parenchyma, typically surrounded by a vascularized capsule. The term *cerebritis* is used to describe a non-encapsulated brain abscess. Predisposing conditions include otitis media and mastoiditis, paranasal sinusitis, pyogenic infections in the chest or other body sites, head trauma, neurosurgical procedures, and dental infections. Many brain

abscesses occur in immunocompromised hosts and are caused less often by bacteria than by fungi and parasites including *Toxoplasma gondii*, *Aspergillus* spp., *Nocardia* spp., *Candida* spp., and *Cryptococcus* neoformans. In Latin America, the most common cause of brain abscess is *Taenia solium* (neurocysticercosis). In India and the Far East, mycobacterial infection (tuberculoma) remains a major cause of focal CNS mass lesions.

■ CLINICAL FEATURES

Brain abscess typically presents as an expanding intracranial mass lesion, rather than as an infectious process. The classic triad of headache, fever, and a focal neurologic deficit is present in <50% of cases.

■ DIAGNOSIS

MRI is superior to CT for demonstrating abscesses in the early (cerebritis) stages and also for abscesses in the posterior fossa. A mature brain abscess appears on CT as a focal area of hypodensity surrounded by ring enhancement. The CT and MRI appearance, particularly of the capsule, may be altered by treatment with glucocorticoids. The distinction between a brain abscess and other focal lesions such as tumors may be facilitated with diffusion-weighted imaging (DWI) sequences in which brain abscesses typically show increased signal due to restricted diffusion.

Microbiologic diagnosis best determined by Gram's stain and culture of abscess material obtained by stereotactic needle aspiration. Up to 10% of pts will also have positive blood cultures. CSF analysis contributes nothing to diagnosis or therapy, and LP increases the risk of herniation.

TREATMENT

Brain Abscess

- Optimal therapy involves a combination of high-dose parenteral antibiotics and neurosurgical drainage.
- Empirical therapy of community-acquired brain abscess in an immunocompetent pt typically includes a third- or fourth-generation cephalosporin (e.g., cefotaxime, ceftriaxone, or cefepime) and metronidazole (see Table 194-2 for antibiotic dosages).
- In pts with penetrating head trauma or recent neurosurgical procedures, treatment should include ceftazidime to enhance coverage of *Pseudomonas* spp. and vancomycin for coverage of resistant staphylococci. Meropenem plus vancomycin also provides good coverage in this setting.
- Aspiration and drainage essential in most cases. Empirical antibiotic coverage is modified based on the results of Gram's stain and culture of the abscess contents.
- Medical therapy alone is reserved for pts whose abscesses are neurosurgically inaccessible and for pts with small (<2–3 cm) or nonencapsulated abscesses (cerebritis).
- All pts should receive a minimum of 6–8 weeks of parenteral antibiotic therapy.
- Pts should receive prophylactic anticonvulsant therapy.
- Glucocorticoids should not be given routinely.
- Serial MRI or CT scans should be obtained on a monthly or twice-monthly basis to document resolution of the abscess.

■ PROGNOSIS

In modern series, the mortality is typically <15%. Significant sequelae including seizures, persisting weakness, aphasia, or mental impairment occur in $\geq 20\%$ of survivors.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

■ CLINICAL FEATURES

A progressive disorder due to infection with the JC virus, a human polyoma virus; multifocal areas of demyelination of varying size distributed throughout the CNS but sparing the spinal cord and optic nerves, with characteristic cytologic alterations in astrocytes and oligodendrocytes. Pts often present with visual deficits (45%), typically a homonymous hemianopia, and mental impairment (38%) (dementia, confusion, personality change), weakness, and ataxia. Seizures occur in $\sim 20\%$ of pts. Almost all pts have an underlying immune disorder or are receiving immunosuppressive therapy. More than 80% of currently diagnosed PML cases occur in pts with AIDS; it has been estimated that up to 5% of AIDS pts will develop PML. Immunosuppressant drugs such as natalizumab have also been associated with PML.

■ DIAGNOSTIC STUDIES

MRI reveals multifocal asymmetric, coalescing white matter lesions located periventricularly, in the centrum semiovale, in the parietal-occipital region, and in the cerebellum. These lesions have increased T2 and decreased T1 signal, are generally nonenhancing (rarely they may show ring enhancement), and are not associated with edema or mass effect. CT scans, which are less sensitive than MRI for the diagnosis of PML, often show hypodense nonenhancing white matter lesions.

The CSF is typically normal, although mild elevation in protein and/or IgG may be found. Pleocytosis occurs in <25% of cases, is predominantly mononuclear, and rarely exceeds 25 cells/ μL . PCR amplification of JC virus DNA from CSF has become an important diagnostic tool. A positive CSF PCR for JC virus DNA in association with typical MRI lesions in the appropriate clinical setting is diagnostic of PML. Pts with negative CSF PCR studies may require brain biopsy for definitive diagnosis as sensitivity of this test is variable; JC virus antigen and nucleic acid can be detected by immunocytochemistry, in situ hybridization, or PCR amplification on tissue. Detection of JC virus antigen or genomic material should be considered diagnostic of PML only if accompanied by characteristic pathologic changes, since both antigen and genomic material have been found in the brains of normal pts. Serologic studies are of no utility for diagnosis given high basal seroprevalence level, but are extremely useful for risk stratification in pts contemplating therapy with immunomodulatory drugs such as natalizumab.

TREATMENT

Progressive Multifocal Leukoencephalopathy

- No effective therapy is available.
- Some pts with HIV-associated PML have shown dramatic clinical gains associated with improvement in immune status following institution of highly active antiretroviral therapy (HAART).
- Pts suspected of having PML who are receiving immunomodulatory antibodies should have therapy halted and circulating antibodies cleared by plasma exchange; discontinuation of therapy may lead to transient clinical and radiologic worsening, termed immune reconstitution inflammatory syndrome (IRIS).

195 Chronic and Recurrent Meningitis



Chronic inflammation of the meninges (pia, arachnoid, and dura) can produce profound neurologic disability and may be fatal if not successfully treated. The causes are varied. Five categories of disease account for most cases of chronic meningitis:

- Meningeal infections
- Malignancy
- Noninfectious inflammatory disorders
- Chemical meningitis
- Parameningeal infections

CLINICAL FEATURES

Neurologic manifestations consist of persistent headache with or without stiff neck and hydrocephalus; cranial neuropathies; radiculopathies; and/or cognitive or personality changes (Table 195-1). The diagnosis is usually made when clinical presentation leads the physician to examine CSF for signs of inflammation; on occasion the diagnosis is made when a neuroimaging study shows contrast enhancement of the meninges.

Two clinical forms exist. In the first, symptoms are chronic and persistent, whereas in the second there are recurrent, discrete episodes with complete resolution of meningeal inflammation between episodes without specific therapy. In the latter group, likely etiologies are herpes simplex virus type 2, chemical meningitis due to leakage from a tumor, a primary inflammatory condition, or drug hypersensitivity.

APPROACH TO THE PATIENT

Chronic Meningitis

Once chronic meningitis is confirmed by CSF examination, effort is focused on identifying the cause (Tables 195-2 and 195-3) by (1) further

TABLE 195-1 Symptoms and Signs of Chronic Meningitis

SYMPTOM	SIGN
Chronic headache	±Papilledema
Neck or back pain/stiffness	Brudzinski's or Kernig's sign of meningeal irritation
Change in personality	Altered mental status—drowsiness, inattention, disorientation, memory loss, frontal release signs (grasp, suck, snout), perseveration
Facial weakness	Peripheral seventh CN paresis
Double vision	Paresis of CNs III, IV, VI
Diminished vision	Papilledema, optic atrophy
Hearing loss	Eighth CN paresis
Arm or leg weakness	Myelopathy or radiculopathy
Numbness in arms or legs	Myelopathy or radiculopathy
Urinary retention/incontinence	Myelopathy or radiculopathy Frontal lobe dysfunction (hydrocephalus)
Clumsiness	Ataxia

Abbreviation: CN, cranial nerve.

TABLE 195-2 Infectious Causes of Chronic Meningitis

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Common bacterial causes			
Partially treated suppurative meningitis	Mononuclear or mixed mononuclear-polymorphonuclear cells	CSF culture and Gram's stain; CSF 16s rRNA PCR	History consistent with acute bacterial meningitis and incomplete treatment
Parameningeal infection	Mononuclear or mixed mononuclear-polymorphonuclear cells	Contrast-enhanced CT or MRI to detect parenchymal, subdural, epidural, or sinus infection	Otitis media, pleuropulmonary infection, right-to-left cardiopulmonary shunt for brain abscess; focal neurologic signs; neck, back, ear, or sinus tenderness
<i>Mycobacterium tuberculosis</i>	Mononuclear cells except polymorphonuclear cells in early infection (commonly <500 WBC/ μ L); low CSF glucose; high protein	Tuberculin skin test may be negative; interferon gamma release assay; PCR and AFB culture of CSF (sputum, urine, gastric contents if indicated); identify tubercle bacillus on acid-fast stain of CSF or protein pellicle	Exposure history; previous tuberculous illness; immunosuppressed, anti-TNF therapy or AIDS; young children; fever, meningismus, night sweats, miliary TB on x-ray or liver biopsy; stroke due to arteritis
Lyme disease (Bannwarth's syndrome) <i>Borrelia burgdorferi</i>	Mononuclear cells; elevated protein	Serum Lyme antibody titer; western blot confirmation; (pts with syphilis may have false-positive Lyme titer)	History of tick bite or appropriate exposure history; erythema chronicum migrans skin rash; arthritis, radiculopathy, Bell's palsy, meningoencephalitis–multiple sclerosis-like syndrome
Syphilis (secondary, tertiary) <i>Treponema pallidum</i>	Mononuclear cells; elevated protein	CSF VDRL; serum VDRL (or RPR); fluorescent treponemal antibody-absorbed (FTA) or MHA-TP; serum VDRL may be negative in tertiary syphilis	Appropriate exposure history; HIV-seropositive individuals at increased risk of aggressive infection; "dementia"; cerebral infarction due to endarteritis

Uncommon bacterial causes			
<i>Actinomyces</i>	Polymorphonuclear cells	Anaerobic culture	Parameningeal abscess or sinus tract (oral or dental focus); pneumonitis
<i>Nocardia</i>	Polymorphonuclear; occasionally mononuclear cells; often low glucose	Isolation may require weeks; weakly acid fast	Associated brain abscess may be present
<i>Brucella</i>	Mononuclear cells (rarely polymorphonuclear); elevated protein; often low glucose	CSF antibody detection; serum antibody detection	Intake of unpasteurized dairy products; exposure to goats, sheep, cows; fever, arthralgia, myalgia, vertebral osteomyelitis
Whipple's disease <i>Tropheryma whippeli</i>	Mononuclear cells	Biopsy of small bowel or lymph node; CSF PCR for <i>T. whippeli</i> ; brain and meningeal biopsy (with PAS stain and EM examination)	Diarrhea, weight loss, arthralgias, fever; dementia, ataxia, paresis, ophthalmoplegia, oculomasticatory myoclonus
Rare bacterial causes			
Leptospirosis (occasionally if left untreated may last 3–4 weeks)			
Fungal causes			
<i>Cryptococcus neoformans</i> and <i>var. gatti</i>	Mononuclear cells; count not elevated in some pts with AIDS	India ink or fungal wet mount of CSF (budding yeast); blood and urine cultures; antigen detection in CSF	AIDS and immune suppression; pigeon exposure for <i>neoformans</i> , decaying wood exposure for <i>var. gatti</i> ; skin and other organ involvement due to disseminated infection
<i>Coccidioides immitis</i>	Mononuclear cells (sometimes 10–20% eosinophils); often low glucose	Antibody detection in CSF and serum, antigen detection in CSF	Exposure history—southwestern United States; increased virulence in dark-skinned races
<i>Candida</i> sp.	Polymorphonuclear or mononuclear	Fungal stain and culture of CSF	IV drug abuse; postsurgery; prolonged IV therapy; disseminated candidiasis, recent epidural injection

(Continued)

TABLE 195-2 Infectious Causes of Chronic Meningitis (Continued)

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
<i>Histoplasma capsulatum</i>	Mononuclear cells; low glucose	Fungal stain and culture of large volumes of CSF; antigen detection in CSF, serum, and urine; antibody detection in serum, CSF	Exposure history—Ohio and central Mississippi River Valley; AIDS; mucosal lesions
<i>Blastomyces dermatitidis</i>	Mononuclear cells	Fungal stain and culture of CSF; biopsy and culture of skin, lung lesions; antibody detection in serum	Midwestern and southeastern United States; usually systemic infection; abscesses, draining sinus, ulcers
<i>Aspergillus</i> sp.	Mononuclear or polymorphonuclear	CSF culture	Sinusitis; granulocytopenia or immunosuppression
<i>Sporothrix schenckii</i>	Mononuclear cells	Antibody detection in CSF and serum; CSF culture	Traumatic inoculation; IV drug use; ulcerated skin lesion
Rare fungal causes			
<i>Xylohypha</i> (formerly <i>Cladosporium</i>) <i>trichoides</i> and other dark-walled (dematiaceous) fungi such as <i>Curvularia</i> ; <i>Drechslera</i> ; <i>Mucor</i> ; and, after water aspiration, <i>Pseudallescheria boydii</i> ; iatrogenic <i>Exserohilum rostratum</i> infection following spinal blocks			
Protozoal causes			
<i>Toxoplasma gondii</i>	Mononuclear cells	Biopsy or response to empirical therapy in clinically appropriate context (including presence of antibody in serum)	Usually with intracerebral abscesses; common in HIV-seropositive pts
Trypanosomiasis <i>Trypanosoma gambiense</i> , <i>T. rhodesiense</i>	Mononuclear cells; elevated protein	Elevated CSF IgM; identification of trypanosomes in CSF and blood smear	Endemic in Africa; chancre, lymphadenopathy; prominent sleep disorder

Rare protozoal causes

Acanthamoeba sp. causing granulomatous amebic encephalitis and meningoencephalitis in immunocompromised and debilitated individuals. *Balamuthia mandrillaris* causing chronic meningoencephalitis in immunocompetent hosts

Helminthic causes

Cysticercosis (infection with cysts of <i>Taenia solium</i>)	Mononuclear cells; may have eosinophils; glucose level may be low	Indirect hemagglutination assay in CSF; ELISA immunoblotting in serum	Usually with multiple cysts in basal meninges and hydrocephalus; cerebral cysts, muscle calcification
<i>Gnathostoma spinigerum</i>	Eosinophils, mononuclear cells	Peripheral eosinophilia	History of eating raw fish; common in Thailand and Japan; subarachnoid hemorrhage; painful radiculopathy
<i>Angiostrongylus cantonensis</i>	Eosinophils, mononuclear cells	Recovery of worms from CSF	History of eating raw shellfish; common in tropical Pacific regions; often benign
<i>Baylisascaris procyonis</i> (raccoon ascarid)	Eosinophils, mononuclear cells		Infection follows accidental ingestion of <i>B. procyonis</i> eggs from raccoon feces; fatal meningoencephalitis

Rare helminthic causes

Trichinella spiralis (trichinosis); *Fasciola hepatica* (liver fluke), *Echinococcus* cysts; *Schistosoma* sp. The former may produce a lymphocytic pleocytosis, whereas the latter two may produce an eosinophilic response in CSF associated with cerebral cysts (*Echinococcus*) or granulomatous lesions of brain or spinal cord

Viral causes

Mumps	Mononuclear cells	Antibody in serum	No prior mumps or immunization; may produce meningoencephalitis; may persist for 3–4 weeks
Lymphocytic choriomeningitis	Mononuclear cells; may have low glucose	Antibody in serum; PCR for LCMV in CSF	Contact with rodents or their excreta; may persist for 3–4 weeks
Echovirus	Mononuclear cells; may have low glucose	Virus isolation from CSF	Congenital hypogammaglobulinemia; history of recurrent meningitis

(Continued)

TABLE 195-2 Infectious Causes of Chronic Meningitis (Continued)

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
HIV (acute retroviral syndrome)	Mononuclear cells	PCR for HIV in blood and CSF	HIV risk factors; rash, fever, lymphadenopathy; lymphopenia in peripheral blood; syndrome may persist long enough to be considered as “chronic meningitis”; or chronic meningitis may develop in later stages (AIDS) due to HIV
Human herpes viruses	Mononuclear cells	PCR for HSV, CMV DNA; CSF antibody for HSV, EBV	Recurrent meningitis due to HSV-2 (rarely HSV-1) often associated with genital recurrences; EBV associated with myeloradiculopathy, CMV with polyradiculopathy

Abbreviations: AFB, acid-fast bacillus; CMV, cytomegalovirus; CSF, cerebrospinal fluid; CT, computed tomography; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; EM, electron microscopy; FTA, fluorescent treponemal antibody absorption test; HSV, herpes simplex virus; MHA-TP, microhemagglutination assay—*T. pallidum*; MRI, magnetic resonance imaging; PAS, periodic acid–Schiff; PCR, polymerase chain reaction; RPR, rapid plasma reagin test; TB, tuberculosis; VDRL, Venereal Disease Research Laboratories test.

TABLE 195-3 Noninfectious Causes of Chronic Meningitis

CAUSATIVE AGENTS	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Malignancy	Mononuclear cells; elevated protein; low glucose	Repeated cytologic examination of large volumes of CSF; CSF exam by polarizing microscopy; clonal lymphocyte markers; deposits on nerve roots or meninges seen on myelogram or contrast-enhanced MRI; meningeal biopsy	Metastatic cancer of breast, lung, stomach, or pancreas; melanoma, lymphoma, leukemia; meningeal gliomatosis; sarcoma; cerebral dysgerminoma
Chemical compounds (may cause recurrent meningitis)	Mononuclear or PMNs; low glucose, elevated protein; xanthochromia from subarachnoid hemorrhage in week prior to presentation with “meningitis”	Contrast-enhanced CT scan or MRI; cerebral angiogram to detect aneurysm. Enhancement and clumping of nerve roots of the cauda equina in arachnoiditis/pachymeningitis	History of recent injection into the subarachnoid space; history of sudden onset of headache; recent resection of acoustic neuroma or craniopharyngioma; epidermoid tumor of brain or spine, sometimes with dermoid sinus tract; pituitary apoplexy
Primary inflammation			
CNS sarcoidosis	Mononuclear cells; elevated protein; often low glucose	Serum and CSF angiotensin-converting enzyme levels; biopsy of extraneural affected tissues or brain lesion/ meningeal biopsy	CN palsy, especially CN VII; hypothalamic dysfunction, especially diabetes insipidus; abnormal chest radiograph; peripheral neuropathy or myopathy
Vogt-Koyanagi-Harada syndrome (recurrent meningitis)	Mononuclear cells		Recurrent meningoencephalitis with uveitis, retinal detachment, alopecia, lightening of eyebrows and lashes, dysacusia, cataracts, glaucoma

(Continued)

TABLE 195-3 Noninfectious Causes of Chronic Meningitis (Continued)

CAUSATIVE AGENTS	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Isolated granulomatous angiitis of the nervous system	Mononuclear cells; elevated protein	Angiography; meningeal biopsy may be necessary if confined to small vessels. VZV PCR in blood and biopsy tissue	Subacute dementia; multiple cerebral infarctions; recent zoster ophthalmicus
Systemic lupus erythematosus	Mononuclear or PMNs	Anti-DNA antibody, antinuclear antibodies	Encephalopathy; seizures; stroke; transverse myelopathy; rash; arthritis
Behçet's syndrome (recurrent meningitis)	Mononuclear or PMNs; elevated protein		Oral and genital aphthous ulcers; iridocyclitis; retinal hemorrhages; pathergic lesions at site of skin puncture
Chronic benign lymphocytic meningitis	Mononuclear cells		Recovery in 2–6 months, diagnosis by exclusion
Mollaret's meningitis (recurrent meningitis)	Large endothelial cells and PMNs in first hours, followed by mononuclear cells	PCR for herpes; MRI/CT to rule out epidermoid tumor or dural cyst	Recurrent meningitis; exclude HSV-2; rare cases due to HSV-1; occasional case associated with dural cyst
Drug hypersensitivity	PMNs; occasionally mononuclear cells or eosinophils	Complete blood count (eosinophilia)	Exposure to nonsteroidal anti-inflammatory agents, sulfonamides, isoniazid, tolmetin, ciprofloxacin, penicillin, carbamazepine, lamotrigine, IV immunoglobulin, OKT3 antibodies, phenazopyridine; improvement after discontinuation of drug; recurrence with repeat exposure

Granulomatosis with polyangiitis (Wegener's)	Mononuclear cells	Chest and sinus radiographs; urinalysis; ANCA antibodies in serum	Associated sinus, pulmonary, or renal lesions; CN palsies; skin lesions; peripheral neuropathy
Neonatal-onset multisystem inflammatory disorder	Mononuclear and PMNs	Gain of function mutation in NLRP3 gene leading to elevated IL-1 β	Recurrent fever, urticaria, arthralgia, sensorineural hearing loss, papilledema, increased ICP
IgG4-related hypertrophic pachymeningitis	Mild lymphocytic pleocytosis in some cases; normal to mildly increased protein; normal glucose	Serum IgG4 levels frequently elevated; ESR and C-reactive protein; meningeal biopsy shows swirling "storiform" fibrosis with lymphocytic infiltrates, obliterative phlebitis and IgG4+ plasma cells	Headache; seizures; focal symptoms from dural involvement in spinal cord/nerve roots, clivus, periorbital, vestibular, and brainstem structures. Systemic IgG4-related disease can involve many tissues including pancreas, thyroid, lungs, and retroperitoneum
Other: multiple sclerosis, Sjögren's syndrome, and rarer forms of vasculitis (e.g., Cogan's syndrome)			

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; CN, cranial nerve; CSF, cerebrospinal fluid; CT, computed tomography; HSV, herpes simplex virus; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PMNs, polymorphonuclear cells.

analysis of the CSF, (2) diagnosis of an underlying systemic infection or non-infectious inflammatory condition, or (3) examination of meningeal biopsy tissue.

Proper analysis of the CSF is essential; if the possibility of raised intracranial pressure (ICP) exists, a brain imaging study should be performed before LP. In pts with communicating hydrocephalus caused by impaired resorption of CSF, LP is safe and may lead to temporary improvement. However, if ICP is elevated because of a mass lesion, brain swelling, or a block in ventricular CSF outflow (obstructive hydrocephalus), then LP carries the potential risk of brain herniation. Obstructive hydrocephalus usually requires direct ventricular drainage of CSF.

Contrast-enhanced MRI or CT studies of the brain and spinal cord can identify meningeal enhancement, parameningeal infections (including brain abscess), encasement of the spinal cord (malignancy or inflammation and infection), or nodular deposits on the meninges or nerve roots (malignancy or sarcoidosis). Imaging studies are also useful to localize areas of meningeal disease prior to meningeal biopsy. Cerebral angiography may identify arteritis.

A meningeal biopsy should be considered in pts who are disabled, who need chronic ventricular decompression, or whose illness is progressing rapidly. The diagnostic yield of meningeal biopsy can be increased by targeting regions that enhance with contrast on MRI or CT; in one series, biopsies most often identified sarcoid (31%) or metastatic adenocarcinoma (25%). Tuberculosis is the most common condition identified in many reports outside of the United States.

The epidemiologic history is of considerable importance in diagnosis of chronic meningitis and may provide direction for selection of laboratory studies. Pertinent features include a history of tuberculosis or exposure; recent epidural injection which led to epidemic of fungal meningitis by *Exserohilum rostratum*, past travel to areas endemic for fungal infections (the San Joaquin Valley in California and southwestern states for coccidioidomycosis, midwestern states for histoplasmosis, southeastern states for blastomycosis); travel to the Mediterranean region or ingestion of imported unpasteurized dairy products (*Brucella*); time spent in wooded areas endemic for Lyme disease; exposure to sexually transmitted disease (syphilis); exposure of an immunocompromised host to pigeons and their droppings (*Cryptococcus neoformans*); exposure to decaying wood in Vancouver Island, South Africa and Australia (*Cryptococcus neoformans var. gatti*), gardening (*Sporothrix schenckii*); ingestion of poorly cooked meat or contact with a household cat (*Toxoplasma gondii*); residence in Thailand or Japan (*Gnathostoma spinigerum*), Latin America (*Paracoccidioides brasiliensis*), or the South Pacific (*Angiostrongylus cantonensis*); rural residence and raccoon exposure (*Baylisascaris procyonis*); and residence in Latin America, the Philippines, sub-Saharan Africa, or Southeast Asia (*Taenia solium/cysticercosis*).

In approximately one-third of cases, the diagnosis is not established despite careful evaluation. A number of the organisms that cause chronic meningitis may take weeks to be identified by culture. It is reasonable to wait until cultures are finalized if symptoms are mild and not progressive. However, in many cases progressive neurologic deterioration occurs, and rapid treatment is required. Empirical therapy in the United States consists of antimycobacterial agents, amphotericin for fungal infection, or glucocorticoids for noninfectious inflammatory causes (most common). It is important

to direct empirical therapy of lymphocytic meningitis at tuberculosis, particularly if the condition is associated with hypoglycorrhachia and sixth and other cranial nerve palsies, since untreated disease can be fatal within weeks. Carcinomatous or lymphomatous meningitis may be difficult to diagnose initially, but the diagnosis becomes evident with time. Important causes of chronic meningitis in HIV pts include infection with *Toxoplasma* (usually presents as intracranial abscesses), *Cryptococcus*, *Nocardia*, *Candida*, or other fungi; syphilis; and lymphoma.

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Peripheral Neuropathies, Including Guillain-Barré Syndrome



APPROACH TO THE PATIENT

Peripheral Neuropathy

Peripheral neuropathy (PN) refers to a peripheral nerve disorder of any cause. Nerve involvement may be single (mononeuropathy) or multiple (polyneuropathy); pathology may be axonal or demyelinating. An approach to pts with suspected neuropathy appears in [Fig. 196-1](#).

Seven initial questions:

1. *What systems are involved?* Determine if symptoms and signs are predominantly motor, sensory, autonomic, or a combination of these. If only weakness is present without sensory or autonomic dysfunction, consider a motor neuropathy, neuromuscular junction disorder, or myopathy; myopathies usually have a proximal, symmetric pattern of weakness.
2. *What is the distribution of weakness?* Polyneuropathy involves widespread and often symmetric dysfunction of the peripheral nerves that is usually distal more than proximal; mononeuropathy involves a single nerve, usually due to trauma or compression; multiple mononeuropathies (mononeuropathy multiplex) can be a result of multiple entrapments, vasculitis, or infiltration.
3. *What is the nature of the sensory involvement?* Temperature loss or burning/stabbing pain suggests small fiber involvement. Vibratory or proprioceptive loss implicates large fibers.
4. *Is there evidence of upper motor neuron involvement?* The most common cause is combined system degeneration with B₁₂ deficiency, but should also consider copper deficiency, HIV infection, severe hepatic disease, and adrenomyeloneuropathy.
5. *What is the temporal evolution?* Most neuropathies are insidious and slowly progressive. Rapidly evolving neuropathies are often inflammatory, including acute inflammatory demyelinating polyneuropathy (AIDP) or *Guillain-Barré syndrome* (GBS); subacute evolution suggests an inflammatory, toxic, or nutritional cause; chronic neuropathies that are long-standing over years may be hereditary.

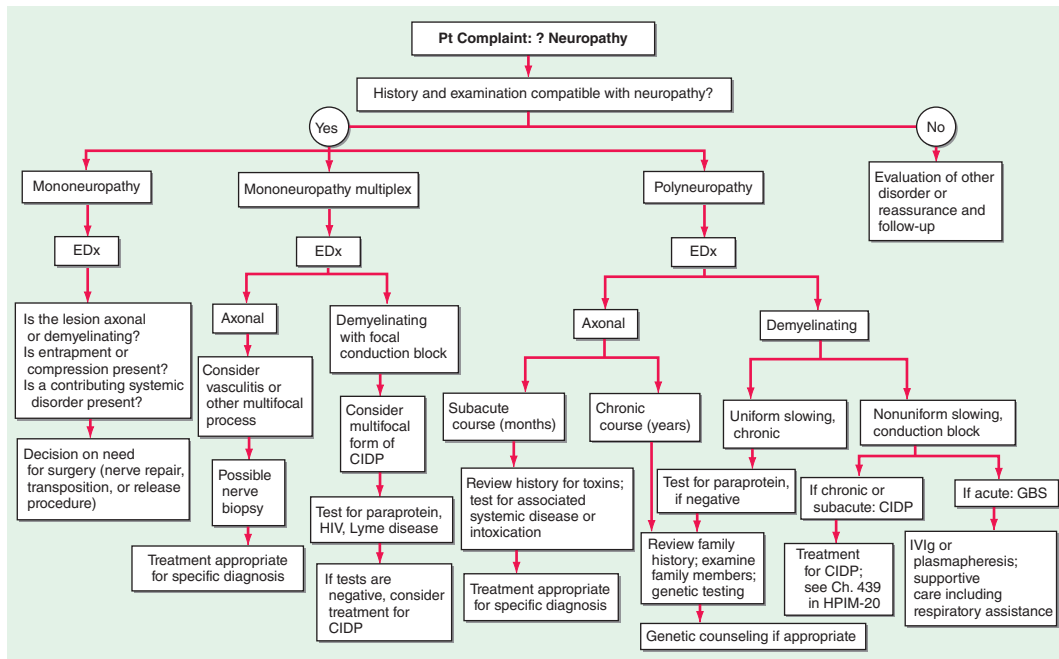


FIGURE 196-1 Approach to the evaluation of peripheral neuropathies. CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EDx, electrodiagnostic; GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin.

6. *Is there evidence for a hereditary neuropathy?* Consider in pts with a slowly progressive distal weakness over many years with few sensory symptoms but significant sensory deficits on clinical examination. Most common is Charcot-Marie-Tooth disease (CMT; look for foot abnormalities such as high or flat arches and hammer toes as well as scoliosis).
7. *Does the pt have other medical conditions?* Inquire about associated medical conditions (e.g., diabetes, systemic lupus erythematosus); preceding or concurrent infections (e.g., diarrheal illness preceding GBS); surgeries (e.g., gastric bypass and nutritional neuropathies); medications (toxic neuropathy); over-the-counter vitamin preparations (B₆); alcohol, dietary habits; and use of dentures (because fixatives contain zinc that can lead to copper deficiency).

Based on the answers to these seven key questions, neuropathic disorders can be classified into several patterns based on the pattern of sensory, motor, and autonomic involvement ([Table 196-1](#)).

■ POLYNEUROPATHY

Diagnostic Evaluation

Screening laboratory studies in a distal, symmetric polyneuropathy may include a complete blood count, basic chemistries including serum electrolytes and tests of renal and hepatic function, fasting blood glucose, HbA_{1c}, urinalysis, thyroid function tests, B₁₂, folate, ESR, rheumatoid factor, antinuclear antibodies (ANA), serum protein electrophoresis (SPEP) and immunoelectrophoresis or immunofixation, and urine for Bence Jones protein. An oral glucose tolerance test is indicated in pts with painful sensory neuropathies even if other screens for diabetes are negative.

Tests to further characterize the neuropathy include nerve conduction studies (NCS), electromyography (EMG), sural nerve biopsy, muscle biopsy, skin biopsies, and quantitative sensory testing. Diagnostic tests are more likely to be informative in pts with asymmetric, motor-predominant, rapid-onset, or demyelinating neuropathies.

Electrodiagnosis

NCS are carried out by stimulating motor or sensory nerves electrically. Demyelination is characterized by slowing of nerve conduction velocities (NCV), dispersion of evoked compound action potentials, conduction block (decreased amplitude of muscle compound action potentials on proximal, as compared to distal, stimulation of the nerve), and prolongation of distal latencies. In contrast, axonal neuropathies exhibit reduced amplitude of evoked compound action potentials with relative preservation of NCV. EMG records electrical potentials from a needle electrode in muscle, at rest and during voluntary contraction; it is most useful for distinguishing myopathic from neuropathic disorders. Myopathic disorders are marked by small, short-duration, polyphasic muscle action potentials; by contrast, neuropathic disorders are characterized by muscle denervation. Denervation decreases the number of motor units (e.g., an anterior horn cell, its axon, and the motor end plates and muscle fibers it innervates). In long-standing denervation, motor unit potentials become large and polyphasic due to collateral reinnervation of denervated muscle fibers by axonal sprouts from surviving motor axons. Other EMG features of denervation include fibrillations

TABLE 196-1 Patterns of Neuropathic Disorders**Pattern 1: Symmetric proximal and distal weakness with sensory loss**

Consider: inflammatory demyelinating polyneuropathy (GBS and CIDP)

Pattern 2: Symmetric distal sensory loss with or without distal weakness

Consider: cryptogenic or idiopathic sensory polyneuropathy (CSPN), diabetes mellitus and other metabolic disorders, drugs, toxins, familial (HSAN), CMT, amyloidosis, and others

Pattern 3: Asymmetric distal weakness with sensory loss

With involvement of multiple nerves

Consider: multifocal CIDP, vasculitis, cryoglobulinemia, amyloidosis, sarcoid, infectious (leprosy, Lyme, hepatitis B, C, or E, HIV, CMV), HNPP, tumor infiltration

With involvement of single nerves/regions

Consider: may be any of the above but also could be compressive mononeuropathy, plexopathy, or radiculopathy

Pattern 4: Asymmetric proximal and distal weakness with sensory loss

Consider: polyradiculopathy or plexopathy due to diabetes mellitus, meningeal carcinomatosis or lymphomatosis, sarcoid, amyloid, hereditary plexopathy (HNPP, HNA), idiopathic

Pattern 5: Asymmetric distal weakness without sensory loss

With upper motor neuron findings

Consider: motor neuron disease

Without upper motor neuron findings

Consider: progressive muscular atrophy, juvenile monomelic amyotrophy (Hirayama's disease), multifocal motor neuropathy, multifocal acquired motor axonopathy

Pattern 6: Symmetric sensory loss and distal areflexia with upper motor neuron findings

Consider: Vitamin B₁₂, vitamin E, and copper deficiency with combined system degeneration with peripheral neuropathy, chronic liver disease, hereditary leukodystrophies (e.g., adrenomyeloneuropathy) HSP-plus

Pattern 7: Symmetric weakness without sensory loss

With proximal and distal weakness

Consider: SMA

With distal weakness

Consider: hereditary motor neuropathy ("distal" SMA) or atypical CMT

Pattern 8: Focal midline proximal symmetric weakness

Neck extensor weakness

Consider: ALS

Bulbar weakness

Consider: ALS/PLS, isolated bulbar ALS (IBALS), Kennedy's syndrome (X-linked, bulbospinal SMA), bulbar presentation GBS

Diaphragm weakness (SOB)

Consider: ALS

(Continued)

TABLE 196-1 Patterns of Neuropathic Disorders (Continued)**Pattern 9: Asymmetric proprioceptive sensory loss without weakness**

Consider causes of a sensory neuropathy (ganglionopathy):

- Cancer (paraneoplastic)
- Sjögren's syndrome
- Idiopathic sensory neuronopathy (possible GBS variant)
- Cisplatin and other chemotherapeutic agents
- Vitamin B₆ toxicity
- HIV-related sensory neuronopathy

Pattern 10: Autonomic symptoms and signs

Consider neuropathies associated with prominent autonomic dysfunction:

- Hereditary sensory and autonomic neuropathy
- Amyloidosis (familial and acquired)
- Diabetes mellitus
- Idiopathic pandysautonomia (may be a variant of Guillain-Barré syndrome)
- Porphyria
- HIV-related autonomic neuropathy
- Vincristine and other chemotherapeutic agents

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; CMT, Charcot-Marie-Tooth disease; CMV, cytomegalovirus; GBS, Guillain-Barré syndrome; HIV, human immunodeficiency virus; HNA, hereditary neuralgic amyotrophy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy; HSP-plus, hereditary spastic paraplegia plus neuropathy; SMA, spinal muscular atrophy; SOB, shortness of breath.

(random, unregulated firing of individual muscle fibers) and fasciculations (random, spontaneous firing of motor units).

TREATMENT**Polyneuropathy**

- Treatment of the underlying disorder, pain management, and supportive care to protect and rehabilitate damaged tissue all need to be considered.
- Examples of specific therapies include tight glycemic control in diabetic neuropathy, vitamin replacement for B₁₂ deficiency, IV immune globulin (IVIg) or plasmapheresis for GBS, and immunosuppression for vasculitis.
- Painful sensory neuropathies can be difficult to treat. Pain management usually begins with tricyclic antidepressants (TCAs), duloxetine hydrochloride, lidocaine patches, or anticonvulsants such as gabapentin or pregabalin (Table 196-2). Topical anesthetic agents including EMLA (lidocaine/prilocaine) and capsaicin cream can provide additional relief.
- Physical and occupational therapy is important. Proper care of denervated areas prevents skin ulceration, which can lead to poor wound healing, tissue resorption, arthropathy, and ultimately amputation.

Specific Polyneuropathies

AIDP or *GBS* is an ascending, usually demyelinating, motor > sensory polyneuropathy accompanied by areflexia, motor paralysis, and elevated CSF total

TABLE 196-2 Treatment of Painful Sensory Neuropathies

THERAPY	ROUTE	DOSE	SIDE EFFECTS
First-line			
Lidoderm 5% patch	Apply to painful area	Up to 3 patches qd	Skin irritation
Tricyclic antidepressants (e.g., amitriptyline, nortriptyline)	PO	10–100 mg qhs	Cognitive changes, sedation, dry eyes and mouth, urinary retention, constipation
Gabapentin	PO	300–1200 mg tid	Cognitive changes, sedation, peripheral edema
Pregabalin	PO	50–100 mg tid	Cognitive changes, sedation, peripheral edema
Duloxetine	PO	30–60 mg qd	Cognitive changes, sedation, dry eyes, diaphoresis, nausea, diarrhea, constipation
Second-line			
Carbamazepine	PO	200–400 mg q 6–8 h	Cognitive changes, dizziness, leukopenia, liver dysfunction
Phenytoin	PO	200–400 mg qhs	Cognitive changes, dizziness, liver dysfunction
Venlafaxine	PO	37.5–150 mg/d	Asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, and blurred vision as well as abnormal ejaculation/orgasm and impotence
Tramadol	PO	50 mg qid	Cognitive changes, gastrointestinal upset
Third-line			
Mexiletine	PO	200–300 mg tid	Arrhythmias
Other agents			
EMLA cream 2.5% lidocaine 2.5% prilocaine	Apply cutaneously	qid	Local erythema
Capsaicin 0.025–0.075% cream	Apply cutaneously	qid	Painful burning skin

Source: Adapted with permission from Amato AA, Russell J (eds): *Neuromuscular Disorders*, 2nd ed. New York, McGraw-Hill, 2016.

protein without pleocytosis. Over two-thirds are preceded by an acute respiratory or gastrointestinal infection. Maximum weakness is usually reached within 2 weeks; demyelination by EMG. Most pts are hospitalized; one-third require ventilatory assistance. Eighty-five percent make a complete or near-complete

recovery with supportive care. Variants of GBS include Fisher syndrome (ophthalmoparesis, facial diplegia, ataxia, areflexia; associated with serum antibodies to ganglioside GQ1b) and acute motor axonal neuropathy (more severe course than demyelinating GBS; antibodies to GM₁ in some cases).

- IVIg (2 g/kg divided over 5 days) or plasmapheresis (40–50 mL/kg daily for 4–5 days) significantly shortens the course.
- Glucocorticoids are ineffective.

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a slowly progressive or relapsing polyneuropathy characterized by diffuse hyporeflexia or areflexia, diffuse weakness, elevated CSF protein without pleocytosis, and demyelination by EMG.

- Begin treatment when progression is rapid or walking is compromised.
- Initial treatment is usually IVIg; most pts require periodic retreatment at 4- to 6-week intervals.
- Other first-line treatment options include plasmapheresis or glucocorticoids.
- Immunosuppressants (azathioprine, methotrexate, cyclosporine, cyclophosphamide, rituximab) used in refractory cases.

Diabetic neuropathy typically presents as a distal symmetric, sensorimotor, axonal polyneuropathy. A mixture of demyelination and axonal loss is frequent. Other variants include: isolated sixth or third cranial nerve palsies, asymmetric proximal motor neuropathy in the legs, truncal neuropathy, autonomic neuropathy, and an increased frequency of entrapment neuropathy (see next).

Mononeuropathy multiplex (MM) is defined as involvement of multiple individual peripheral nerves. When an inflammatory disorder is the cause, *mononeuritis multiplex* is the term used. Both systemic (67%) and nonsystemic (33%) vasculitis may present as MM. Immunosuppressive treatment of the underlying disease (usually with glucocorticoids and cyclophosphamide) is indicated. A tissue diagnosis of vasculitis should be obtained before initiating treatment; a positive biopsy helps to justify the necessary long-term treatment with immunosuppressive medications, and pathologic confirmation is difficult after treatment has commenced.

■ MONONEUROPATHY

Clinical Features

Mononeuropathies are usually caused by trauma, compression, or entrapment. Sensory and motor symptoms are in the distribution of a single nerve—most commonly the ulnar or median nerve in the arm or peroneal (fibular) nerve in the leg. Intrinsic factors making pts more susceptible to entrapment include arthritis, fluid retention (pregnancy), amyloid, hypothyroidism, tumors, and diabetes mellitus. Clinical features favoring conservative management of median neuropathy at the wrist (carpal tunnel syndrome) or ulnar neuropathy at the elbow include sudden onset, no motor deficit, few or no sensory findings (pain or paresthesias may be present), and no evidence of axonal loss by EMG. Surgical decompression is considered for chronic mononeuropathies that are unresponsive to conservative treatment if the site of entrapment is clearly defined. The most common mononeuropathies are summarized in [Table 196-3](#).

TABLE 196-3 Mononeuropathies

	SYMPTOMS	PRECIPITATING ACTIVITIES	EXAMINATION	ELECTRO-DIAGNOSIS	DIFFERENTIAL DIAGNOSIS	TREATMENT
Carpal tunnel syndrome	Numbness, pain, or paresthesias in fingers	Sleep or repetitive hand activity	Sensory loss in thumb, second, and third fingers Weakness in thenar muscles; inability to make a circle with thumb and index finger Tinel sign, Phalen maneuver	Slowing of sensory and motor conduction across carpal tunnel	C6 radiculopathy	Splint Surgery definitive treatment
Ulnar nerve entrapment (UNE) at the elbow	Numbness or paresthesias in ulnar aspect of hand	Elbow flexion during sleep; elbow resting on desk	Sensory loss in the little finger and ulnar half of ring finger Weakness of the interossei and thumb adductor; claw-hand	Focal slowing of nerve conduction velocity at the elbow	Thoracic outlet syndrome C8–T1 radiculopathy	Elbow pads Avoid further injury Surgery when conservative treatment fails
UNE at the wrist	Numbness or weakness in the ulnar distribution in the hand	Unusual hand activities with tools, bicycling	Like UNE but sensory examination spares dorsum of the hand, and selected hand muscles affected	Prolongation of distal motor latency in the hand	UNE	Avoid precipitating activities

Radial neuropathy at the spiral groove	Wrist drop	Sleeping on arm after inebriation with alcohol—"Saturday night palsy"	Wrist drop with sparing of elbow extension (triceps sparing); finger and thumb extensors paralyzed; sensory loss in radial region of wrist	Early—conduction block along the spiral groove Late—denervation in radial muscles; reduced radial SNAP	Posterior cord lesion; deltoid also weak Posterior interosseous nerve (PIN); isolated finger drop C7 radiculopathy	Splint Spontaneous recovery provided no ongoing injury
Thoracic outlet syndrome	Numbness, paresthesias in medial arm, forearm, hand, and fingers	Lifting heavy objects with the hand	Sensory loss resembles ulnar nerve and motor loss resembles median nerve	Absent ulnar sensory response and reduced median motor response	UNE	Surgery if correctable lesion present
Femoral neuropathy	Buckling of knee, numbness or tingling in thigh/medial leg	Abdominal hysterectomy; lithotomy position; hematoma, diabetes	Wasting and weakness of quadriceps; absent knee jerk; sensory loss in medial thigh and lower leg	EMG of quadriceps, iliopsoas, paraspinal muscles, adductor muscles	L2–4 radiculopathy Lumbar plexopathy	Physiotherapy to strengthen quadriceps and mobilize hip joint Surgery if needed
Obturator neuropathy	Weakness of the leg, thigh numbness	Stretch during hip surgery; pelvic fracture; childbirth	Weakness of hip adductors; sensory loss in upper medial thigh	EMG—denervation limited to hip adductors sparing the quadriceps	L3–4 radiculopathy Lumbar plexopathy	Conservative management Surgery if needed

(Continued)

TABLE 196-3 Mononeuropathies (Continued)

	SYMPTOMS	PRECIPITATING ACTIVITIES	EXAMINATION	ELECTRO-DIAGNOSIS	DIFFERENTIAL DIAGNOSIS	TREATMENT
Meralgia paresthetica	Pain or numbness in the anterior lateral thigh	Standing or walking Recent weight gain	Sensory loss in the pocket of the pant distribution	Sometimes slowing of sensory response can be demonstrated across the inguinal ligament	L2 radiculopathy	Usually resolves spontaneously
Peroneal nerve entrapment at the fibular head	Footdrop	Usually an acute compressive episode identifiable; weight loss	Weak dorsiflexion, eversion of the foot Sensory loss in the anterolateral leg and dorsum of the foot	Focal slowing of nerve conduction across fibular head Denervation in tibialis anterior and peroneus longus muscles	L5 radiculopathy	Foot brace; remove external source of compression
Sciatic neuropathy	Flail foot and numbness in foot	Injection injury; fracture/dislocation of hip; prolonged pressure on hip (comatose pt)	Weakness of hamstring, plantar, and dorsiflexion of foot; sensory loss in tibial and peroneal nerve distribution	NCS—abnormal sural, peroneal, and tibial amplitudes EMG—denervation in sciatic nerve distribution sparing glutei and paraspinal	L5–S1 radiculopathies Common peroneal neuropathy (partial sciatic nerve injury) LS plexopathies	Conservative follow-up for partial sciatic nerve injuries Brace and physiotherapy Surgical exploration if needed
Tarsal tunnel syndrome	Pain and paresthesias in the sole of the foot but not in the heel	At the end of the day after standing or walking; nocturnal	Sensory loss in the sole of the foot Tinel sign at tarsal tunnel	Reduced amplitude in sensory or motor components of medial and planter nerves	Polyneuropathy, foot deformity, poor circulation	Surgery if no external cause identified

197 Myasthenia Gravis



An autoimmune neuromuscular junction (NMJ) disorder resulting in weakness and fatigability of skeletal muscles, usually due to autoantibodies directed against acetylcholine receptors (AChRs).

■ CLINICAL FEATURES

May present at any age but peak incidences occur in women in their twenties and thirties and in men in their fifties and sixties. Symptoms fluctuate throughout the day and are provoked by exertion. Characteristic distribution: cranial muscles (eyelids, extraocular muscles, facial weakness, “nasal” or slurred speech, dysphagia); in 85%, limb muscles (often proximal and asymmetric) become involved. Reflexes and sensation normal. May be limited to extraocular muscles only. Complications: aspiration pneumonia (weak bulbar muscles), respiratory failure (weak chest wall muscles), exacerbation of myasthenia due to administration of drugs with NMJ blocking effects (quinolones, macrolides, aminoglycosides, procainamide, propranolol, nondepolarizing muscle relaxants).

■ PATHOPHYSIOLOGY

Anti-AChR antibodies reduce the number of available AChRs at the NMJ. Postsynaptic folds are flattened or “simplified,” with resulting inefficient neuromuscular transmission. During repeated or sustained muscle contraction, decrease in amount of ACh released per nerve impulse (“presynaptic rundown,” a normal occurrence), combined with disease-specific decrease in postsynaptic AChRs, results in pathologic fatigue. Thymus is abnormal in 75% of pts (65% hyperplasia, 10% thymoma). Other autoimmune diseases may coexist: Hashimoto’s thyroiditis, Graves’ disease, rheumatoid arthritis, systemic lupus erythematosus.

■ DIFFERENTIAL DIAGNOSIS

Lambert-Eaton syndrome (autoantibodies to calcium channels in presynaptic motor nerve terminals): reduced ACh release; may be associated with malignancy

Neurasthenia: weakness/fatigue without underlying organic disorder

Drug-induced myasthenia: penicillamine may cause myasthenia gravis (MG); resolves weeks to months after discontinuing drug. Checkpoint inhibitors for treatment of cancer also implicated more recently.

Botulism: toxin inhibits presynaptic ACh release; most common form is food-borne.

Diplopia from an intracranial mass lesion: compression of nerves to extraocular muscles or brainstem lesions affecting cranial nerve nuclei

Hyperthyroidism

Progressive external ophthalmoplegia: seen in rare mitochondrial disorders that can be detected with muscle biopsy

■ LABORATORY EVALUATION

- AChR antibodies: levels do not correlate with disease severity; 85% of all MG pts are positive; only 50% with pure ocular findings are positive; positive antibodies are diagnostic. Muscle-specific kinase (MuSK) antibodies present in 40% of AChR antibody-negative pts with generalized MG.
- Tensilon (edrophonium) test: a short-acting anticholinesterase—look for rapid and transient improvement of strength, now mainly reserved for those with negative antibody testing. False-positive (placebo response, motor neuron disease) and false-negative tests occur. Atropine IV should be on hand if symptoms such as bradycardia occur.

- EMG: low-frequency (2–4 Hz) repetitive stimulation produces rapid decrement in amplitude (>10%) of evoked motor responses.
- Chest CT/MRI: search for thymoma.
- Consider thyroid and other studies (e.g., ANA) for associated autoimmune disease.
- Measurements of baseline respiratory function are useful.

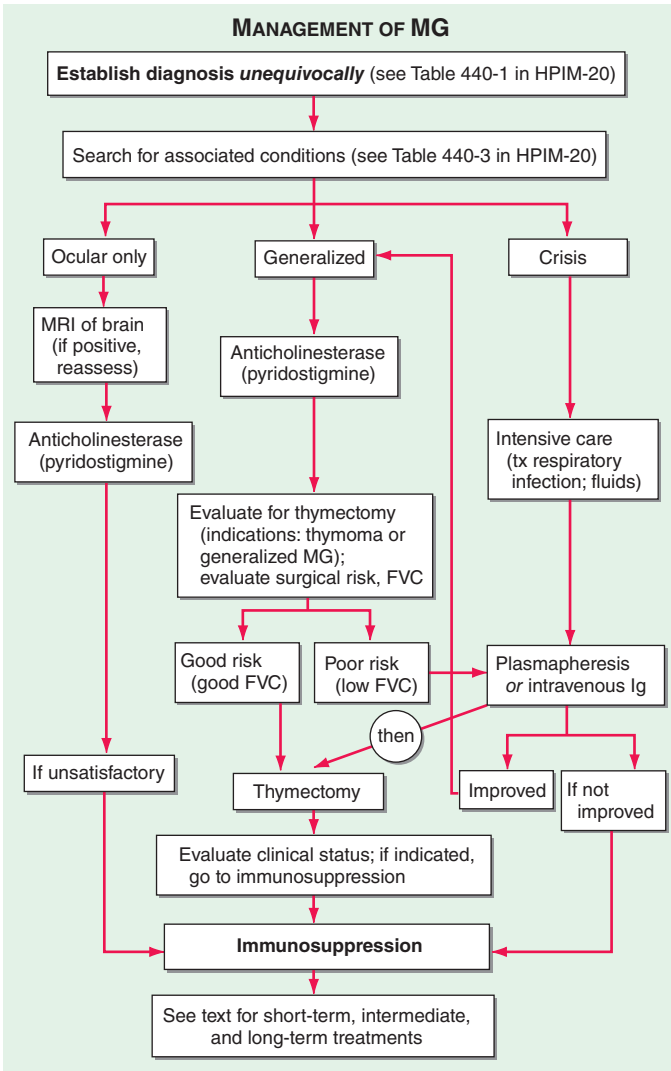


FIGURE 197-1 Algorithm for the management of myasthenia gravis. FVC, forced vital capacity; MRI, magnetic resonance imaging.

TREATMENT**Myasthenia Gravis (See Fig. 197-1)**

- The anticholinesterase drug pyridostigmine (Mestinon) titrated to assist pt with functional activities (chewing, swallowing, strength during exertion); usual initial dose of 30–60 mg 3–4 times daily; long-acting tablets help at night, but have variable absorption so are not reliable during the day. Muscarinic side effects (diarrhea, abdominal cramps, salivation, nausea) blocked with atropine/diphenoxylate or loperamide if required.
- Plasmapheresis or IV immune globulin (IVIg; 400 mg/kg per day for 5 days) provides temporary boost for seriously ill pts; used to improve condition prior to surgery or during myasthenic crisis (see below).
- Thymectomy improves likelihood of long-term remission in adult pts (~85% improve; of these, ~35% achieve drug-free remission); benefit is usually delayed by months to years; unclear if there is benefit in pts with pure ocular disease, antibody negative pts, children, or those age >55.
- Glucocorticoids are a mainstay of chronic immunosuppressive treatment; begin prednisone at low dose (15–25 mg/d), increase by 5 mg/d every 2–3 days until marked clinical improvement or dose of 50–60 mg/d is reached. Maintain high dose for about a month, then decrease to alternate-day regimen. Immunosuppressive drugs (mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, and occasionally cyclophosphamide) may spare dose of prednisone required long-term to control symptoms.
- A growing body of evidence indicates that rituximab is effective in many MG pts, especially those with MuSK antibody.
- Myasthenic crisis is defined as an exacerbation of weakness, usually with respiratory failure, sufficient to endanger life; expert management in an intensive care setting essential as is prompt treatment with IVIg or plasmapheresis to hasten recovery.
- A number of drugs may exacerbate MG, potentially leading to crisis, and therefore should be avoided (Table 197-1).

TABLE 197-1 Drugs with Interactions in Myasthenia Gravis (MG)**Drugs that may exacerbate MG****Antibiotics**

Aminoglycosides: e.g., streptomycin, tobramycin, kanamycin

Quinolones: e.g., ciprofloxacin, levofloxacin, ofloxacin, gatifloxacin

Macrolides: e.g., erythromycin, azithromycin

Nondepolarizing muscle relaxants for surgery

D-Tubocurarine (curare), pancuronium, vecuronium, atracurium

Beta-blocking agents

Propranolol, atenolol, metoprolol

Local anesthetics and related agents

Procaine, Xylocaine in large amounts

Procainamide (for arrhythmias)

(Continued)

TABLE 197-1 Drugs with Interactions in Myasthenia Gravis (MG)
(Continued)**Botulinum toxin**

Botox exacerbates weakness

Quinine derivatives

Quinine, quinidine, chloroquine, mefloquine (Lariam)

Magnesium

Decreases acetylcholine release

Penicillamine

May cause MG

Checkpoint inhibitors

May cause MG and other autoimmune neuromuscular disorders (e.g., myositis, inflammatory neuropathy)

Drugs with important interactions in MG**Cyclosporine and Tacrolimus**

Broad range of drug interactions, which may raise or lower levels

Azathioprine

Avoid allopurinol—combination may result in myelosuppression

198 Muscle Diseases

**APPROACH TO THE PATIENT****Muscle Disease**

Muscle diseases (*myopathies*) may be intermittent or persistent and usually present with proximal, symmetric weakness with preserved reflexes and sensation. An associated sensory loss suggests injury to peripheral nerve or the central nervous system rather than myopathy; on occasion, disorders affecting the anterior horn cells, the neuromuscular junction, or peripheral nerves can mimic myopathy. Any disorder causing muscle weakness may be accompanied by *fatigue*, referring to an inability to maintain or sustain a force; this must be distinguished from *asthenia*, a type of fatigue caused by excess tiredness or lack of energy. Fatigue without abnormal clinical or laboratory findings almost never indicates a true myopathy.

Muscle disorders are usually painless; however, *myalgias*, or muscle pains, may occur. Myalgias must be distinguished from *muscle cramps*, i.e., painful, involuntary muscle contractions, usually due to neurogenic disorders. A *muscle contracture* due to an inability to relax after an active muscle contraction is associated with energy failure in glycolytic disorders. *Myotonia* is a condition of prolonged muscle contraction followed by slow muscle relaxation.

CK is the preferred muscle enzyme to measure in the evaluation of suspected myopathies. Electrodiagnostic studies (nerve conduction studies and electromyography, NCS/EMG) are usually necessary to distinguish myopathies from neuropathies and neuromuscular junction disorders. An approach to muscle weakness is presented in [Figs. 198-1](#) and [198-2](#).

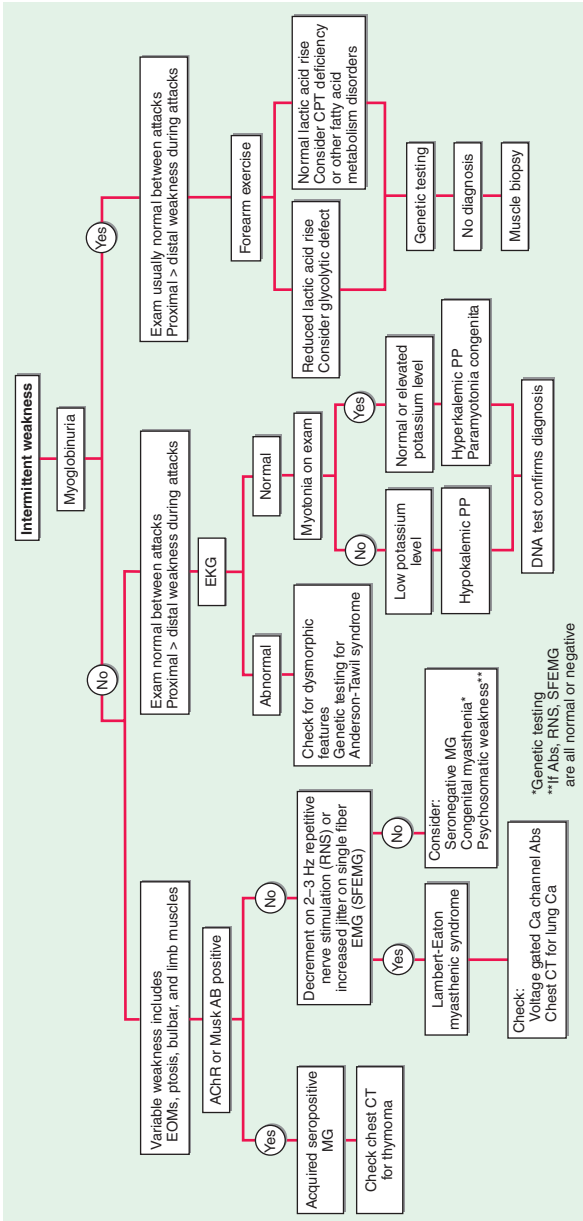


FIGURE 198-1 Diagnostic evaluation of intermittent weakness. AChR AB, acetylcholine receptor antibody; CPT, carnitine palmitoyltransferase; EOMs, extraocular muscles; MG, myasthenia gravis; PP, periodic paralysis.

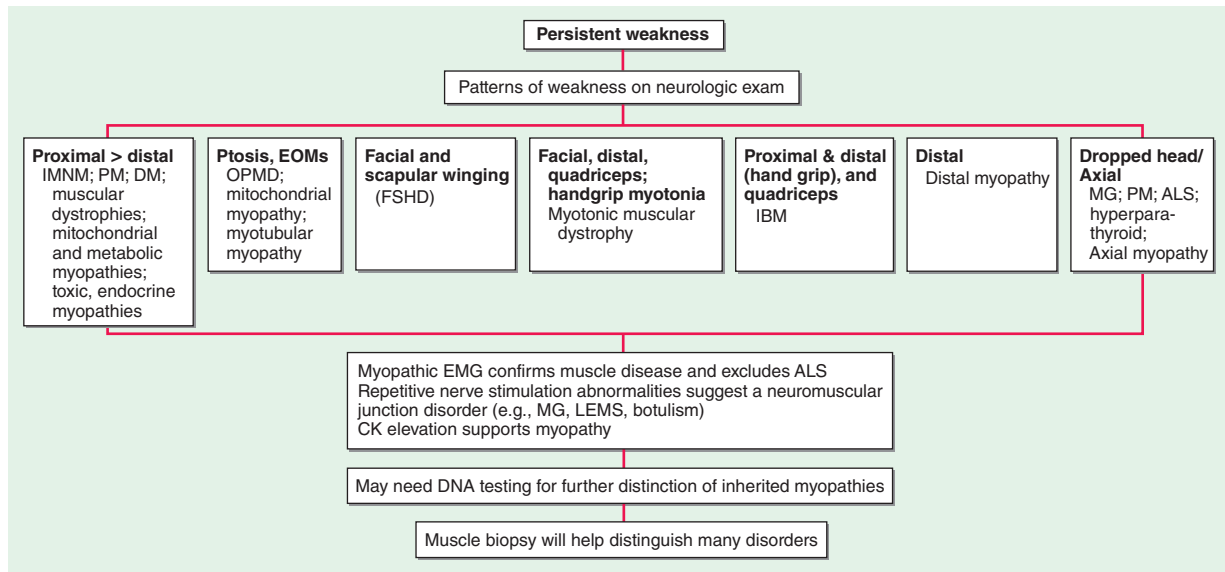


FIGURE 198-2 Diagnostic evaluation of persistent weakness. Examination reveals one of seven patterns of weakness. The pattern of weakness in combination with the laboratory evaluation leads to a diagnosis. ALS, amyotrophic lateral sclerosis; CK, creatinine kinase; DM, dermatomyositis; EMG, electromyography; EOMs, extraocular muscles; FSHD, facioscapulohumeral dystrophy; IBM, inclusion body myositis; IMNM, immune-mediated necrotizing myopathy; MG, myasthenia gravis; OPMD, oculopharyngeal muscular dystrophy; PM, polymyositis.

MUSCULAR DYSTROPHIES

A varied group of inherited, progressive degenerations of muscle, each with unique phenotypic and genetic features.

■ DUCHENNE'S MUSCULAR DYSTROPHY

X-linked recessive mutation of the dystrophin gene that affects males almost exclusively. Progressive weakness in hip and shoulder girdle muscles beginning by age 5; by age 12, the majority were nonambulatory in the era prior to the use of glucocorticoids. Survival beyond age 25 is rare. Associated problems include tendon and muscle contractures, progressive kyphoscoliosis, impaired pulmonary function, cardiomyopathy, and intellectual impairment. Palpable enlargement and firmness of some muscles. Becker dystrophy is a less severe form, with a slower course and later age of onset (usually 5–15 years) but similar clinical, laboratory, and genetic features.

Laboratory findings include massive elevations (20–100 × normal) of serum CK, a myopathic pattern on EMG testing, and evidence of groups of necrotic muscle fibers with regeneration, phagocytosis, and fatty replacement of muscle on biopsy. Diagnosis is established by determination of dystrophin deficiency in peripheral blood; muscle biopsy is now rarely needed. Testing is available for detecting carriers and prenatal diagnosis. Dystrophin is part of a large complex of muscle membrane glycoproteins, disruption of which weakens the cell membrane.

TREATMENT

Duchenne's Muscular Dystrophy

- Glucocorticoids (prednisone [0.75 mg/kg]/d) slow progression of disease for up to 3 years; some pts cannot tolerate this therapy due to weight gain and increased risk of fractures.
- Recent evidence suggests clinical benefit in selected cases from short oligonucleotides that permit skipping of mutant exons resulting in expression of a functional dystrophin protein. Small molecule approaches also have been tried in small studies with early success.

■ LIMB-GIRDLE DYSTROPHY

A constellation of diseases with proximal weakness involving the pelvic and shoulder girdle musculature. Age of onset, rate of progression, severity of manifestations, inheritance pattern (autosomal dominant or autosomal recessive), and associated complications (e.g., cardiac, respiratory) vary with the specific subtype of disease.

■ MYOTONIC DYSTROPHY

Type 1 is an autosomal dominant disorder with genetic anticipation. Weakness typically becomes obvious in the second to third decade and initially involves the muscles of the face, neck, and distal extremities. This results in a distinctive facial appearance ("hatchet-faced") with ptosis, temporal wasting, drooping of the lower lip, and sagging of the jaw. Myotonia manifests as an inability to relax muscles rapidly following a strong exertion (e.g., after tight hand grip) usually by the age of 5, and by sustained contraction of muscles following percussion (e.g., of tongue or thenar eminence).

Associated findings can include frontal baldness, posterior subcapsular cataracts, gonadal atrophy, respiratory and cardiac problems, endocrine

abnormalities, intellectual impairment, and hypersomnia. Cardiac disturbances, including complete heart block, may be life-threatening. Respiratory function should be carefully followed, as chronic hypoxia may lead to cor pulmonale.

Laboratory studies show normal or mildly elevated CK, characteristic myotonia and myopathic features on EMG, and a typical pattern of muscle fiber injury on biopsy. Myotonic dystrophy type 1 is caused by an unstable expansion of a CTG trinucleotide repeat in a protein kinase gene (named *DMPK*) on chromosome 19q13.3. Genetic testing for early detection and prenatal diagnosis is possible.

TREATMENT

Myotonic Dystrophy

- Mexiletine may help alleviate myotonia, although pts are rarely bothered by this symptom.
- Pacemaker or implantable defibrillator insertion may be required for syncope or heart block.
- Orthoses may control foot drop, stabilize the ankle, and decrease falls.
- Excessive daytime somnolence with or without sleep apnea is not uncommon; sleep studies, noninvasive respiratory support (BiPAP), and treatment with modafinil may be beneficial.

■ FACIOSCAPULOHUMERAL (FSH) DYSTROPHY

An autosomal dominant, slowly progressive disorder with onset in childhood or young adulthood. Weakness involves facial (usually the initial manifestation), shoulder girdle, and proximal arm muscles and can result in atrophy of biceps, triceps, and scapular winging. Facial weakness results in inability to smile, whistle, or fully close the eyes. Foot drop and leg weakness may cause falls and progressive difficulty with ambulation.

Laboratory studies reveal normal or slightly elevated CK and usually myopathic features on EMG and muscle biopsy. Type 1 FSD is caused by deletions at chromosome 4q35 leading to toxic expression of the *DUX4* gene. Genetic testing is available for carrier detection and prenatal diagnosis.

TREATMENT

Facioscapulohumeral Dystrophy

- Ankle-foot orthoses are helpful for foot drop.
- Scapular stabilization procedures may help scapular winging but may not improve function.

■ OCULOPHARYNGEAL DYSTROPHY

Onset in the fourth to sixth decade of ptosis, limitation of extraocular movements, and facial and cricopharyngeal weakness. One of several disorders characterized by progressive external ophthalmoplegia (CPEO). Dysphagia may be life-threatening. Most pts are of French-Canadian or Spanish-American descent. Mutation in a poly-RNA binding protein responsible.

INFLAMMATORY MYOPATHIES

The most common group of acquired and potentially treatable skeletal muscle disorders. Five major forms: dermatomyositis (DM), inclusion body myositis (IBM), polymyositis (PM), immune-mediated necrotizing myopathy, and

antisyntetase syndrome. Usually present as progressive and symmetric muscle weakness; extraocular muscles spared but pharyngeal weakness (dysphagia) and head drop from neck muscle weakness are common. Respiratory muscles may be affected in advanced cases. IBM is characterized by early involvement of quadriceps (leading to falls) and distal muscles; IBM may have an asymmetric pattern. Progression is over weeks or months in PM and DM, but typically over years in IBM. Skin involvement in DM may consist of a heliotrope rash (blue-purple discoloration) on the upper eyelids with edema, a flat red rash on the face and upper trunk, or erythema over knuckles (*Gottron's sign*). A variety of cancers are associated with DM. Features of each disorder are summarized in [Table 198-1](#).

TREATMENT

Inflammatory Myopathies

Often effective for all the disorders except for IBM.

- Step 1: Glucocorticoids (prednisone, 0.75–1 mg/kg per day for 3–4 weeks, then tapered very gradually)
- Step 2: Approximately 75% of pts require additional therapy with other immunosuppressive drugs. Azathioprine (up to 3 mg/kg per day), methotrexate (7.5 mg/week gradually increasing to 25 mg/week), or mycophenolate mofetil (up to 2.5–3 g/day in 2 divided doses) commonly used.
- Step 3: IV immunoglobulin (2 g/kg divided over 2–5 days)
- Step 4: Rituximab (750 mg/m² [up to 1 g] IV with a second infusion 2 weeks later and repeat courses every 6–18 months as needed)

DISORDERS OF MUSCLE ENERGY METABOLISM

The two principal sources of energy for skeletal muscle are fatty acids and glucose. Abnormalities in either glucose or lipid utilization can be associated with distinct clinical presentations that can range from an acute, painful syndrome with rhabdomyolysis and myoglobinuria to a chronic, progressive muscle weakness simulating muscular dystrophy. Diagnosis usually requires biochemical-enzymatic studies of biopsied muscle.

Progressive muscle weakness usually beginning in the third or fourth decade can be due to the adult form of *acid maltase deficiency* (*Pompe's disease*). Respiratory failure is often the initial manifestation; treatment with enzyme replacement may be of benefit. Progressive weakness beginning after puberty occurs with *debranching enzyme deficiency*. Glycolytic defects, including *myophosphorylase deficiency* (McArdle's disease) or *phosphofructokinase deficiency*, present as exercise intolerance with myalgias. Disorders of fatty acid metabolism present with a similar picture. In adults, the most common cause is *carnitine palmitoyltransferase deficiency*. Exercise-induced cramps and myoglobinuria are common; strength is normal between attacks. Dietary approaches (frequent meals and a low-fat high-carbohydrate diet, or a diet rich in medium-chain triglycerides) are of uncertain value.

MITOCHONDRIAL MYOPATHIES

These result from defects in mitochondrial DNA. Clinical presentations vary greatly: muscle symptoms may include weakness, ophthalmoparesis, pain, or stiffness, or they may even be absent; age of onset ranges from infancy to adulthood; associated clinical presentations include ataxia, encephalopathy, seizures,

TABLE 198-1 Inflammatory Myopathies: Clinical and Laboratory Features

DISORDER	SEX	AGE OF ONSET	RASH	PATTERN OF WEAKNESS	LABORATORY FEATURES	MUSCLE BIOPSY	CELLULAR INFILTRATE	RESPONSE TO IS THERAPY	COMMON ASSOCIATED CONDITIONS
DM	F > M	Childhood and adult	Yes	Proximal > distal	Normal or increased CK (up to 50× normal or higher); various MSAs (anti-MDA5, anti-TIF1, anti-Mi-2, anti-NXP2)	Perimysial and perivascular inflammation; IFN-1 regulated proteins (MHC-1, MxA), MAC deposition on capillaries	CD4+ Dendritic cells; B cells; macrophages	Yes	Myocarditis, ILD, malignancy, vasculitis, other CTDs
PM	F > M	Adult	No	Proximal > distal	Increased CK (up to 50× normal or higher)	Endomysial and perivascular inflammation; ubiquitous expression of MHC-1	CD8+ T-cells; macrophages; plasma cells	Yes	Myocarditis, ILD, other CTDs
NM	M = F	Children and adults	No	Proximal > distal	Elevated CK (> 10× normal or higher); anti-HMGCR or anti-SRP antibodies	Necrotic muscle fibers; minimal inflammatory infiltrate	Macrophages in necrotic fibers undergoing phagocytosis	Yes	Malignancy, CTD, HMGCR antibody cases can be triggered by statin use

ASS	F > M	Children and adults	Sometimes	Proximal > distal	Elevated CK (>10× normal or higher); antisynthetase antibodies	Perimysial and perivascular inflammation; perimysial fragmentation with alkaline phosphatase staining; perimysial muscle damage with necrosis	CD4+ Dendritic cells; B cells; macrophages	Yes	Non-erosive arthritis, ILD, Raynaud phenomenon, mechanic hands, and fever
IBM	M > F	Older adults (>50 yrs)	No	Proximal and distal; predilection for: finger/wrist flexors, knee extensors	Normal or mildly increased CK (usually <10× normal); anti-cN-1A antibodies; large granular lymphocytes on flow cytometry and reduced CD4/CD8 ratio with increased CD8 count	Endomysial and perivascular inflammation; ubiquitous expression of MHC-1; rimmed vacuoles; p62, LC3, TDP-43 aggregates; EM: 15–18 nm tubulofilaments; ragged red and COX negative fibers	CD8+ T-cells; macrophages; plasma cells; myeloid dendritic cells; large granular lymphocytes	None or minimal	Granular lymphocytic leukemia/lymphocytosis, sarcoidosis, SICCA or Sjogren's syndrome

Abbreviations: CK, creatine kinase; cN-1A, cytosolic 5'-nucleotidase 1A; CTDs, connective tissue diseases; COX, cytochrome oxidase; DM, dermatomyositis; F, female; g, immunoglobulin; IBM, inclusion body myositis; IFN-1, type 1 interferon; ILD, interstitial lung disease; IS, immunosuppressive; M, male; MAC, membrane attack complex; MDA5, melanoma differentiation antigen; MHC-1, major histocompatibility antigen 1; NCP2, nuclear matrix protein 2 (NXP2); NM, necrotizing myopathy; PM, polymyositis; TIF1, transcriptional intermediary factor 1.

Source: Adapted with permission from Amato AA, Russell JA (eds): *Neuromuscular Disorders*, 2nd ed. New York, McGraw-Hill; 2016.

TABLE 198-2 Drug-Induced Myopathies

DRUGS	MAJOR TOXIC REACTION
Lipid-lowering agents HMG-CoA reductase inhibitors Fibric acid derivatives Niacin (nicotinic acid)	Drugs belonging to all three of the major classes of lipid-lowering agents can produce a spectrum of toxicity: asymptomatic serum creatine kinase elevation, myalgias, exercise-induced pain, rhabdomyolysis, and myoglobinuria.
Glucocorticoids	Acute, high-dose glucocorticoid treatment can cause acute quadriplegic myopathy. These high doses of steroids are often combined with nondepolarizing neuromuscular blocking agents but the weakness can occur without their use. Chronic steroid administration produces predominantly proximal weakness.
Nondepolarizing neuromuscular blocking agents	Acute quadriplegic myopathy can occur with or without concomitant glucocorticoids.
Zidovudine	Mitochondrial myopathy with ragged red fibers
Drugs of abuse Alcohol Amphetamines Cocaine Heroin Phencyclidine Meperidine	All drugs in this group can lead to widespread muscle breakdown, rhabdomyolysis, and myoglobinuria. Local injections cause muscle necrosis, skin induration, and limb contractures.
Autoimmune myopathy Statins Checkpoint inhibitors D-Penicillamine	Use of statins may cause an immune-mediated necrotizing myopathy associated with HMG-CoA reductase antibodies. Check point inhibitors can be complicated by myositis, myasthenia gravis, and immune-mediated neuropathies. Myasthenia gravis has also been reported with penicillamine.
Amphophilic cationic drugs Amiodarone Chloroquine Hydroxychloroquine	All amphophilic drugs have the potential to produce painless, proximal weakness associated with necrosis and autophagic vacuoles in the muscle biopsy.
Antimicrotubular drugs Colchicine	This drug produces painless, proximal weakness especially in the setting of renal failure. Muscle biopsy shows necrosis and fibers with autophagic vacuoles.

stroke-like episodes, and recurrent vomiting. Three groups: CPEO; skeletal muscle–central nervous system syndromes; and pure myopathy syndromes simulating muscular dystrophy. The characteristic finding on muscle biopsy is “ragged red fibers,” which are muscle fibers with accumulations of abnormal mitochondria. Affected families often have a maternal pattern of inheritance because mitochondrial genes are inherited almost exclusively from the oocyte.

PERIODIC PARALYSES

Muscle membrane excitability is affected in a group of disorders referred to as *channelopathies*. Onset is usually in childhood or adolescence. Episodes typically occur after rest or sleep, often following earlier exercise. May be due to genetic

disorders of calcium (hypokalemic periodic paralysis [hypoKPP]), sodium (hyperkalemic periodic paralysis), chloride, or potassium channels.

- Attacks of hypoKPP are treated with potassium chloride (usually oral). Prophylaxis with acetazolamide (125–1000 mg/d in divided doses) or dichlorphenamide is usually effective in hypoKPP type 1.
- Attacks of thyrotoxic periodic paralysis (usually in Asian men) resemble those of hypoKPP; attacks abate with treatment of the underlying thyroid condition.

ENDOCRINE AND METABOLIC MYOPATHIES

Abnormalities of thyroid function can cause a wide array of muscle disorders. Hypothyroidism is associated with muscle cramps, pain, and stiffness, and proximal muscle weakness occurs in one-third of pts; the relaxation phase of muscle stretch reflexes is prolonged, and serum CK is often elevated (up to 10 times normal).

Hyperthyroidism can produce proximal muscle weakness and atrophy; bulbar, respiratory, and even esophageal muscles are occasionally involved, causing dysphagia, dysphonia, and aspiration. Other neuromuscular disorders associated with hyperthyroidism include hypoKPP, myasthenia gravis, and a progressive ocular myopathy associated with proptosis (*Graves' ophthalmopathy*).

Parathyroid, adrenal, and pituitary disorders, as well as diabetes mellitus, can also produce myopathy. Deficiency of vitamin D is a rare cause of muscle weakness.

DRUG-INDUCED MYOPATHIES

Drugs (including glucocorticoids and lipid-lowering agents) and toxins (e.g., alcohol) are associated with myopathies ([Table 198-2](#)). In most cases, weakness is symmetric and involves proximal limb girdle muscles; myalgia and cramps may also occur. An elevated CK is often found. Diagnosis often depends on resolution of signs and symptoms with removal of offending agent.

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199 Psychiatric Disorders



Psychiatric disorders are common in medical practice and may present either as a primary disorder or as a comorbid condition. The prevalence of mental or substance use disorders in the United States is ~30%, but only one-third of those individuals are currently receiving treatment.

Disorders of mood, thinking, and behavior may be due to a primary psychiatric diagnosis or a personality disorder or may be secondary to metabolic abnormalities, drug toxicities, focal cerebral lesions, seizure disorders, or degenerative neurologic disease. Any pt presenting with new onset of psychiatric symptoms must be evaluated for underlying psychoactive substance abuse and/or medical or neurologic illness. Psychiatric medications are discussed in [Chap. 200](#).

MAJOR PSYCHIATRIC DISORDERS (AXIS I DIAGNOSES)

■ MOOD DISORDERS (MAJOR AFFECTIVE DISORDERS)

Mood disorders are characterized by a disturbance in the regulation of mood, behavior, and affect; subdivided into (1) depressive disorders, (2) bipolar disorders (depression plus manic or hypomanic episodes), and (3) depression in association with medical illness or alcohol and substance abuse (see [Chaps. 202, 203, and 204](#)).

Major Depression

CLINICAL FEATURES Affects 15% of the general population at some point in life; 6–8% of all outpatients in primary care settings satisfy diagnostic criteria. Diagnosis is made when five (or more) of the following symptoms have been present for 2 weeks (at least one of the symptoms must be #1 or #2 below):

1. Depressed mood
2. Loss of interest or pleasure
3. Change in appetite or weight
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or inappropriate guilt
8. Decreased ability to concentrate and make decisions
9. Recurrent thoughts of death or suicide

A small number of pts with major depression will have psychotic symptoms (hallucinations and delusions) with their depressed mood. Negative life events can precipitate depression, but genetic factors influence the sensitivity to these events.

Onset of a first depressive episode is typically in early adulthood, although major depression can occur at any age. Untreated episodes generally resolve spontaneously in a few months to a year; however, a sizable number of pts suffer from chronic, unremitting depression, or from a partial treatment response. Half of all pts experiencing a first depressive episode will go on to a recurrent course. Untreated or partially treated episodes put the pt at risk for future problems with mood disorders. Within an individual, the nature of episodes may be similar over time. A family history of mood disorder is common and tends to predict a

recurrent course. Major depression can also be the initial presentation of bipolar disorder (manic depressive illness).

SUICIDE Approximately 4–5% of all depressed pts will commit suicide, and most will have sought help from a physician within 1 month of their death. Physicians must always inquire about suicide when evaluating a pt with depression.

DEPRESSION WITH MEDICAL ILLNESS Virtually every class of medication can potentially induce or worsen depression. Antihypertensive drugs, anticholesterolemic agents, and antiarrhythmic agents are common triggers of depressive symptoms. Among the antihypertensive agents, β -adrenergic blockers and, to a lesser extent, calcium channel blockers are most likely to cause depressed mood. Iatrogenic depression should also be considered in pts receiving glucocorticoids, antimicrobials, systemic analgesics, antiparkinsonian medications, and anticonvulsants.

Between 20% and 30% of cardiac pts manifest a depressive disorder. Tricyclic antidepressants (TCAs) are contraindicated in pts with bundle branch block, and TCA-induced tachycardia is an additional concern in pts with congestive heart failure. Selective serotonin reuptake inhibitors (SSRIs) appear not to induce ECG changes or adverse cardiac events, and thus, are reasonable first-line drugs for pts at risk for TCA-related complications. SSRIs may interfere with hepatic metabolism of warfarin, however, causing increased anticoagulation.

In *cancer*, the prevalence of depression is 25%, but it occurs in 40–50% of pts with cancers of the pancreas or oropharynx. Extreme cachexia from cancer may be misinterpreted as depression. Antidepressant medications in cancer pts improve quality of life as well as mood.

Diabetes mellitus is another consideration; the severity of the mood state correlates with the level of hyperglycemia and the presence of diabetic complications. Monoamine oxidase inhibitors (MAOIs) can induce hypoglycemia and weight gain. TCAs can produce hyperglycemia and carbohydrate craving. SSRIs, like MAOIs, may reduce fasting plasma glucose, but they are easier to use and may also improve dietary and medication compliance.

Depression may also occur with *hypothyroidism* or *hyperthyroidism*, in *neurologic disorders*, in *HIV-positive individuals*, and in *chronic hepatitis C infection*. Some chronic disorders of uncertain etiology, such as *chronic fatigue syndrome* and *fibromyalgia*, are strongly associated with depression.

TREATMENT

Major Depression

- Pts with suicidal ideation require treatment by a psychiatrist and may require hospitalization.
- Most other pts with an uncomplicated unipolar major depression (a major depression that is not part of a cyclical mood disorder, such as a bipolar disorder) can be successfully treated by a nonpsychiatric physician.
- Vigorous intervention and successful treatment appear to decrease the risk of future relapse.
- Pts who do not respond fully to standard treatment should be referred to a psychiatrist.
- Antidepressant medications are the mainstay of treatment, although combined treatment with psychotherapy improves outcome. Symptoms are ameliorated after 6–8 weeks at a therapeutic dose in 60–70% of pts.

MEDICAL MANAGEMENT OF MAJOR DEPRESSIVE DISORDER ALGORITHM

Determine whether there is a history of good response to a medication in the pt or a first-degree relative; if yes, consider treatment with this agent if compatible with considerations in step 2.

Evaluate pt characteristics and match to drug; consider health status, side effect profile, convenience, cost, pt preference, drug interaction risk, suicide potential, and medication compliance history.

Begin new medication at 1/3 to 1/2 target dose if drug is a TCA, bupropion, venlafaxine, or mirtazapine, or full dose as tolerated if drug is an SSRI.

If problem side effects occur, evaluate possibility of tolerance; consider temporary decrease in dose or adjunctive treatment.

If unacceptable side effects continue, taper drug over 1 week and initiate new trial; consider potential drug interactions in choice.

Evaluate response after 6 weeks at target dose; if response is inadequate, increase dose in stepwise fashion as tolerated.

If inadequate response after maximal dose, consider tapering and switching to a new drug vs adjunctive treatment; if drug is a TCA, obtain plasma level to guide further treatment.

FIGURE 199-1 A guideline for the medical management of major depressive disorder. SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

- A guideline for the medical management of depression is shown in [Fig. 199-1](#).
- Once remission is achieved, antidepressants should be continued for 6–9 months. Pts must be monitored carefully after termination of treatment since relapse is common.
- Pts with two or more episodes of depression should be considered for indefinite maintenance treatment.
- Electroconvulsive therapy is generally reserved for treatment-resistant depression unresponsive to medication or for pts in whom the use of antidepressants is medically contraindicated.
- Transcranial magnetic stimulation (TMS) is approved for treatment-resistant depression.
- Vagus nerve stimulation (VNS) has been approved for treatment-resistant depression as well, but its degree of efficacy is controversial.

- Other emerging approaches for refractory depression include low intensity transcranial current stimulation (tCS), intravenous or intranasal forms of ketamine, and deep brain stimulation of the internal capsule and cingulate region.

Bipolar Disorder (Manic Depressive Illness)

CLINICAL FEATURES A cyclical mood disorder in which episodes of major depression are interspersed with episodes of mania or hypomania; 1.5% of the population is affected. Most pts initially present with a manic episode in adolescence or young adulthood. Antidepressant therapy may provoke a manic episode; pts with a major depressive episode and a prior history of “highs” (mania or hypomania—which can be pleasant/euphoric or irritable/impulsive) and/or a family history of bipolar disorder should not be treated with antidepressants, but instead referred promptly to a psychiatrist.

With mania, an elevated, expansive mood, irritability, angry outbursts, and impulsivity are characteristic. Specific symptoms include (1) unusual talkativeness, (2) flight of ideas and racing thoughts, (3) inflated self-esteem that can become delusional, (4) decreased need for sleep (often the first feature of an incipient manic episode), (5) increase in goal-directed activity or psychomotor agitation, (6) distractibility, and (7) excessive involvement in risky activities (buying sprees, sexual indiscretions). Pts with full-blown mania can become psychotic. Hypomania is characterized by attenuated manic symptoms and is greatly underdiagnosed, as are “mixed episodes,” where both depressive and manic or hypomanic symptoms coexist simultaneously.

Untreated, a manic or depressive episode typically lasts for several weeks but can last for 8–12 months. Variants of bipolar disorder include rapid and ultrarapid cycling (manic and depressed episodes occurring at cycles of weeks, days, or hours). In many pts, especially females, antidepressants trigger rapid cycling and worsen the course of illness. Bipolar disorder has a strong genetic component; the concordance rate for monozygotic twins approaches 80%.

TREATMENT

Bipolar Disorder

- Bipolar disorder is a serious, chronic illness that requires lifelong monitoring by a psychiatrist.
- Acutely manic pts often require hospitalization to reduce environmental stimulation and to protect themselves and others from the consequences of their reckless behavior.
- The recurrent nature of bipolar disorder necessitates maintenance treatment.
- Mood stabilizers (lithium, valproic acid, second-generation antipsychotic drugs, carbamazepine) are effective for the resolution of acute episodes and for prophylaxis of future episodes.

■ SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS

Schizophrenia

CLINICAL FEATURES Characterized by perturbations of language, perception, thinking, social activity, affect, and volition. Occurs in 0.85% of the population worldwide; lifetime prevalence is ~1–1.5%. Pts usually present in late adolescence, often after an insidious premorbid course of

subtle psychosocial difficulties. Core psychotic features last ≥ 6 months and include positive symptoms (such as conceptual disorganization, delusions, or hallucinations) and negative symptoms (loss of function, anhedonia, decreased emotional expression, impaired concentration, and diminished social engagement). Negative symptoms predominate in one-third and are associated with a poor long-term outcome and poor response to treatment.

Prognosis depends not on symptom severity but on the response to antipsychotic medication. A permanent remission without recurrence does occasionally occur. About 10% of schizophrenic pts commit suicide. Comorbid substance abuse is common.

TREATMENT

Schizophrenia

- Hospitalization is required for acutely psychotic pts who may be dangerous to themselves or others.
- Conventional antipsychotic medications are effective against hallucinations, delusions, and thought disorder.
- Newer generation antipsychotic medications—risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, lurasidone, and clozapine—are helpful in pts unresponsive to conventional neuroleptics and may also be more useful for negative and cognitive symptoms.
- Drug treatment by itself is insufficient, and educational efforts directed toward families and relevant community resources are necessary to maintain stability and optimize outcomes.

■ ANXIETY DISORDERS

Characterized by severe, persistent anxiety or sense of dread or foreboding. Most prevalent group of psychiatric illnesses seen in the community; present in 15–20% of medical clinic pts.

Panic Disorder

Occurs in 2–3% of the population; familial aggregation may occur. Onset in late adolescence or early adulthood. Initial presentation is almost always to a non-psychiatric physician, frequently in the ER, as a possible heart attack or serious respiratory problem. The disorder is often initially unrecognized or misdiagnosed. Three-quarters of pts with panic disorder will also satisfy criteria for major depression at some point.

CLINICAL FEATURES Characterized by panic attacks, which are sudden, unexpected, overwhelming paroxysms of terror and apprehension with multiple associated somatic symptoms. Attacks usually reach a peak within 10 min, then slowly resolve spontaneously, occurring in an unexpected fashion. Diagnostic criteria for panic disorder include recurrent panic attacks and at least 1 month of concern or worry about the attacks or a change in behavior related to them. Panic attacks are accompanied by palpitations, sweating, trembling, dyspnea, chest pain, dizziness, and a fear of impending doom or death.

When the disorder goes unrecognized and untreated, pts often experience significant morbidity: they become afraid of leaving home and may develop anticipatory anxiety, agoraphobia, and other spreading phobias; many turn to self-medication with alcohol or benzodiazepines.

Panic disorder must be differentiated from cardiovascular and respiratory disorders. Other conditions that may mimic or worsen panic attacks include hyperthyroidism, pheochromocytoma, hypoglycemia, drug ingestions (amphetamines, cocaine, caffeine, sympathomimetic nasal decongestants), and drug withdrawal (alcohol, barbiturates, opiates, minor tranquilizers).

TREATMENT

Panic Disorder

- The cornerstone of drug therapy is antidepressant medication.
- SSRIs benefit the majority of pts and do not have the adverse effects of the TCAs.
- Benzodiazepines are often used in the short term while waiting for antidepressants to take effect although there is no good evidence that they work more quickly.
- Early psychotherapeutic intervention and education aimed at symptom control enhance the effectiveness of drug treatment.
- Psychotherapy (identifying and aborting panic attacks through relaxation and breathing techniques) can be effective.

Generalized Anxiety Disorder (GAD)

Characterized by persistent, chronic anxiety; occurs in 5–6% of the population.

CLINICAL FEATURES Pts experience persistent, excessive, and/or unrealistic worry associated with muscle tension, impaired concentration, autonomic arousal, feeling “on edge” or restless, and insomnia. Pts worry excessively over minor matters, with life-disrupting effects; unlike panic disorder, complaints of shortness of breath, palpitations, and tachycardia are relatively rare. Secondary depression is common, as is social phobia and comorbid substance abuse.

TREATMENT

Generalized Anxiety Disorder

- A combination of pharmacologic and psychotherapeutic interventions is most effective; complete symptom relief is rare.
- Benzodiazepines are the initial agents of choice when generalized anxiety is severe and acute enough to warrant drug therapy; physicians must be alert to psychological and physical dependence on benzodiazepines.
- A subgroup of pts respond to buspirone, a nonbenzodiazepine anxiolytic.
- Some SSRIs also are effective at doses comparable to their efficacy in major depression.
- Anticonvulsants with GABAergic properties (gabapentin, oxcarbazepine, tiagabine, pregabalin, divalproex) may also be effective against anxiety.

Obsessive-Compulsive Disorder (OCD)

A severe disorder present in 2–3% of the population and characterized by recurrent obsessions (persistent intrusive thoughts) and compulsions (repetitive behaviors) that impair everyday functioning. Pts are often ashamed of their symptoms; physicians must ask specific questions to screen for this disorder including asking about recurrent thoughts and behaviors.

CLINICAL FEATURES Common obsessive thoughts and compulsive behaviors include fears of germs or contamination, handwashing, counting behaviors, and having to check and recheck such actions as whether a door is locked.

Onset is usually in early adulthood (childhood onset is not rare); more common in males and first-born children. Comorbid conditions are common, the most frequent being depression, other anxiety disorders, eating disorders, and tics. The course of OCD is usually episodic with periods of incomplete remission; some cases may show a steady deterioration in psychosocial functioning.

TREATMENT

Obsessive-Compulsive Disorder

- Clomipramine and the SSRIs (fluoxetine, fluvoxamine, sertraline) are effective, but only 50–60% of pts show adequate improvement with pharmacotherapy alone.
- A combination of drug therapy and cognitive-behavioral psychotherapy is most effective for the majority of pts.

Posttraumatic Stress Disorder (PTSD)

Occurs in some individuals exposed to a severe life-threatening trauma. If the reaction occurs shortly after the event, it is termed *acute stress disorder*, but if the reaction is delayed and subject to recurrence, PTSD is diagnosed. Predisposing factors include a past psychiatric history and personality characteristics of extroversion and high neuroticism.

CLINICAL FEATURES Individuals experience associated symptoms of detachment and loss of emotional responsiveness. The pt may feel depersonalized and unable to recall specific events of the trauma, although it is reexperienced through intrusions in thought, dreams, or flashbacks. Comorbid substance abuse and other mood and anxiety disorders are common. This disorder is extremely debilitating; most pts require referral to a psychiatrist for ongoing care.

TREATMENT

Posttraumatic Stress Disorder

- SSRIs, venlafaxine, nefazodone, and topiramate all are somewhat effective.
- Hydrocortisone, intranasal oxytocin, and opiates such as morphine given during the acute stress period may prevent the development of PTSD.
- Adjunctive naltrexone can be effective when comorbid alcoholism is present.
- Low dose trazodone and mirtazapine are frequently used at night to help with insomnia.
- Psychotherapeutic strategies help the pt overcome avoidance behaviors and master fear of recurrence of the trauma.

Phobic Disorders

CLINICAL FEATURES Recurring, irrational fears of specific objects, activities, or situations, with subsequent avoidance behavior of the phobic stimulus. Diagnosis is made only when the avoidance behavior interferes with social or occupational functioning. Affects ~10% of the population. Common phobias include fear of closed places (claustrophobia), fear of blood,

and fear of flying. Social phobia is distinguished by a specific fear of social or performance situations in which the individual is exposed to unfamiliar individuals or to possible examination and evaluation by others (e.g., having to converse at a party, use of public restrooms, meeting strangers).

TREATMENT

Phobic Disorders

- Agoraphobia is treated as for panic disorder.
- Beta blockers (e.g., propranolol, 20–40 mg PO 2 h before the event) are particularly effective in the treatment of “performance anxiety” (but not general social phobia).
- SSRIs and MAOIs are very helpful in treating social phobias.
- Social and simple phobias respond well to behaviorally focused psychotherapy.

Somatic Symptom Disorder

CLINICAL FEATURES Pts with multiple somatic complaints that cannot be explained by a known medical condition or by the effects of substances; seen commonly in primary care practice (prevalence of 5–7%). Pts may present with multiple physical complaints referable to different organ systems; pts with somatic symptom disorder can be impulsive and demanding. In *conversion disorder*, the symptoms involve voluntary motor or sensory function. In *factitious illnesses*, the pt consciously and voluntarily produces physical symptoms; the sick role is gratifying. *Munchausen's syndrome* refers to individuals with dramatic, chronic, or severe factitious illness. A variety of signs, symptoms, and diseases have been simulated in factitious illnesses; most common are chronic diarrhea, fever of unknown origin, intestinal bleeding, hematuria, seizures, and hypoglycemia. In *malingering*, the fabrication of illness derives from a desire for an external reward (narcotics, disability).

TREATMENT

Somatic Symptom Disorder

- Pts with somatic symptom disorder are usually subjected to multiple diagnostic tests and exploratory surgeries in an attempt to find their “real” illness. This approach is doomed to failure.
- Successful treatment is achieved through behavior modification, in which access to the physician is adjusted to provide a consistent, sustained, and predictable level of support that is not contingent on the pt's level of presenting symptoms or distress.
- Visits are brief, supportive, and structured and are not associated with a need for diagnostic or treatment action.
- Pts may benefit from antidepressant treatment.
- Consultation with a psychiatrist is essential.

PERSONALITY DISORDERS

Characteristic patterns of thinking, feeling, and interpersonal behavior that are relatively inflexible and cause significant functional impairment or subjective distress for the individual. Individuals with personality disorders are often regarded as “difficult pts.”

Three overlapping major categories of personality disorders; pts usually present with a combination of features.

■ CLUSTER A PERSONALITY DISORDERS

Includes individuals who are odd and eccentric and who maintain an emotional distance from others. The *paranoid* personality has pervasive mistrust and suspiciousness of others. The *schizoid* personality is interpersonally isolated, cold, and indifferent, while the *schizotypal* personality is eccentric and superstitious, with magical thinking and unusual perceptual experiences.

■ CLUSTER B PERSONALITY DISORDERS

Describe individuals whose behavior is impulsive, excessively emotional, and erratic. The *borderline* personality is impulsive and manipulative, with unpredictable and fluctuating intense moods and unstable relationships, a fear of abandonment, and occasional rage episodes. The *histrionic* pt is dramatic, engaging, seductive, and attention seeking. The *narcissistic* pt is self-centered and has an inflated sense of self-importance combined with a tendency to devalue or de-mean others, while pts with *antisocial* personality disorder use other people to achieve their own ends and engage in exploitative and manipulative behavior with no sense of remorse.

■ CLUSTER C PERSONALITY DISORDERS

Enduring traits are anxiety and fear. The *dependent* pt fears separation, tries to engage others to assume responsibility, and often has a help-rejecting style. Pts with *obsessive-compulsive* personality disorder are meticulous and perfectionistic but also inflexible and indecisive. *Avoidant* pts are anxious about social contact and have difficulty assuming responsibility for their isolation.

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Psychiatric Medications



Four major classes are commonly used in adults: (1) antidepressants (ADs), (2) anxiolytics, (3) antipsychotics, and (4) mood-stabilizing agents. All physicians should become familiar with one or two drugs in each of the first three classes so that the indications, dose range, efficacy, potential side effects, and interactions with other medications are well known.

GENERAL PRINCIPLES OF USE

1. Most treatment failures are due to undermedication and impatience. For a proper medication trial to take place, an effective dose must be taken for an adequate amount of time. For ADs, antipsychotics, and mood stabilizers, full effects may take weeks or months to occur.
2. History of a positive response to a medication usually indicates that a response to the same drug will occur again. A family history of a positive response to a specific medication is also useful.
3. Pts who fail to respond to one drug will often respond to another in the same class; one should attempt another trial with a drug that has a different mechanism of action or a different chemical structure. Treatment failures should be referred to a psychiatrist, as should all pts with psychotic symptoms or who require mood stabilizers.

4. Avoid polypharmacy; a pt who is not responding to standard monotherapy requires referral to a psychiatrist.
5. Pharmacokinetics may be altered in the elderly, with smaller volumes of distribution, reduced renal and hepatic clearance, longer biologic half-lives, and greater potential for CNS toxicity. The rule with elderly pts is to “start low and go slow.”
6. Never stop treatment abruptly, especially true for ADs and anxiolytics. In general, medications should be slowly tapered and discontinued over 2–4 weeks.
7. Review possible side effects each time a drug is prescribed; educate pts and family members about side effects and need for patience in awaiting a response.

ANTIDEPRESSANTS

Useful to group according to known actions on CNS monoaminergic systems (Table 200-1). The selective serotonin reuptake inhibitors (SSRIs) have predominant effects on serotonergic neurotransmission, also reflected in side-effect profile. The TCAs, or tricyclic ADs, affect noradrenergic and, to a lesser extent, serotonergic neurotransmission but also have anticholinergic and antihistaminic effects. Venlafaxine, desvenlafaxine, duloxetine, mirtazapine, vilazodone, vortioxetine, and levomilnacipran have mixed noradrenergic and serotonergic effects. Bupropion is a novel AD that enhances noradrenergic function. Trazodone and amoxapine have mixed effects on serotonin receptors and on other neurotransmitter systems. The monoamine oxidase inhibitors (MAOIs) inhibit monoamine oxidase, the primary enzyme responsible for the degradation of monoamines in the synaptic cleft.

ADs are effective against major depression, particularly when neurovegetative symptoms and signs are present. Despite the widespread use of SSRIs, there is no convincing evidence that they are more efficacious than TCAs, although their safety profile in overdose is more favorable than that of the TCAs. ADs are also useful in treatment of panic disorder, posttraumatic stress disorder, chronic pain syndromes, and generalized anxiety disorder. The TCA clomipramine and the SSRIs successfully treat obsessive-compulsive disorder.

All ADs require at least 2 weeks at a therapeutic dose before clinical improvement is observed. All ADs also have the potential to trigger a manic episode or rapid cycling when given to a pt with bipolar disorder. The MAOIs must not be prescribed concurrently with other ADs or with narcotics, as potentially fatal reactions may occur. “Withdrawal syndromes” usually consisting of malaise can occur when ADs are stopped abruptly.

ANXIOLYTICS

Benzodiazepines bind to sites on the γ -aminobutyric acid receptor and are cross-tolerant with alcohol and with barbiturates. Four clinical properties: (1) sedative, (2) anxiolytic, (3) skeletal muscle relaxant, and (4) antiepileptic. Individual drugs differ in terms of potency, onset of action, duration of action (related to half-life and presence of active metabolites), and metabolism (Table 200-2). Benzodiazepines have additive effects with alcohol; like alcohol, they can produce tolerance and physiologic dependence, with serious withdrawal syndromes (tremors, seizures, delirium, and autonomic hyperactivity) if discontinued too quickly, especially for those with short half-lives.

Buspirone is a nonbenzodiazepine anxiolytic that is nonsedating, is not cross-tolerant with alcohol, and does not induce tolerance or dependence. It requires at least 2 weeks at therapeutic doses to achieve full effects.

TABLE 200-1 Antidepressants

NAME	USUAL DAILY DOSE, mg	SIDE EFFECTS	COMMENTS
SSRIs			
Fluoxetine (Prozac)	10–80	Headache; nausea and other GI effects; jitteriness; insomnia; sexual dysfunction; can affect plasma levels of other medicines (except sertraline); akathisia rare	Once-daily dosing, usually in the morning; fluoxetine has very long half-life; must not be combined with MAOIs
Sertraline (Zoloft)	50–200		
Paroxetine (Paxil)	20–60		
Fluvoxamine (Luvox)	100–300		
Citalopram (Celexa)	20–60		
Escitalopram (Lexapro)	10–30		
TCAs and tetracyclics			
Amitriptyline (Elavil)	150–300	Anticholinergic (dry mouth, tachycardia, constipation, urinary retention, blurred vision); sweating; tremor; postural hypotension; cardiac conduction delay; sedation; weight gain	Once-daily dosing, usually qhs; blood levels of most TCAs available; can be lethal in overdose (lethal dose = 2 g); nortriptyline best tolerated, especially by elderly FDA approved for OCD
Nortriptyline (Pamelor)	50–200		
Imipramine (Tofranil)	150–300		
Desipramine (Norpramin)	150–300		
Doxepin (Sinequan)	150–300		
Clomipramine (Anafranil)	150–300		
Maprotiline (Ludiomil)	25–150		

(Continued)

TABLE 200-1 Antidepressants (Continued)

NAME	USUAL DAILY DOSE, mg	SIDE EFFECTS	COMMENTS
Mixed norepinephrine/serotonin reuptake inhibitors (SNRI) and receptor blockers			
Venlafaxine (Effexor)	75–375	Nausea; dizziness; dry mouth; headaches; increased blood pressure; anxiety and insomnia	Bid-tid dosing (extended release available); lower potential for drug interactions than SSRIs; contraindicated with MAOIs
Desvenlafaxine (Pristiq)	50–400	Nausea, dizziness, insomnia	Primary metabolite of venlafaxine; no increased efficacy with higher dosing
Duloxetine (Cymbalta)	40–60	Nausea, dizziness, headache, insomnia, constipation	May have utility in treatment of neuropathic pain and stress incontinence
Mirtazapine (Remeron)	15–45	Somnolence, weight gain; neutropenia rare	Once-a-day dosing
Vilazodone (Viibryd)	40	Nausea, diarrhea, headache; dosage adjustment if given with CYP3A4 inhibitor/stimulator	Also 5-HT _{1a} receptor partial agonist
Vortioxetine (Brintellix)	5–20	Nausea, diarrhea, sweating, headache; low incidence of sedation or weight gain	No specific p450 effects; 5-HT _{3a} and 5-HT ₇ receptor antagonist, 5-HT _{1b} partial agonist, and 5-HT _{1a} agonist
Levomilnacipran (Fetzima)	40–120	Nausea, constipation, sweating; rare increase in blood pressure/pulse	Most noradrenergic of SNRIs
Mixed-action drugs			
Bupropion (Wellbutrin)	250–450	Jitteriness; flushing; seizures in at-risk pts; anorexia; tachycardia; psychosis	Tid dosing, but sustained release also available; fewer sexual side effects than SSRIs or TCAs; may be useful for adult ADD
Trazodone (Desyrel)	200–600	Sedation; dry mouth; ventricular irritability; postural hypotension; priapism rare	Useful in low doses for sleep because of sedating effects with no anticholinergic side effects

Trazodone extended release (Olepro)	150–375	Daytime somnolence, dizziness, nausea	
Amoxapine (Asendin)	200–600	Sexual dysfunction	Lethality in overdose; EPS possible
MAOIs			
Phenelzine (Nardil)	45–90	Insomnia; hypotension; edema; anorgasmia; weight gain; neuropathy; hypertensive crisis; toxic reactions with SSRIs; narcotics	May be more effective in pts with atypical features or treatment-refractory depression
Tranlycypromine (Parnate)	20–50		
Isocarboxazid (Marplan)	20–60		Less weight gain and hypotension than phenelzine
Transdermal selegiline (Emsam)	6–12	Local skin reaction hypertension	No dietary restrictions with 6-mg dose

Abbreviations: ADD, attention deficit disorder; EPS, extrapyramidal symptoms; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; MAOIs, monoamine oxidase inhibitors; OCD, obsessive-compulsive disorder; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

TABLE 200-2 Anxiolytics

NAME	EQUIVALENT PO DOSE, mg	ONSET OF ACTION	HALF-LIFE, h	COMMENTS
Benzodiazepines				
Diazepam (Valium)	5	Fast	20–70	Active metabolites; quite sedating
Flurazepam (Dalmane)	15	Fast	30–100	Flurazepam is a prodrug; metabolites are active; quite sedating
Triazolam (Halcion)	0.25	Intermediate	1.5–5	No active metabolites; can induce confusion and delirium, especially in elderly
Lorazepam (Ativan)	1	Intermediate	10–20	No active metabolites; direct hepatic glucuronide conjugation; quite sedating; FDA approved for anxiety with depression
Alprazolam (Xanax)	0.5	Intermediate	12–15	Active metabolites; not too sedating; FDA approved for panic disorder and anxiety with depression; tolerance and dependence develop easily; difficult to withdraw
Chlordiazepoxide (Librium)	10	Intermediate	5–30	Active metabolites; moderately sedating
Oxazepam (Serax)	15	Slow	5–15	No active metabolites; direct glucuronide conjugation; not too sedating
Temazepam (Restoril)	15	Slow	9–12	No active metabolites; moderately sedating
Clonazepam (Klonopin)	0.5	Slow	18–50	No active metabolites; moderately sedating; FDA approved for panic disorder
Clorazepate (Tranxene)	15	Fast	40–200	Low sedation; unreliable absorption
Nonbenzodiazepines				
Buspirone (BuSpar)	7.5	2 weeks	2–3	Active metabolites; tid dosing—usual daily dose 10–20 mg tid; nonsedating; no additive effects with alcohol; useful for controlling agitation in demented or brain-injured pts

Abbreviation: FDA, U.S. Food and Drug Administration.

ANTIPSYCHOTIC MEDICATIONS

These include the first-generation (typical) neuroleptics, which act by blocking dopamine D_2 receptors, and the second-generation (atypical) neuroleptics, which act on dopamine, serotonin, and other neurotransmitter systems. Some antipsychotic effect may occur within hours or days of initiating treatment, but full effects usually require 6 weeks to several months of daily, therapeutic dosing.

■ FIRST-GENERATION ANTIPSYCHOTICS

Useful to group into high-, mid-, and low-potency neuroleptics (Table 200-3). High-potency neuroleptics are least sedating, have almost no anticholinergic side effects, and have a strong tendency to induce extrapyramidal side effects (EPSEs). The EPSEs occur within several hours to several weeks of beginning treatment and include acute dystonias, akathisia, and pseudo-parkinsonism. Extrapyramidal symptoms respond well to trihexyphenidyl, 2 mg twice daily, or benztropine mesylate, 1–2 mg twice daily. Akathisia may respond to beta blockers. Low-potency neuroleptics are very sedating, may cause orthostatic hypotension, are anticholinergic, and tend not to induce EPSEs frequently.

Up to 20% of pts treated with conventional antipsychotic agents for >1 year develop tardive dyskinesia (probably due to dopamine receptor supersensitivity), an abnormal involuntary movement disorder most often observed in the face and distal extremities. Treatment includes gradual withdrawal of the neuroleptic, with possible switch to a novel neuroleptic; anticholinergic agents can worsen the disorder. Valbenazine, a vesicular monoamine transporter 2 inhibitor that depletes presynaptic dopamine, has recently received FDA approval for treatment of tardive dyskinesia.

Rarely, pts exposed to neuroleptics develop neuroleptic malignant syndrome (NMS), a life-threatening complication with a mortality rate as high as 25%; hyperpyrexia, autonomic hyperactivity, muscle rigidity, obtundation, and agitation are characteristics associated with increased WBC, increased creatine phosphokinase, and myoglobinuria. Treatment involves immediate discontinuation of neuroleptics, supportive care, and use of dantrolene and bromocriptine.

■ SECOND-GENERATION ANTIPSYCHOTICS

A class of agents that has become the first line of treatment (Table 200-3); efficacious in treatment-resistant pts, tend not to induce EPSEs or tardive dyskinesia, and appear to have uniquely beneficial properties on negative symptoms and cognitive dysfunction. Main problem is side effect of weight gain (most prominent with clozapine and in olanzapine; can induce diabetes). The CATIE study, a large-scale investigation of antipsychotic agents in the “real world,” revealed a high rate of discontinuation of all medications over 18 months; olanzapine was modestly more effective than other agents but with a higher discontinuation rate due to side effects.

MOOD-STABILIZING AGENTS

Four mood stabilizers in common use: lithium, valproic acid, carbamazepine/oxcarbazepine, and lamotrigine (Table 200-4). Lithium is the gold standard and the best studied, and along with carbamazepine and valproic acid, is used for treatment of acute manic episodes; 1–2 weeks to reach full effect. As prophylaxis, the mood stabilizers reduce frequency and severity of both manic and depressed episodes in cyclical mood disorders. In refractory bipolar disorder, combinations of mood stabilizers may be beneficial.

TABLE 200-3 Antipsychotic Agents

NAME	USUAL PO DAILY DOSE, mg	SIDE EFFECTS	SEDATION	COMMENTS
First-generation antipsychotics				
Low potency				
Chlorpromazine (Thorazine)	100–1000	Anticholinergic effects; orthostasis; photosensitivity; cholestasis; QT prolongation	+++	EPSEs usually not prominent; can cause anticholinergic delirium in elderly pts
Thioridazine (Mellaril)	100–600			
Midpotency				
Trifluoperazine (Stelazine)	2–50	Fewer anticholinergic side effects	++	Well tolerated by most pts
Perphenazine (Trilafon)	4–64	Fewer EPSEs than with higher potency agents	++	
Loxapine (Loxitane)	30–100	Frequent EPSEs	++	
Molindone (Moban)	30–100	Frequent EPSEs	0	Little weight gain
High potency				
Haloperidol (Haldol)	5–20	No anticholinergic side effects; EPSEs often prominent	0/+	Often prescribed in doses that are too high; long-acting injectable forms of haloperidol and fluphenazine available
Fluphenazine (Prolixin)	1–20	Frequent EPSEs	0/+	
Thiothixene (Navane)	2–50	Frequent EPSEs	0/+	
Second-generation antipsychotics				
Clozapine (Clozaril)	150–600	Agranulocytosis (1%); weight gain; seizures; drooling; hyperthermia	++	Requires weekly WBC count for first 6 months, then biweekly if stable
Risperidone (Risperdal)	2–8	Orthostasis	+	Requires slow titration; EPSEs observed with doses >6 mg qd
Olanzapine (Zyprexa)	10–30	Weight gain	++	Mild prolactin elevation
Quetiapine (Seroquel)	350–800	Sedation; weight gain; anxiety	+++	Bid dosing

Ziprasidone (Geodon)	120–200	Orthostatic hypotension	+ / ++	Minimal weight gain; increases QT interval
Aripiprazole (Abilify)	10–30	Nausea, anxiety, insomnia	0 / +	Mixed agonist/antagonist; ER available
Paliperidone (Invega)	3–12	Restlessness, EPSEs, increased prolactin, headache	+	Active metabolite of risperidone
lloperidone (Fanapt)	12–24	Dizziness, hypotension	0 / +	Requires dose titration; long-acting injectable available
Asenapine (Saphris)	10–20	Dizziness, anxiety, EPSEs, minimal weight gain	++	Sublingual tablets; bid dosing
Lurasidone (Latuda)	40–80	Nausea, EPSEs	++	Uses CYP3A4
Brexipiprazole (Rexulti)	1–4	Anxiety, dizziness, fatigue	++	CYP3A4 and 2D6 interactions
Pimavanserin (Nuplazid)	34	Edema, confusion, sedation	++	Approved for Parkinson's disease psychosis
Cariprazine (Vraylar)	1.5–6	EPSEs, vomiting	++	Preferential D3 receptor affinity

Abbreviations: EPSEs, extrapyramidal side effects; WBC, white blood cell.

TABLE 200-4 Clinical Pharmacology of Mood Stabilizers

AGENT AND DOSING	SIDE EFFECTS AND OTHER EFFECTS
Lithium Starting dose: 300 mg bid or tid Therapeutic blood level: 0.8–1.2 meq/L	Common Side Effects Nausea/anorexia/diarrhea, fine tremor, thirst, polyuria, fatigue, weight gain, acne, folliculitis, neutrophilia, hypothyroidism Blood level is increased by thiazides, tetracyclines, and NSAIDs Blood level is decreased by bronchodilators, verapamil, and carbonic anhydrase inhibitors <i>Rare side effects:</i> Neurotoxicity, renal toxicity, hypercalcemia, ECG changes
Valproic Acid Starting dose: 250 mg tid Therapeutic blood level: 50–125 µg/mL	Common Side Effects Nausea/anorexia, weight gain, sedation, tremor, rash, alopecia Inhibits hepatic metabolism of other medications <i>Rare side effects:</i> Pancreatitis, hepatotoxicity, Stevens-Johnson syndrome
Carbamazepine/Oxcarbazepine Starting dose: 200 mg bid for carbamazepine, 150 mg bid for oxcarbazepine Therapeutic blood level: 4–12 µg/mL for carbamazepine	Common Side Effects Nausea/anorexia, sedation, rash, dizziness/ataxia Carbamazepine, but not oxcarbazepine, induces hepatic metabolism of other medications <i>Rare side effects:</i> Hyponatremia, agranulocytosis, Stevens-Johnson syndrome
Lamotrigine Starting dose: 25 mg/d	Common Side Effects Rash, dizziness, headache, tremor, sedation, nausea <i>Rare side effect:</i> Stevens-Johnson syndrome

Abbreviations: ECG, electrocardiogram; NSAIDs, nonsteroidal anti-inflammatory drugs.

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Eating Disorders



■ DEFINITIONS AND EPIDEMIOLOGY

Feeding and eating disorders constitute a group of conditions in which there is persistent disturbance of eating or associated behaviors that significantly impair an individual's physical health or psychosocial functioning. *Anorexia nervosa* is characterized by restriction of caloric intake to a degree that body weight deviates significantly from age, gender, health, and developmental norms accompanied by a fear of gaining weight and an associated disturbance in body image. *Bulimia nervosa* is characterized by recurrent episodes of binge eating followed

by abnormal compensatory behaviors, such as self-induced vomiting, laxative abuse, or excessive exercise; weight is in the normal range or above. *Binge eating disorder* is similar to bulimia nervosa but lacks the compensatory behavior element.

Both anorexia nervosa and bulimia nervosa occur primarily among previously healthy young women who become overly concerned with body shape and weight. Binge eating and purging behavior may be present in both conditions, with the critical distinction between the two resting on the weight of the individual. In women, the lifetime prevalence of anorexia nervosa is up to 4% and of bulimia nervosa approximately 2%. There is at least a 10:1 female-to-male ratio for both conditions. Typically, the onset of anorexia is mid-adolescence and bulimia early adulthood. Both can occur later, but onset is uncommon after age 40.

These disorders are most common in postindustrialized and urbanized countries. Affected pts frequently exhibit perfectionist and obsessional tendencies and often have comorbid anxiety disorders. Pursuit of activities that emphasize thinness (ballet, modeling, distance running) is prevalent, as is a drive for high scholastic achievement. Risk factors are a family history of mood disturbance, childhood obesity, and psychological or physical abuse during childhood.

■ CLINICAL FEATURES

Anorexia Nervosa

- General: feeling cold
- Skin, hair, nails: alopecia, lanugo hair, acrocyanosis, edema
- Cardiovascular: bradycardia, hypotension
- Gastrointestinal: salivary gland enlargement, slow gastric emptying, constipation, elevated liver enzymes
- Hematopoietic: normochromic, normocytic anemia; leukopenia
- Fluid/electrolyte: increased blood urea nitrogen, increased creatinine, hyponatremia, hypokalemia. Hypokalemia can become life threatening.
- Endocrine: low luteinizing hormone and follicle-stimulating hormone with secondary amenorrhea, hypoglycemia, normal thyroid-stimulating hormone with low normal thyroxine, increased plasma cortisol, osteopenia

Bulimia Nervosa

- Gastrointestinal: salivary gland enlargement, dental erosion from gastric acid exposure
- Fluid/electrolyte: hypokalemia, hypochloremia, alkalosis (from vomiting), or acidosis (from laxative abuse)
- Other: callus or scar on dorsum of hand (from repeated scraping against teeth during induced vomiting)

TREATMENT

Eating Disorders

ANOREXIA NERVOSA

Maudsley family-based therapy is effective, with strict behavioral contingencies used when weight loss becomes critical. No pharmacologic intervention has proven to be specifically beneficial, but comorbid depression and anxiety should be treated. Weight gain should be undertaken gradually with a goal of 0.5–1 lb per week to prevent complications from rapid refeeding (fluid retention, congestive heart failure, acute gastric dilatation). Most individuals are able to achieve remission within 5 years of the original diagnosis.

BULIMIA NERVOSA

Effective treatment approaches include selective serotonin reuptake inhibitors (SSRIs) antidepressants, usually in combination with cognitive-behavioral, emotion regulation, or interpersonal-based psychotherapies.

■ PROGNOSIS

The prognosis of anorexia nervosa is variable, with some individuals recovering after a single episode, while others exhibit recurrent episodes or a chronic course. Untreated mortality is 5.1/1000 annually, the highest among psychiatric conditions. Bulimia nervosa has a more benign outcome but 10–15% will transition to anorexia.

202 Alcohol Use Disorder

Alcohol use disorder is defined as repeated alcohol-related difficulties in at least 2 of 11 life areas that cluster together in the same 12-month period ([Table 202-1](#)).

■ CLINICAL FEATURES

Lifetime risk for alcohol use disorder is 10–15% for men and 5–8% for women. Typically, the first major life problem from excessive alcohol use appears in early adulthood, followed by periods of exacerbation and remission. The course is

TABLE 202-1 *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Classification of Alcohol Use Disorder (AUD)*

Criteria

Two or more of the following items occurring in the same 12-month period must be endorsed for the diagnosis of an alcohol use disorder^a:

- Drinking resulting in recurrent failure to fulfill role obligations
- Recurrent drinking in hazardous situations
- Continued drinking despite alcohol-related social or interpersonal problems
- Tolerance
- Withdrawal, or substance use for relief/avoidance of withdrawal
- Drinking in larger amounts or for longer than intended
- Persistent desire/unsuccessful attempts to stop or reduce drinking
- Great deal of time spent obtaining, using, or recovering from alcohol
- Important activities given up/reduced because of drinking
- Continued drinking despite knowledge of physical or psychological problems caused by alcohol
- Alcohol craving

^aMild AUD: 2–3 criteria required; Moderate AUD: 4–5 items endorsed; Severe AUD: 6 or more items endorsed.

not hopeless; following treatment, between half and two-thirds of pts maintain abstinence for years and often permanently. If the alcoholic continues to drink, life span is shortened by an average of 10 years with leading causes of increased death stemming from enhanced rates of heart disease, cancer, accidents, or suicide.

Screening for alcoholism is important given its high prevalence. Standardized questionnaires can be helpful in busy clinical practices including the 10-item Alcohol Use Disorders Identification Test (AUDIT) (Table 202-2).

Routine medical care requires attention to potential alcohol-related illness and to alcoholism itself:

1. Neurologic: blackouts, seizures, delirium tremens (DTs), cerebellar degeneration, neuropathy, myopathy
2. GI: esophagitis, gastritis, pancreatitis, hepatitis, cirrhosis, GI hemorrhage
3. Cardiovascular: hypertension, cardiomyopathy
4. Hematologic: macrocytosis, folate deficiency, thrombocytopenia, leukopenia
5. Endocrine: gynecomastia, testicular atrophy, amenorrhea, infertility
6. Skeletal: fractures, osteonecrosis
7. Cancer: breast cancer, oral and esophageal cancers, rectal cancers

TABLE 202-2 The Alcohol Use Disorders Identification Test (AUDIT)^a

ITEM	5-POINT SCALE (LEAST TO MOST)
1. How often do you have a drink containing alcohol?	Never (0) to 4+ per week (4)
2. How many drinks containing alcohol do you have on a typical day?	1 or 2 (0) to 10+ (4)
3. How often do you have six or more drinks on one occasion?	Never (0) to daily or almost daily (4)
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never (0) to daily or almost daily (4)
5. How often during the last year have you failed to do what was normally expected from you because of drinking?	Never (0) to daily or almost daily (4)
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never (0) to daily or almost daily (4)
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never (0) to daily or almost daily (4)
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never (0) to daily or almost daily (4)
9. Have you or someone else been injured as a result of your drinking?	No (0) to yes, during the last year (4)
10. Has a relative, friend, doctor, or other health worker been concerned about your drinking or suggested that you should cut down?	No (0) to yes, during the last year (4)

^aThe AUDIT is scored by simply summing the values associated with the endorsed response. A score ≥ 8 may indicate harmful alcohol use.

Alcohol Intoxication

Alcohol is a CNS depressant that acts on receptors for γ -aminobutyric acid (GABA), the major inhibitory neurotransmitter in the nervous system. Behavioral, cognitive, and psychomotor changes can occur at blood alcohol levels as low as 0.02–0.04 g/dL, a level achieved after the ingestion of one or two typical drinks. “Legal intoxication” in most states is based on a blood alcohol concentration of 0.08 g/dL; levels twice this can lead to deep but disturbed sleep. Incoordination, tremor, ataxia, confusion, stupor, coma, and even death occur at progressively higher blood alcohol levels.

Alcohol Withdrawal

Chronic alcohol use produces CNS dependence, and the earliest sign of alcohol withdrawal is tremulousness (“shakes” or “jitters”), occurring 5–10 h after decreasing ethanol intake. This may be followed by generalized seizures in the first 24–48 h; these do not require initiation of antiseizure medications. With severe withdrawal, autonomic hyperactivity ensues (sweating, hypertension, tachycardia, tachypnea, fever), accompanied by insomnia, nightmares, anxiety, and GI symptoms.

Delirium Tremens (DTs)

A very severe withdrawal syndrome characterized by profound autonomic hyperactivity, extreme confusion, agitation, vivid delusions, and hallucinations (often visual and tactile) that begins 3–5 days after the last drink. Mortality is as high as 5%.

Wernicke’s Encephalopathy

An alcohol-related syndrome characterized by ataxia, ophthalmoplegia, and confusion, often with associated nystagmus, peripheral neuropathy, cerebellar signs, and hypotension; there is impaired short-term memory, inattention, and emotional lability. Wernicke-Korsakoff’s syndrome follows, characterized by anterograde and retrograde amnesia and confabulation. Wernicke-Korsakoff’s syndrome is caused by chronic thiamine deficiency, resulting in damage to thalamic nuclei, mammillary bodies, and brainstem and cerebellar structures.

LABORATORY FINDINGS

Include mild anemia with macrocytosis, folate deficiency, thrombocytopenia, granulocytopenia, abnormal liver function tests, hyperuricemia, and elevated triglycerides. Two blood tests with $\geq 60\%$ sensitivity and specificity for heavy alcohol consumption are γ -glutamyl transferase (GGT) (>35 U) and carbohydrate-deficient transferrin (CDT) (>20 U/L or $>2.6\%$); the combination of the two is likely to be more accurate than either alone. A variety of diagnostic studies may show evidence of alcohol-related organ dysfunction.

TREATMENT**Alcoholism****ACUTE WITHDRAWAL**

- Acute alcohol withdrawal is treated with multiple B vitamins including thiamine (50–100 mg IV or PO daily for ≥ 1 week) to replenish depleted stores; use the IV route if Wernicke-Korsakoff’s syndrome is suspected since intestinal absorption is unreliable in alcoholics.
- CNS depressant drugs are used when seizures or autonomic hyperactivity is present to halt the rapid state of withdrawal in the CNS and allow for a slower,

more controlled reduction of the substance. Low-potency benzodiazepines with long half-lives are preferred (e.g., diazepam 10 mg PO q4–6h, chlordiazepoxide 25–50 mg PO q4–6h on the first day and then decreased over the next 5 days) because they produce fairly steady blood levels of drug within a wide dose range. Risks include overmedication and oversedation, which occur less commonly with shorter-acting agents (e.g., oxazepam, lorazepam).

- In severe withdrawal or DTs, high doses of benzodiazepines are usually required. Fluid and electrolyte status and blood glucose levels should be closely followed. Cardiovascular and hemodynamic monitoring is crucial, as hemodynamic collapse and cardiac arrhythmia are not uncommon.
- Generalized withdrawal seizures rarely require aggressive pharmacologic intervention beyond that given to the usual pt undergoing withdrawal, i.e., adequate doses of benzodiazepines.

RECOVERY AND SOBRIETY

Counseling, Education, and Cognitive Approaches

- First, attempts should be made to help the alcoholic achieve and maintain a high level of motivation toward abstinence. These include education about alcoholism and instructing family and/or friends to stop protecting the person from the problems caused by alcohol.
- A second goal is to help the pt to readjust to life without alcohol and to reestablish a functional lifestyle through counseling, vocational rehabilitation, and self-help groups such as alcoholics anonymous (AA).
- A third component, called *relapse prevention education*, helps the pt to identify situations in which a return to drinking is likely, formulate ways of managing these risks or avoid the risky situation, and develop coping strategies that increase the chances of a return to abstinence quickly after an episode of drinking.
- There is no convincing evidence that inpatient rehabilitation is more effective than outpatient care.

Drug Therapy

Several medications may be useful in alcoholic rehabilitation; usually medications are continued for 6–12 months if a positive response is seen.

- The opioid-antagonist drug naltrexone (50–150 mg/d PO or monthly 380-mg injection) decreases the probability of a return to drinking and shortens periods of relapse.
 - A second medication, acamprosate (2 g/d divided into three oral doses), an *N*-methyl-D-aspartate receptor inhibitor, may be used; efficacy appears similar to naltrexone.
 - A combination of naltrexone and acamprosate may be superior to either drug alone, although not all studies agree.
 - Disulfiram (250 mg/d), an aldehyde dehydrogenase inhibitor, produces an unpleasant and potentially dangerous reaction in the presence of alcohol.
 - Additional drugs under investigation include another opioid antagonist nalmefene, the nicotinic receptor agonist varenicline, the serotonin antagonist ondansetron, the α -adrenergic agonist prazosin, the GABA_B receptor agonist baclofen, the anticonvulsant topiramate, and cannabinol receptor antagonists; few data yet offer solid support for their routine use in clinical settings.
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203 Narcotic Abuse



Narcotics, or opioids, are primarily used for pain management, but due to ease of availability individuals procure and misuse these drugs, with dire consequences including opioid use disorder and overdose. Nearly 4 million individuals in the United States are current misusers of pain relievers, and globally opioid misuse causes the greatest global burden of morbidity and mortality; disease transmission; increased health care, crime, and law enforcement costs; and less tangible costs of family distress and lost productivity.

Opioids bind to specific opioid receptors in the CNS and elsewhere in the body. These receptors mediate the opiate effects of analgesia, euphoria, respiratory depression, and constipation. Endogenous opiate peptides (enkephalins and endorphins) are natural ligands for the opioid receptors and play a role in analgesia, memory, learning, reward, mood regulation, and stress tolerance.

The prototypic opiates, morphine and codeine, are derived from the juice of the opium poppy. The semisynthetic drugs produced from morphine include hydromorphone (Dilaudid), diacetylmorphine (heroin), and oxycodone (OxyContin). The purely synthetic opioids and their cousins include meperidine, propoxyphene, diphenoxylate, fentanyl, buprenorphine, tramadol, methadone, and pentazocine. All produce analgesia and euphoria as well as physical dependence when taken in high enough doses for prolonged periods of time.

■ CLINICAL FEATURES

The diagnosis of opioid use disorder as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* requires the repeated use of the opiate while producing problems in two or more areas in a 12-month period. The areas include tolerance, withdrawal, use of greater amounts of opioids than intended, craving, and use despite adverse consequences. A striking recent aspect of illicit opioid use has been its marked increase as the gateway to illicit drugs in the United States. Since 2007, prescription opiates have surpassed marijuana as the most common illicit drug that adolescents initially use, although overall rates of opioid use are far lower than marijuana. The most commonly used opioids are diverted prescriptions for oxycodone and hydrocodone, followed by heroin and morphine, and—among health professionals—meperidine and fentanyl.

Acute Effects

All opiates have the following CNS effects: sedation, euphoria, decreased pain perception, decreased respiratory drive, and vomiting. In larger doses, markedly decreased respirations, bradycardia, pupillary miosis, stupor, and coma ensue. Additionally, the adulterants used to “cut” street drugs (quinine, phenacetin, strychnine, antipyrine, caffeine, powdered milk) can produce permanent neurologic damage, including peripheral neuropathy, amblyopia, myelopathy, and leukoencephalopathy; adulterants can also produce an “allergic-like” reaction characterized by decreased alertness, frothy pulmonary edema, and an elevation in blood eosinophil count.

Chronic Effects

Tolerance and withdrawal commonly occur with chronic daily use after 6–8 weeks depending on the dose and frequency; the ever-increasing amounts of drug needed to sustain euphoriant effects and avoid discomfort of withdrawal strongly reinforce dependence once started.

Withdrawal

Symptoms of opioid withdrawal begin 8–10 h after the last dose; lacrimation, rhinorrhea, yawning, and sweating appear first. Restless sleep followed by weakness, chills, gooseflesh (“cold turkey”), nausea and vomiting, muscle aches, and involuntary movements (“kicking the habit”), hyperpnea, hyperthermia, and hypertension occur in later stages. The acute course of withdrawal may last 7–10 days. A secondary phase of protracted abstinence lasts for 26–30 weeks, characterized by hypotension, bradycardia, hypothermia, mydriasis, and decreased responsiveness of the respiratory center to carbon dioxide.

Heroin users in particular tend to use opioids intravenously and are likely to be polydrug users, also using alcohol, sedatives, cannabinoids, and stimulants. In these situations the pt with opioid withdrawal might also be withdrawing from alcohol or sedatives, which might be more dangerous and more difficult to manage.

TREATMENT**Narcotic Abuse****OVERDOSE (SEE CHAP. 13)****Withdrawal**

- Principles of detoxification are to substitute a longer-acting, orally active, pharmacologically equivalent medication for the substance being used, stabilize the pt on that medication, and then gradually withdraw the substituted medication.
- Methadone (a full mu-opioid receptor agonist) or buprenorphine (a partial agonist) are most frequently used drugs for detoxification. Dose-tapering regimens for methadone range from 2–3 weeks to as long as 180 days, but this approach is controversial given the relative effectiveness of methadone maintenance and low success rates; the vast majority of pts relapse during or after the detoxification period, indicating the chronic and relapsing nature of opioid use disorder. Buprenorphine produces fewer withdrawal symptoms compared with methadone but does not appear to produce better outcomes.
- Several α_2 -adrenergic agonists have relieved opioid withdrawal and achieved detoxification by suppressing central noradrenergic activity. Clonidine and lofexidine are commonly used orally in three to four doses per day.
- Rapid opiate detoxification can be accomplished with naltrexone combined with an α_2 -adrenergic agonist. Completion rates are high. Ultrarapid opiate detoxification using anesthetics is an extension of this approach but is highly controversial due to medical risks including mortality.

OPIOID MAINTENANCE

- Methadone maintenance is widely used in management of opiate addiction. Methadone is a long-acting opioid optimally dosed at 80–150 mg/d (gradually increased over time).
- Buprenorphine can also be used. It has a low risk of unintentional overdose but efficacy is limited to pts who need equivalent of only 60–70 mg of methadone; many pts in methadone maintenance require higher doses up to 150 mg daily. Buprenorphine is combined with naloxone at a 4:1 ratio to reduce abuse potential. A subcutaneous buprenorphine implant that lasts up to 6 months is also available.

OPIATE ANTAGONISTS FOR OPIOID DEPENDENCE

- Rationale is that blocking the action of self-administered opioids should eventually extinguish the habit; poorly accepted by many pts.
- Naltrexone can be given three times a week (100- to 150-mg dose); pts must first be detoxified from opioids before starting naltrexone. A depot form for monthly injection is available and improves adherence and retention, and decreases opioid use.

DRUG-FREE PROGRAMS

- Medication-free treatments in inpatient, residential, or outpatient settings have poor 1- to 5-year outcomes compared with pharmacotherapy; exceptions are residential programs lasting 6–18 months, which require full immersion in a regimented system.

■ PREVENTION

Preventing opiate abuse is a critically important challenge for physicians. In the United States, sources of opiates for adolescents are most commonly family members, not drug dealers or the Internet. Except for the terminally ill, physicians should carefully monitor opioid drug use in pts, keeping doses as low as is practical and administering them over as short a period as the level of pain requires. Pts must dispose of any remaining opiates after treatment. Physicians must be vigilant regarding their own risk for opioid abuse and dependence, never prescribing these drugs for themselves.

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Cocaine and Other Commonly Used Drugs

Stimulants and hallucinogens have been used to induce euphoria and alter consciousness for centuries. Cocaine and marijuana are two of the most commonly used drugs today. Polydrug use involving concurrent use of several drugs with different pharmacologic effects is increasingly found. Sometimes one drug is used to enhance the effects of another, as with the combined use of cocaine and nicotine, or cocaine and heroin in methadone-maintained pts. Some forms of polydrug use, such as the combined use of IV heroin and cocaine, are especially dangerous and account for many hospital ER visits. Chronic drug use is associated with immune system dysfunction and increased vulnerability to infections, including risk for HIV infection. The concurrent use of cocaine and opiates (“speedball”) is frequently associated with needle sharing by people using drugs intravenously.

■ PSYCHOSTIMULANTS—PHARMACOKINETICS/ PHARMACODYNAMICS, NEUROBIOLOGY, AND EPIDEMIOLOGY

Cocaine

- A powerful stimulant drug made from the cocoa plant.
- Local anaesthetic, vasoconstrictor, and stimulant properties.
- A Schedule II drug, which means that it has high potential for abuse but can be administered by a physician for legitimate medical uses.

Cocaine salt is an acidic, water-soluble powder with a high melting point, used by snorting or sniffing intranasally or by dissolving it in water and injecting it intravenously. Freebase cocaine can be vaporized and inhaled, or crystallized and sold as crack or rock, which is also smoked or inhaled. Street dealers often dilute (or “cut”) cocaine with nonpsychoactive substances such as cornstarch, talcum powder, flour, or baking soda, or adulterate it to increase profits.

Smoked or inhaled cocaine reaches the brain quickly and produces a rapid and intense (yet transient) high, which enhances its addictive potential. Cocaine binds to the dopamine (DA) transporter and blocks DA reuptake, which increases synaptic levels of the monoamine neurotransmitters DA, norepinephrine (NE), and serotonin.

The National Survey on Drug Use and Health (NSDUH), in 2015 estimated that 1.9 million people (approximately 0.7% of the population) were current users of cocaine.

Methamphetamine

- A stimulant drug usually used as a white, bitter-tasting powder or a pill.
- Crystal methamphetamine can be inhaled/smoked, swallowed (pill), snorted, or injected after being dissolved in water or alcohol.

Methamphetamine has a similar structure to the DA, NE, serotonin, and vesicular monoamine transporters and reverses their endogenous function, resulting in release of monoamines from storage vesicles into the synapse.

Methamphetamine is more potent and more efficacious than amphetamine; pharmacokinetics and low cost often result in a chronic and continuous, high dose self-administered use pattern.

According to the NSDUH, approximately 897,000 people (0.3% of the population) aged ≥ 12 were current users of methamphetamine in 2015.

MDMA and Cathinones

- MDMA (3,4-methylenedioxymethamphetamine) is an illegal drug that has stimulant and psychedelic effects.
- Individuals experience increased physical and mental energy, distortions in time and perception, emotional warmth, empathy toward others, a general sense of well-being, decreased anxiety, and an enhanced enjoyment of tactile experience.
- Binds to serotonin transporters, increasing release of serotonin, NE, and DA.
- Usually taken orally in a tablet, capsule, or liquid form; effects last approximately 3–6 h.
- MDMA is a Schedule I drug, along with other substances, with no proven therapeutic value.

Adulteration of MDMA tablets with methamphetamine, ketamine, caffeine, the over-the-counter cough suppressant dextromethorphan, the diet drug ephedrine, and cocaine is common. MDMA is rarely used alone and is often mixed with other substances, such as alcohol and marijuana.

Cathinone is an alkaloid psychostimulant found in the *khât* (*Catha edulis*) plant. Actions are similar to amphetamines, and misusers are at increased risk for acute myocardial infarction and stroke, due to inotropic and chronotropic effects on the heart, vasospasm of coronary arteries, and catecholamine-induced platelet aggregation.

Prescribed Psychostimulants

Methylphenidate, amphetamine, and methamphetamine are psychostimulants approved in the United States for treatment of attention deficit hyperactivity disorder (ADHD), weight control, and narcolepsy. Phenylpropanolamine, a psychostimulant used primarily for weight control, was found to be related to hemorrhagic stroke in women and removed from the market in 2005.

Increased use of nonprescribed amphetamines or methylphenidate as a study aid among college students, and an energy and productivity booster for so-called “supermoms.” According to the NSDUH, of the 7.7 million people, aged ≥ 12 , who had a past year stimulant-use disorder (SUD) related to their use of illicit drugs, 0.4 million misused prescription stimulants.

■ PSYCHOSTIMULANTS—CLINICAL MANIFESTATIONS

All psychostimulants produce the same acute CNS effects: euphoria, increased energy/decreased fatigue, reduced need for sleep, decreased appetite, decreased distractibility, increased self-confidence and alertness, increased libido, and prolonged orgasm, independent of the specific psychostimulant or route of administration. Peripheral effects may include tremor, diaphoresis, hypertonia, tachypnea, hyperreflexia, and hyperthermia. Many of the effects are biphasic; for example, low doses improve psychomotor performance, while higher doses may cause tremors or convulsions. Alpha-adrenergically mediated cardiovascular effects are also biphasic, with low doses resulting in increased vagal tone and decreased heart rate, and high doses causing increased heart rate and blood pressure. Psychostimulant use can result in restlessness, irritability, and insomnia and, at higher doses, suspiciousness, repetitive stereotyped behaviors, and bruxism. Endocrine effects may include impotence, gynecomastia, menstrual function disruptions, and hyperprolactinemia.

Overdose presents as sympathetic nervous system overactivity with psychomotor agitation, hypertension, tachycardia, headache, and mydriasis, and can lead to convulsions, cerebral hemorrhage or infarction, cardiac arrhythmias or ischemia, respiratory failure, or rhabdomyolysis. It is a medical emergency; treatment is largely symptomatic and should occur in an intensive care or telemetry unit. Inhalation of crack cocaine that is vaporized at high temperatures can cause airway burns, bronchospasm and other symptoms of pulmonary disease. MDMA can raise body temperature and result in liver, kidney, or heart failure, or death.

Psychostimulants are often used with other drugs, including opioids and alcohol, whose CNS-depressant effects tend to attenuate psychostimulant-induced CNS stimulation.

Adulteration of psychostimulants, particularly cocaine, with other drugs is common and can have additional potential health consequences.

Withdrawal from psychostimulants often includes hypersomnia, increased appetite, and depressed mood. Acute withdrawal typically lasts 7–10 days, but residual symptoms, possibly associated with neurotoxicity, may persist for several months. Psychostimulant withdrawal is not thought to be a driver of ongoing use.

■ PSYCHOSTIMULANTS—SCREENING AND DIAGNOSIS

The Diagnostic and Statistical Manual of Psychiatric Disorders, 5th edition (DSM-5) defines a SUD as a pattern of use of amphetamine-type substances, cocaine, or other stimulants leading to clinically significant impairment or distress, as manifested by at least two of the following 11 problems within a 12-month period: taking larger amounts, or over a longer period of time, than intended; persistent desire or unsuccessful efforts to cut down or control; a great deal of time spent in activities necessary to obtain, use, or recover; craving; use resulting in failure to fulfill major role obligations; continued use, despite recurrent social or interpersonal problems; giving up social, occupational, or recreational activities; recurrent use in physically hazardous situations; continued use despite persistent or recurrent physical or psychological problems; tolerance; and withdrawal symptoms, or avoidance of withdrawal symptoms, by continued use.

TREATMENT**Psychostimulants****COCAINE ACUTE INTOXICATION**

First ensure a patent airway, breathing, and circulation. With cocaine use, succinylcholine is relatively contraindicated in rapid sequence intubation; consider rocuronium (1 mg/kg IV) or another nondepolarizing agent as an alternative. If psychomotor agitation occurs, rule out hypoglycemia and hypoxemia first and then administer benzodiazepines (e.g., diazepam 10 mg IV and then 5–10 mg IV every 3–5 min until agitation controlled). Benzodiazepines are usually sufficient to address cardiovascular side effects. Severe or symptomatic hypertension can be treated with phentolamine, nitroglycerin, or nitroprusside. Hyperthermic pts should be cooled with the goal to achieve a core body temperature of <102°F. Evaluation of chest pain should exclude myocardial infarction. Many instances of cocaine-related mortality have been associated with concurrent use of other illicit drugs (particularly heroin), thus the physician must be prepared to institute effective emergency treatment for multiple drug toxicities.

COAINE USE DISORDERS

Treatment of cocaine use disorders requires the combined efforts of primary care physicians, psychiatrists, and psychosocial care providers. Early abstinence often complicated by depression and guilt, insomnia, and anorexia, which can last for months or years after use has stopped.

Behavioral therapies are mainstay of treatment for stimulant-use disorders and show modest benefit. No approved medications exist for psychostimulant addiction.

HALLUCINOGENS

A diverse group of drugs causing alteration of thoughts, feelings, sensations, and perceptions. They include ayahuasca (a tea made from Amazonian plants containing *dimethyltryptamine* [DMT], the primary mind-altering ingredient); DMT (also known as Dimitri, can also be synthesized in a lab); *D-lysergic acid diethylamide* (LSD, clear or white odorless material made from lysergic acid found in rye and other grain fungus); peyote (mescaline, derived from a cactus or made synthetically); and *4-phosphoryloxy-N,N-dimethyltryptamine* (psilocybin, from South and North American mushrooms).

A subgroup of hallucinogens produces the added sensation of feeling out of control or disconnected from one's body or surroundings, these include: dextromethorphan (DXM, an over-the-counter cough suppressant, when used in high doses); ketamine (a human and veterinary anesthetic); phencyclidine (PCP, cyclohexylamine derivative and dissociative anesthetic); and *Salvia divinorum* (salvia, a Mexican, Central, and South American plant).

Hallucinogens are used in a wide variety of ways, including smoking, snorting, and transmucosally. Except for salvia, whose effects last 30 min, onset of action is within 20 to 90 min and the duration as long as 6–12 h. Hallucinogens disrupt the neurotransmitters serotonin and glutamate.

According to the NSDUH, in 2015, an estimated 1.2 million (0.5%) of people aged ≥12 reported current hallucinogen use. The highest rates were among young adults aged 18–25, with 1.8% (636,000) young adults reporting current use.

Clinical manifestations include hallucinations, intensified feelings, heightened sensory experiences, and time perturbations. Additional physiologic responses

include nausea, increased heart rate, blood pressure, respiratory rate, or body temperature, loss of appetite, xerostomia, sleep problems, synesthesia, impaired coordination, and hyperhidrosis. “Bad trips” (negative experiences with hallucinogen use) can include panic, paranoia, and psychosis, and may persist for up to 24 h. Such experiences are best treated with supportive reassurance. Some evidence that chronic effects of hallucinogen use can occur, including persistent psychosis, memory loss, anxiety, depression, and flashbacks.

No approved medications exist for treatment of hallucinogen addiction.

■ MARIJUANA

Marijuana policies in several states in the United States have legalized marijuana for medical and/or recreational use. Marijuana refers to the dried leaves, flowers, stems, and seeds from the hemp plant, *Cannabis sativa*. Delta-9-tetrahydrocannabinol (THC) is the main psychoactive chemical, responsible for most of the intoxicating effects. Stronger forms of marijuana include sinsemilla (from specially tended female plants) and concentrated resins, including honey-like *hash oil*, waxy *budder*, and hard amberlike *shatter*.

When smoked, marijuana is quickly absorbed from the lungs into the blood and then sequestered in tissues and metabolized by the liver.

Can also be baked into foods (edibles) and eaten with a resulting slower onset of action of 30–60 min.

Cannabinoid receptors (CB₁ and CB₂) have been identified in the CNS (cerebral cortex, basal ganglia, and hippocampus) and PNS, as well as on T and B lymphocytes.

Cannabinoid effects occur in the limbic system, impacting the reward pathway and areas of pain perception. Effects include altered senses, altered sense of time, laughter, changes in mood, psychomotor retardation, difficulty with thinking and problem-solving, and impaired memory.

Marijuana is the most commonly used illicit drug in the United States, with 22.2 million (8.3%) current marijuana users aged ≥12 (i.e., users in the past 30 days). ER visits involving marijuana have increased, which may be due to increased THC levels resulting in a greater chance of a harmful reaction.

Acute intoxication brings a perceived sense of relaxation and mild euphoria, accompanied by impairment in memory, concentration, judgement, and perceptual and psychomotor function, as well as anxiety, paranoia, and rarely, psychosis. Physical signs of marijuana use include conjunctival injection and tachycardia. Adverse effects include respiratory problems due to inhaled pulmonary irritants and lower birth weights in pregnancy.

Chronic marijuana use may also have adverse psychological effects, which may not be permanent, such as impaired concentration and learning, insomnia, and worsening symptoms in schizophrenia. Upon cessation, or cutting back, there is evidence of a withdrawal syndrome consisting of irritability, insomnia, anorexia, anxiety, and craving. Individuals who begin marijuana use at age <17 may be more prone to cognitive deficits, and may be at higher risk for future polydrug addiction.

No approved medications exist for marijuana use disorder. Behavioral therapies and symptomatic treatment of withdrawal, for example selective serotonin reuptake inhibitors (SSRIs) to treat anxiety, may be effective.

Therapeutic use of marijuana includes as an antiemetic in chemotherapy, appetite promotor in AIDS, intraocular pressure reducer in glaucoma, and spasticity reducer in multiple sclerosis and other neurologic disorders.

- National Institute on Drug Abuse, <https://www.drugabuse.gov/drugs-abuse>

205

Routine Disease Screening



A primary goal of health care is to prevent disease or to detect it early enough that interventions will be more effective. The ultimate goal of preventive strategies is to avoid premature death. However, as longevity has increased dramatically worldwide over the last century (largely as a result of public health practices), increasing emphasis is placed on prevention for the purpose of preserving quality of life and extending the healthspan, not just the life span. Focusing on health promotion, rather than just disease prevention, may also provide greater motivation for pts to pursue lifestyle changes or adhere to clinician recommendations. Empowering pts with strategies to achieve positive health goals after discussing risks (i.e., smoking) can provide more effective adherence and better long-term outcomes.

In general, screening is most effective when applied to relatively common disorders that carry a large disease burden and have a long latency period. Early detection of disease has the potential to reduce both morbidity and mortality; however, screening asymptomatic individuals carries some risk. False-positive results can lead to unnecessary laboratory tests and invasive procedures and can increase pt anxiety. Several measurements have been derived to better assess the potential gain from screening and prevention interventions:

- Number of subjects needed to be screened to alter the outcome in one individual
- Absolute impact of screening on disease (e.g., lives saved per thousand screened)
- Relative impact of screening on disease outcome (e.g., the % reduction in deaths)
- The cost per year of life saved
- The increase in average life expectancy for a population

As part of a routine health care examination, history should include medication use, allergies, vaccination history, dietary history, use of alcohol and tobacco, sexual practices, safety practices (seat belt and helmet use, gun possession), and a thorough family history. Routine measurements should include assessments of height, weight, body-mass index, and blood pressure. Screening should also be considered for domestic violence and depression.

Counseling by health care providers should be performed at health care visits. Tobacco and alcohol use, diet, and exercise represent the vast majority of factors that influence preventable deaths. While behavioral changes are frequently difficult to achieve, it should be emphasized that studies show even brief (<5 min) tobacco counseling by physicians results in a significant rate of long-term smoking cessation. Instruction about self-examination (e.g., skin, breast, testicular) should also be provided during preventative visits.

The top causes of age-specific mortality and corresponding preventative strategies are listed in [Table 205-1](#). Formal recommendations from the U.S. Preventive Services Task Force are listed in [Table 205-2](#).

In addition to the general recommendations applicable to all persons, screening for specific diseases and preventive measures need to be individualized based on family history, travel history, or occupational history. For example, when there is a significant family history of breast, colon, or prostate cancer, it is

TABLE 205-1 Age-Specific Causes of Mortality and Corresponding Preventive Options

AGE GROUP	LEADING CAUSES OF AGE-SPECIFIC MORTALITY	SCREENING PREVENTION INTERVENTIONS TO CONSIDER FOR EACH SPECIFIC POPULATION
15–24	<ol style="list-style-type: none"> 1. Accident 2. Homicide 3. Suicide 4. Malignancy 5. Heart disease 	<ul style="list-style-type: none"> • Counseling on routine seat belt use, bicycle/motorcycle/ATV helmets (1) • Counseling on diet and exercise (5) • Discuss dangers of alcohol use while driving, swimming, boating (1) • Assess and update vaccination status (tetanus, diphtheria, hepatitis B, MMR, rubella, varicella, meningitis, HPV) • Ask about gun use and/or gun possession (2,3) • Assess for substance abuse history including alcohol (2,3) • Screen for domestic violence (2,3) • Screen for depression and/or suicidal/homicidal ideation (2,3) • Pap smear for cervical cancer screening after age 21 (4) • Discuss skin, breast awareness, and testicular self-examinations (4) • Recommend UV light avoidance and regular sunscreen use (4) • Measurement of blood pressure, height, weight, and body mass index (5) • Discuss health risks of tobacco use, consider emphasis on cosmetic and economic issues to improve quit rates for younger smokers (4,5) • Chlamydia and gonorrhea screening and contraceptive counseling for sexually active females, discuss STD prevention • Hepatitis B, and syphilis testing if there is high-risk sexual behavior(s) or any prior history of sexually transmitted disease • HIV testing • Continue annual influenza vaccination

(Continued)

TABLE 205-1 Age-Specific Causes of Mortality and Corresponding Preventive Options (Continued)

AGE GROUP	LEADING CAUSES OF AGE-SPECIFIC MORTALITY	SCREENING PREVENTION INTERVENTIONS TO CONSIDER FOR EACH SPECIFIC POPULATION
25–44	<ol style="list-style-type: none"> 1. Accident 2. Malignancy 3. Heart disease 4. Suicide 5. Homicide 6. HIV 	<p><i>As above plus consider the following:</i></p> <ul style="list-style-type: none"> • Readdress smoking status, encourage cessation at every visit (2,3) • Obtain detailed family history of malignancies and begin early screening/prevention program if pt is at significant increased risk (2) • Assess all cardiac risk factors (including screening for diabetes and hyperlipidemia) and consider primary prevention with aspirin for pts at >3% 5-year risk of a vascular event (3) • Assess for chronic alcohol abuse, risk factors for viral hepatitis, or other risks for development of chronic liver disease • Consider individualized breast cancer screening with mammography at age 40 (2)
45–64	<ol style="list-style-type: none"> 1. Malignancy 2. Heart disease 3. Accident 4. Diabetes mellitus 5. Cerebrovascular disease 6. Chronic lower respiratory disease 7. Chronic liver disease and cirrhosis 8. Suicide 	<ul style="list-style-type: none"> • Consider prostate cancer screen with annual PSA and digital rectal examination at age 50 (or possibly earlier in African Americans or pts with family history) (1) • Begin colorectal cancer screening at age 50 with fecal occult blood testing, flexible sigmoidoscopy, or colonoscopy (1) • Reassess and update vaccination status at age 50 and vaccinate all smokers against <i>S. pneumoniae</i> at age 50 (6) • Consider screening for coronary disease in higher-risk pts (2,5) • Consider screening for hepatitis C in adults born between 1945 and 1965 (7) • Zoster vaccination at age 60 • Begin mammography screening by age 50

(Continued)

TABLE 205-1 Age-Specific Causes of Mortality and Corresponding Preventive Options (Continued)

AGE GROUP	LEADING CAUSES OF AGE-SPECIFIC MORTALITY	SCREENING PREVENTION INTERVENTIONS TO CONSIDER FOR EACH SPECIFIC POPULATION
≥65	<ol style="list-style-type: none"> Heart disease Malignancy Cerebrovascular disease Chronic lower respiratory disease Alzheimer's disease Influenza and pneumonia Diabetes mellitus Kidney disease Accidents Septicemia 	<p>As above plus consider the following:</p> <ul style="list-style-type: none"> Readdress smoking status, encourage cessation at every visit (1,2,3,4) One-time ultrasound for AAA in men 65–75 who have ever smoked Consider pulmonary function testing for all long-term smokers to assess for development of chronic obstructive pulmonary disease (4,6) Screen all postmenopausal women (and all men with risk factors) for osteoporosis Continue annual influenza vaccination and vaccinate against <i>S. pneumoniae</i> at age 65 (4,6) Screen for visual and hearing problems, home safety issues, and elder abuse (9)

Note: The numbers in parentheses refer to areas of risk in the mortality column affected by the specified intervention.

Abbreviations: AAA, abdominal aortic aneurysm; ATV, all-terrain vehicle; HPV, human papillomavirus; MMR, measles-mumps-rubella; PSA, prostate-specific antigen; STD, sexually transmitted disease; UV, ultraviolet.

TABLE 205-2 Screening Tests Recommended by the U.S. Preventive Services Task Force for Average-Risk Adults

DISEASE	TEST	POPULATION	FREQUENCY
Abdominal aortic aneurysm	Ultrasound	Men 65–75 who have ever smoked	Once
Alcohol misuse	Alcohol Use Disorders Identification Test	All adults	Unknown
Breast cancer	Mammography with or without clinical breast examination	Women 50–75	Every 2 years
Cervical cancer	Pap smear	Women 21–65	Every 3 years
	Pap smear and HPV testing	Women 30–65	Every 5 years if HPV negative
Chlamydia/gonorrhea	Nucleic acid amplification test on urine or cervical swab	Sexually active women <25	Unknown

(Continued)

TABLE 205-2 Screening Tests Recommended by the U.S. Preventive Services Task Force for Average-Risk Adults (Continued)

DISEASE	TEST	POPULATION	FREQUENCY
Colorectal cancer	Fecal occult blood testing	50–75	Every year
	Sigmoidoscopy	50–75	Every 5 years
	Colonoscopy (or occult blood testing combined with sigmoidoscopy)	50–75	Every 10 years
Depression	Screening questions	All adults	Periodically
Diabetes	Fasting blood glucose or HgbA1c	Adults overweight, obese, or with hypertension	Every 3 years
Hepatitis C	Anti-HCV antibody followed by confirmatory PCR	Adults born between 1945 and 1965	Once
HIV	Reactive immunoassay or rapid HIV followed by confirmatory test	15–65	At least once
Hyperlipidemia	Cholesterol	40–75	Unknown
Hypertension	Blood pressure	All adults	Periodically
Intimate partner violence	Screening questions	Women of childbearing age	Unknown
Obesity	Body mass index	All adults	Unknown
Osteoporosis	DEXA	Women >65 or >60 with risk factors	Unknown

Abbreviations: DEXA, dual-energy x-ray absorptiometry; HCV, hepatitis C virus; HPV, human papillomavirus; PCR, polymerase chain reaction.

Source: Adapted from the U.S. Preventive Services Task Force 2017. www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/.

prudent to initiate screening about 10 years before the age at which the youngest family member developed cancer.

Specific recommendations for disease prevention can also be found in subsequent chapters on “Cardiovascular Disease Prevention” (Chap. 207), “Prevention and Early Detection of Cancer” (Chap. 208), “Smoking Cessation” (Chap. 209), and “Women’s Health” (Chap. 210).

206 Vaccines



- Vaccines are unrivaled in the twenty-first century for their effects on longevity, economic savings, and quality of life.
 - Although most vaccines developed in the twentieth century targeted common acute infectious diseases of childhood, more recently developed vaccines prevent chronic conditions prevalent among adults (e.g., human papillomavirus vaccines for cervical and anogenital cancers, herpes zoster vaccine).

Recommended immunization schedule for adults aged 19 years or older by age group, United States, 2018

This figure should be reviewed with the accompanying footnotes. This figure and the footnotes describe indications for which vaccines, if not previously administered, should be administered unless noted otherwise.

Vaccine	19–21 years	22–26 years	27–49 years	50–64 years	≥65 years
Influenza ¹	1 dose annually				
Tdap ² or Td ²	1 dose Tdap, then Td booster every 10 yrs				
MMR ³	1 or 2 doses depending on indication (if born in 1957 or later)				
VAR ⁴	2 doses				
RZV ⁵ (preferred) or ZVL ⁵					2 doses RZV (preferred) or 1 dose ZVL
HPV–Female ⁶	2 or 3 doses depending on age at series initiation				
HPV–Male ⁶	2 or 3 doses depending on age at series initiation				
PCV13 ⁷	1 dose				
PPSV23 ⁷	1 or 2 doses depending on indication				1 dose
HepA ⁸	2 or 3 doses depending on vaccine				
HepB ⁹	3 doses				
MenACWY ¹⁰	1 or 2 doses depending on indication, then booster every 5 yrs if risk remains				
MenB ¹⁰	2 or 3 doses depending on vaccine				
Hib ¹⁰	1 or 3 doses depending on indication				

Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection
 Recommended for adults with other indications
 No recommendation

Recommended immunization schedule for adults aged 19 years or older by medical condition and other indications, United States, 2018

This figure should be reviewed with the accompanying footnotes. This figure and the footnotes describe indications for which vaccines, if not previously administered, should be administered unless noted otherwise.

Vaccine	Pregnancy ¹⁴	Immunocompromised (excluding HIV infection) ^{17,18,19}	HIV infection CD4+ count (cells/μL) ^{27,28,19}	Asplenia, complement deficiencies ^{29,30,31}	End-stage renal disease, on hemodialysis ³²	Heart or lung disease, alcoholism ⁷	Chronic liver disease ³³	Diabetes ³⁴	Health care personnel ^{34,35}	Men who have sex with men ^{34,35}
Influenza ¹	1 dose annually									
Tdap ² or Td ²	1 dose Tdap each pregnancy	1 dose Tdap, then Td booster every 10 yrs								
MMR ³	contraindicated		1 or 2 doses depending on indication							
VAR ⁴	contraindicated		2 doses							
RZV ⁵ (preferred) or ZVL ⁵	contraindicated		2 doses RZV at age ≥50 yrs (preferred) or 1 dose ZVL at age ≥60 yrs							
HPV–Female ⁶	3 doses through age 26 yrs		2 or 3 doses through age 26 yrs							
HPV–Male ⁶	3 doses through age 26 yrs		2 or 3 doses through age 21 yrs							
PCV13 ⁷	1 dose									
PPSV23 ⁷	1, 2, or 3 doses depending on indication									
HepA ⁸	2 or 3 doses depending on vaccine									
HepB ⁹	3 doses									
MenACWY ¹⁰	1 or 2 doses depending on indication, then booster every 5 yrs if risk remains									
MenB ¹⁰	2 or 3 doses depending on vaccine									
Hib ¹¹	3 doses HSCT recipients only		1 dose							

Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection
 Recommended for adults with other indications
 Contraindicated
 No recommendation

FIGURE 206-1 Recommended adult immunization schedules, United States, 2018. Additional information, including footnotes for each vaccine, contraindications, and precautions, can be found at <https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html>. The recommendations in this schedule were approved by the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians (AAFP), the American College of Physicians (ACP), the American College of Obstetricians and Gynecologists (ACOG), and the American College of Nurse-Midwives (ACNM). For complete statements by the ACIP, visit www.cdc.gov/vaccines/hcp/acip-recs/.

- Seventeen diseases are now preventable through vaccines routinely administered in the United States, and rates of vaccine-preventable diseases of childhood are at historic lows.
- Vaccines protect the immunized individual (a direct effect). Many also confer *herd immunity* (an indirect effect), in which transmission of infections to unimmunized populations is reduced.
- Immunization programs are associated with controlling, eliminating, or eradicating a disease.
 - Smallpox is the only human infection to be eradicated, although ongoing efforts are targeting the global eradication of polio.
- The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) makes recommendations for the administration of vaccines approved by the FDA for use in children and adults (Fig. 206-1).
 - Pregnant women and immunocompromised pts should not receive live-virus vaccines.
- Administering immunizations to adults involves a number of processes, such as deciding whom to vaccinate, assessing vaccine contraindications and precautions, providing vaccine information statements (VISs), ensuring appropriate storage and handling of vaccines, administering vaccines, and maintaining vaccine records.

207

Cardiovascular Disease Prevention



Atherosclerotic cardiovascular disease is the leading cause of death worldwide; prevention is targeted at modifiable risk factors (Table 207-1). Identification and control of these attributes reduce cardiovascular event rates.

■ ESTABLISHED RISK FACTORS

Cigarette Smoking

Cigarette smoking increases the incidence of, and mortality associated with, coronary heart disease (CHD). Observational studies show that smoking cessation reduces the risk of coronary events within months. For pts who smoke, implement counseling and, as needed, pharmacologic therapy to assist cessation. Consider a one-time ultrasound study to screen for abdominal aortic aneurysm in men aged 65–75 who have ever smoked.

Lipid Disorders

(See Chap. 181) Both elevated LDL and low HDL cholesterol are associated with cardiovascular events. Each 1-mg/dL increase in serum LDL correlates with a 2–3% rise in CHD risk; each 1-mg/dL decrease in HDL heightens risk by 3–4%. A screening lipid profile in adults should include total cholesterol, triglycerides, HDL, and LDL (calculated or directly measured). Regular physical activity, dietary improvements, and achieving desirable body weight are recommended for all pts with dyslipidemia. Pharmacologic approaches depend on presence or risk of clinical atherosclerotic disease (ASCVD). Treatment should be most aggressive in pts with established disease and in those at the highest risk as shown in Table 207-2, the cornerstone of which is statin therapy. In pts with

TABLE 207-1 Atherosclerotic Risk Factors**Modifiable Risk Factors**

Cigarette smoking
 Dyslipidemias (\uparrow LDL or \downarrow HDL)
 Hypertension
 Diabetes mellitus
 Obesity
 Sedentary lifestyle

Unmodifiable Risk Factors

Premature coronary heart disease in first-degree relatives (age <55 in men, <65 in women)
 Age (men ≥ 45 years; women ≥ 55 years)
 Male sex

TABLE 207-2 Guideline Recommendations for Lipid-Lowering Drug Therapy

GROUP	RECOMMENDATION
Clinical atherosclerotic disease (ASCVD)	High-intensity statin ^a to achieve $\geq 50\%$ LDL reduction; If LDL remains ≥ 70 mg/dL: Consider adding ezetimibe; If very high risk ^b and LDL still ≥ 70 mg/dL on maximally tolerated statin + ezetimibe: Consider adding PCSK9 inhibitor
LDL cholesterol ≥ 190 mg/dL	High-intensity statin ^a to achieve $\geq 50\%$ LDL reduction; If $<50\%$ LDL reduction achieved, or LDL remains ≥ 100 mg/dL: Consider adding ezetimibe; If LDL reduction still $<50\%$: Consider adding bile acid sequestrant (do not add if triglycerides >300 mg/dL); If pt has heterozygous familial hypercholesterolemia and LDL still ≥ 100 mg/dL (or if baseline LDL ≥ 220 mg/dL, age 40–75, and LDL still ≥ 130 mg/dL): Consider adding PCSK9 inhibitor
Diabetics Age 40–75 • Regardless of ASCVD risk profile • Multiple ASCVD risk factors • 10-year ASCVD risk $\geq 20\%$ Age >75 Age 20–39	Moderate-intensity statin ^c High-intensity statin ^a to achieve $\geq 50\%$ LDL reduction Add ezetimibe, if needed, to reduce LDL $\geq 50\%$ Data is limited; statin therapy reasonable after discussion of benefits and risks with pt Consider statin if diabetes of long duration, estimated GFR <60 mL/min/1.73 m ² , or presence of albuminuria, retinopathy, neuropathy, or reduced ankle-brachial index (<0.9)

(Continued)

TABLE 207-2 Guideline Recommendations for Lipid-Lowering Drug Therapy (Continued)

GROUP	RECOMMENDATION
Primary prevention (age 40–75, nondiabetic, LDL 70–189 mg/dL) with <ul style="list-style-type: none"> • 10-year cardiac risk^d <5% • 10-year cardiac risk^d 5–7.5%^d • 10-year risk^d 7.5–20% 	Lifestyle improvements If risk enhancers present, ^e consider moderate-intensity statin ^c Moderate-intensity statin, ^c especially if risk enhancers present, ^e to achieve 30–50% LDL reduction (if decision to treat uncertain, consider obtaining coronary calcium score) If insufficient reduction of LDL due to statin intolerance, consider adding ezetimibe or bile acid sequestrant Moderate-high intensity statin ^{a,c} to achieve ≥50% LDL reduction
<ul style="list-style-type: none"> • 10-year risk^d ≥20% 	Moderate-high intensity statin ^{a,c} to achieve ≥50% LDL reduction

^aHigh-intensity statin: Atorvastatin 40–80 mg daily or rosuvastatin 20–40 mg daily; for age ≥75, or statin adverse effect, consider moderate-intensity statin^e instead.

^bVery high-risk includes prior major ASCVD events (recent acute coronary syndrome, history of MI, ischemic stroke, symptomatic peripheral vascular disease) or one major ASCVD event and multiple high-risk attributes (age ≥65, heterozygous familial hypercholesterolemia, prior coronary artery bypass graft surgery or percutaneous coronary intervention, diabetes, hypertension, smoking, chronic kidney disease).

^cModerate-intensity statin: Atorvastatin 10–20 mg daily, rosuvastatin 5–10 mg daily, or simvastatin 20–40 mg daily.

^d10-year ASCVD risk can be estimated using the online calculator: <http://my.americanheart.org/cvriskcalculator>.

^eASCVD risk enhancers: Family history premature CAD, persistently elevated LDL ≥160 mg/dL, chronic kidney disease, metabolic syndrome, inflammatory diseases (rheumatoid arthritis, psoriasis, HIV), South Asian ancestry, premature menopause, elevated triglycerides (≥175 mg/dL), high-sensitivity C-reactive protein ≥2.0 mg/L, lipoprotein (a) >50 mg/dL, and ankle-brachial index <0.9.

Source: Data from Grundy SM et al: 2018 Guideline on the management of blood cholesterol. *Circulation* 139:e1046, 2019.

isolated low HDL, encourage beneficial lifestyle measures: smoking cessation, weight loss, and increased physical activity (see **Chap. 181**).

Hypertension

(See **Chap. 119**) Systolic or diastolic bp >115/75 mmHg is associated with heightened risk of cardiovascular disease; each increase of 20 mmHg systolic, or 10 mmHg diastolic, above this value doubles the risk. Treatment of elevated blood pressure reduces the rate of stroke, congestive heart failure, and coronary events. Cardiovascular event rates in elderly pts with isolated systolic hypertension are also reduced by antihypertensive therapy.

Beneficial lifestyle modifications for elevated blood pressure include weight reduction (goal BMI <25 kg/m²); sodium restriction; diet rich in fruits, vegetables, and low-fat dairy products; regular exercise; and moderation of alcohol consumption. See **Chap. 119** for antihypertensive treatment recommendations. 2017 Hypertension Guidelines recommend initiating antihypertensive drug therapy when systolic bp ≥140 mmHg or diastolic bp ≥90 mmHg (note that if

10-year atherosclerotic event risk is $\geq 10\%$, or if pt has had prior cardiovascular event, initiate drug treatment for systolic ≥ 130 or diastolic ≥ 80). On treatment, bp goal is $< 130/80$ mmHg.

Diabetes Mellitus/Insulin Resistance/Metabolic Syndrome

(See [Chaps. 120](#) and [176](#)) Pts with diabetes most often succumb to cardiovascular disease. LDL levels are typically near average in diabetic pts, but LDL particles are smaller, denser, and more atherogenic; low HDL and elevated triglyceride levels are common. Tight control of serum glucose in type 2 diabetics reduces microvascular diabetic complications (retinopathy, renal disease), but has historically had less impact on macrovascular events (CAD, stroke). In distinction, newer groups of glucose-lowering drugs (e.g., glucagon-like peptide-1 [GLP-1] receptor agonists and sodium-glucose co-transporter 2 [SGLT2] inhibitors) have been shown to reduce cardiovascular event rates in type 2 diabetics. In addition, successful management of associated risk factors (e.g., dyslipidemia and hypertension) significantly reduces cardiovascular events in diabetics and should be vigorously pursued.

Individuals without overt diabetes but who have “metabolic syndrome” (constellation of insulin resistance, central obesity, hypertension, hypertriglyceridemia, low HDL—see [Chap. 120](#)) are also at high risk of cardiovascular events. Dietary counseling, weight loss, and increased physical activity are important in reducing the prevalence of this syndrome.

Male Sex/Postmenopausal State

Coronary risk is greater in men compared to that of premenopausal women of same age, but female risk accelerates after menopause. Estrogen-replacement therapy lowers LDL and raises HDL in postmenopausal women and in observational studies has been associated with reduced coronary events. However, prospective clinical trials do not support such a benefit, and hormone-replacement therapy should not be prescribed for the purpose of cardiovascular risk reduction, especially in older women.

■ PREVENTION

Antithrombotic Therapy in Primary Prevention

Thrombosis at the site of disrupted atherosclerotic plaque is the most common cause of acute coronary syndromes. The antithrombotic drug aspirin reduces future additional cardiovascular events and mortality (i.e., benefits secondary prevention) and should be prescribed at a dose of 75–100 mg/d. In primary prevention trials, chronic low-dose aspirin therapy has been shown to reduce the risk of a first MI in men and the risk of stroke in women. However, aspirin also increases the occurrence of major bleeding. Recent prospective randomized trials have concluded that the cardiovascular benefits and bleeding risk of aspirin in primary prevention closely match one another. Whether or not to prescribe aspirin for primary prevention should be based on a discussion with the pt about the potential benefits and risks in his/her specific case so that a mutual decision can be made.

Lifestyle Modifications

Encourage beneficial exercise habits (> 30 min moderate intensity physical activity daily) and sensible diet (low in saturated and trans fat; inclusion of fish, vegetables, whole grains, fruits; balance caloric consumption with energy expenditure). Advise moderation in ethanol intake (no more than 1–2 drinks/d).

208

Prevention and Early Detection of Cancer



One of the most important functions of medical care is to prevent disease or discover it early enough that treatment might be more effective. All risk factors for cancer have not yet been defined. However, a substantial number of factors that elevate risk are within a person's control. Some of these factors are listed in [Table 208-1](#). Every physician visit is an opportunity to teach and reinforce the elements of a healthy lifestyle. Cancer screening in the asymptomatic population at average risk is a complex issue. To be of value, screening must detect disease at a stage that is more readily curable than disease that is treated after symptoms appear. For cervix cancer and colon cancer, screening has been shown to save lives. For other tumors, benefit is less clear. Screening can cause harm; complications may ensue from the screening test or the tests done to validate a positive screening test or from treatments for the underlying disease. Furthermore, quality of life can be adversely affected by false-positive tests. Evaluation of screening tools can be biased and needs to rely on prospective randomized studies. *Lead-time bias* occurs when the natural history of disease is unaffected by the diagnosis, but the pt is diagnosed earlier in the course of disease than normal; thus, the pt spends more of his/her life span knowing the diagnosis. *Length bias* occurs when slow-growing cancers that might never have come to medical attention are detected during screening. *Overdiagnosis* is a form of length bias in which a cancer is detected when it is not growing and is not an influence on length of survival. *Selection bias* is the term for the fact that people who volunteer for screening trials may be different from the general population. Volunteers might have family history concerns that actually elevate their risk, or they may be generally more health-conscious, which can affect outcome.

The various groups that evaluate and recommend screening practice guidelines have used varying criteria to make their recommendations ([Table 208-2](#)). The absence of data on survival for a number of diseases has led to a lack of consensus. In particular, four areas are worth noting:

1. *Prostate cancer*: Prostate-specific antigen (PSA) levels are elevated in prostate cancer, but a substantial number of the cancers detected appear to be non-life-threatening. PSA screening has not been shown to improve survival. Efforts are underway to develop better tests (predominantly using bound vs. free and rate of increase of PSA) to distinguish lethal and nonlethal cancers. Genetic profiling has not yet provided useful distinctions.
2. *Breast cancer*: The data on annual mammography support its use in women age >50 years. However, the benefit for women age 40–49 years is quite small. One study shows some advantage for women who are screened starting at

TABLE 208-1 Lifestyle Factors That Reduce Cancer Risk

Do not use any tobacco products
Maintain a healthy weight; eat a well-balanced diet ^a ; maintain caloric balance
Exercise at least 3 times a week
Prevent sun exposure
Avoid excessive alcohol intake
Practice safe sex; use condoms

^aNot precisely defined, but current recommendations include five servings of fruits and vegetables per day, 25 g fiber, and <30% of calories coming from fat.

TABLE 208-2 Screening Recommendations for Asymptomatic Subjects Not Known to Be at Increased Risk for the Target Condition^a

CANCER TYPE	TEST OR PROCEDURE	USPSTF	ACS
Breast	Self-examination	“D” ^b (Not in current recommendations; from 2009)	Women, all ages: No specific recommendation
	Clinical examination	Women ≥40 years: “I” (as a stand-alone without mammography) (Not in current recommendations; from 2009)	Women, all ages: Do not recommend
	Mammography	Women 40–49 years: The decision to start screening mammography in women prior to age 50 years should be an individual one. Women who place a higher value on the potential benefit than the potential harms may choose to begin biennial screening between the ages of 40 and 49 years. (“C”) Women 50–74 years: Every 2 years (“B”) Women ≥75 years: “I”	Women 40–44 years: Provide the opportunity to begin annual screening Women 45–54 years: Screen annually Women ≥55 years: Transition to biennial screening or have the opportunity to continue annual screening Women ≥40 should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer
	Magnetic resonance imaging (MRI)	“I” (Not in current recommendations; from 2009)	Women with >20% lifetime risk of breast cancer: Screen with MRI plus mammography annually
			Women with 15–20% lifetime risk of breast cancer: Discuss option of MRI plus mammography annually
			Women with <15% lifetime risk of breast cancer: Do not screen annually with MRI
	Tomosynthesis	Women, all ages: “I”	No specific recommendation

Cervical	Pap test (cytology)	Women 21–65 years: Screen every 3 years (“A”)	Women 21–29 years: Screen every 3 years
		Women <21 years: “D” Women >65 years, with adequate, normal prior Pap screenings: “D”	Women 30–65 years: Acceptable approach to screen with cytology every 3 years (see HPV test below) Women <21 years: No screening Women >65 years: No screening following adequate negative prior screening
		Women after total hysterectomy for noncancerous causes: “D”	Women after total hysterectomy for noncancerous causes: Do not screen
	HPV test	Women 30–65 years: Screen in combination with cytology every 5 years if woman desires to lengthen the screening interval (see Pap test above) (“A”) Women <30 years: “D” Women >65 years, with adequate, normal prior Pap screenings: “D” Women after total hysterectomy for noncancerous causes: “D”	Women 30–65 years: Preferred approach to screen with HPV and cytology co-testing every 5 years (see Pap test above) Women <30 years: Do not use HPV testing Women >65 years: No screening following adequate negative prior screening Women after total hysterectomy for noncancerous causes: Do not screen

(Continued)

TABLE 208-2 Screening Recommendations for Asymptomatic Subjects Not Known to Be at Increased Risk for the Target Condition^a (Continued)

CANCER TYPE	TEST OR PROCEDURE	USPSTF	ACS
Colorectal	Sigmoidoscopy	Adults, 50–75 years: “A” Screen for colorectal cancer; the risks and benefits of the different screening methods vary Adults, 76 to 85 years: “C” The decision to screen should be an individual one, taking into account the pt’s overall health and prior screening history Every 5 years; modeling suggests improved benefit if performed every 10 years in combination with annual FIT	Adults ≥50 years: Screen every 5 years
	Fecal occult blood testing (FOBT)	Every year	Adults ≥50 years: Screen every year
	Colonoscopy	Every 10 years	Adults ≥50 years: Screen every 10 years
	Fecal DNA testing	Every 1 or 3 years	Adults ≥50 years: Screen, but interval uncertain
	Fecal immuno-chemical testing (FIT)	Every year	Adults ≥50 years: Screen every year
	CT colonography	Every 5 years	Adults ≥50 years: Screen every 5 years
Lung	Low-dose computed tomography (CT) scan	Adults 55–80 years, with a ≥30 pack-year smoking history, still smoking or have quit within past 15 years: “B” Discontinue once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability to have curative lung surgery	Men and women, 55–74 years, with ≥30 pack-year smoking history, still smoking or have quit within past 15 years: Discuss benefits, limitations, and potential harms of screening; only perform screening in facilities with the right type of CT scanner and with high expertise/specialists

Ovarian	CA-125 Transvaginal ultrasound	Women, all ages: “D” Women, all ages: “D”	There is no sufficiently accurate test proven effective in the early detection of ovarian cancer. For women at high risk of ovarian cancer and/or who have unexplained, persistent symptoms, the combination of CA-125 and transvaginal ultrasound with pelvic exam may be offered
Prostate	Prostate-specific antigen (PSA)	Men, all ages: “D”	Starting at age 50, men should talk to a doctor about the pros and cons of testing so they can decide if testing is the right choice for them. If African American or have a father or brother who had prostate cancer before age 65, men should have this talk starting at age 45. How often they are tested will depend on their PSA level
	Digital rectal examination (DRE)	No individual recommendation	As for PSA; if men decide to be tested, they should have the PSA blood test with or without a rectal examination
Skin	Complete skin examination by clinician or pt	Adults, all ages: “I”	Self-examination monthly; clinical examination as part of routine cancer-related checkup

^aSummary of the screening procedures recommended for the general population by the USPSTF and the ACS. These recommendations refer to asymptomatic persons who are not known to have risk factors, other than age or gender, for the targeted condition.

^bUSPSTF lettered recommendations are defined as follows: “A”: The USPSTF recommends the service, because there is high certainty that the net benefit is substantial; “B”: The USPSTF recommends the service, because there is high certainty that the net benefit is moderate or moderate certainty that the net benefit is moderate to substantial; “C”: The USPSTF recommends selectively offering or providing this service to individual pts based on professional judgment and pt preferences; there is at least moderate certainty that the net benefit is small; “D”: The USPSTF recommends against the service because there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits; “I”: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service.

Abbreviations: ACS, American Cancer Society; USPSTF, U.S. Preventive Services Task Force.

age 40 that appears 15 years later; however, it is unclear if this benefit would not have also been derived by starting screening at age 50 years. Women age 40–49 years have a much lower incidence of breast cancer and a higher false-positive rate on mammography. Nearly half of women screened during their forties will have a false-positive test. Refined methods of screening are in development. Women with familial breast cancer may benefit from MRI screening.

3. *Colon cancer*: Annual fecal occult blood testing after age 50 years is felt to be useful. Colonoscopy is the gold standard in colorectal cancer detection, but it is expensive and has not been shown to be cost-effective in asymptomatic people. Commercial tests that combine detection of occult blood and the presence of genetic abnormalities in stool (e.g., Cologuard) have improved upon tests that only detect occult blood in stool.
4. *Lung cancer*: Chest radiographs and sputum cytology in smokers appear to identify more early-stage tumors, but paradoxically, the screened pts do not have improved survival. Low-dose spiral CT scanning performed annually for 3 years reduces lung cancer death in older smokers by 20% compared with annual chest x-ray. However, 96% of the positive tests are false-positives and overall survival is improved by only 6.7%.

CANCER PREVENTION IN HIGH-RISK GROUPS

■ BREAST CANCER

Risk factors include age, early menarche, nulliparity or late first pregnancy, high body mass index, radiation exposure before age 30 years, hormone-replacement therapy (HRT), alcohol consumption, family history, presence of mutations in *BRCA1* or *BRCA2*, and prior history of breast neoplasia. Models are able to predict a woman's risk level (see www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional#Section_627).

Diagnosis

MRI scanning is a more effective screening tool than mammography in women with a familial breast cancer risk.

Interventions

Women whose risk exceeds 1.66% in the next 5 years have been shown to have a 50% reduction in breast cancer from taking tamoxifen or raloxifene. Aromatase inhibitors have generally been superior to tamoxifen in the adjuvant treatment of hormone-sensitive breast cancer, and one of them (exemestane) reduces the risk of breast cancer by 65% in postmenopausal women at increased risk. Women with strong family histories should undergo testing for mutations in *BRCA1* and *BRCA2*. Mutations in these genes carry a lifetime probability of >80% for developing breast cancer. Bilateral prophylactic mastectomy prevents at least 90% of these cancers but is a more radical prevention than the usual treatment for the disease. In addition, bilateral salpingo-oophorectomy reduces ovarian and fallopian tube cancer risk by about 96% in women with *BRCA1* or *BRCA2* mutations.

■ COLORECTAL CANCER

Risk factors include diets high in saturated fats and low in fruits and vegetables, smoking, and alcohol consumption. Stronger but less prevalent risk factors are the presence of inflammatory bowel disease or genetic disorders such as familial polyposis (autosomal dominant germline mutation in *APC*) and hereditary non-polyposis colorectal cancer (mutations in DNA mismatch repair genes *hMSH2* and *hMLH1*).

Interventions

Pts with ulcerative colitis and familial polyposis generally undergo total colectomy. In familial polyposis, nonsteroidal anti-inflammatory drugs (NSAIDs)

reduce the number and size of polyps. Celecoxib, sulindac, and even aspirin appear to be effective, and celecoxib is approved by the U.S. Food and Drug Administration for this indication. Calcium supplementation can lead to a decrease in the recurrence of adenomas, but it is not yet clear that the risk of colorectal cancer is decreased and survival increased. The Women's Health Study noted a significant reduction in the risk of colorectal cancer in women taking HRT, but the increase in thrombotic events and breast cancers counterbalanced this benefit. Studies are underway to assess NSAIDs with and without inhibitors of the epidermal growth factor (EGF) receptor in other risk groups.

■ LUNG CANCER

Risk factors include smoking, exposure to radiation, asbestos, radon.

Interventions

Smoking cessation is the only effective prevention (Chap. 209). NSAIDs and EGF receptor inhibitors are being evaluated. Carotenoids, selenium, retinoids, and α -tocopherol do not work.

■ PROSTATE CANCER

Risk factors include age, family history, and possibly dietary fat intake. African Americans are at increased risk. The disease is highly prevalent, with autopsy studies finding prostate cancer in 70–80% of men age >70.

Interventions

In a group of men age ≥ 55 years with normal rectal examinations and PSA levels <3 ng/mL, daily finasteride reduced the incidence of prostate cancer by 25%. Finasteride also prevents the progression of benign prostate hyperplasia. However, some men experience decreased libido as a side effect. The Gleason grade of tumors seen in men taking finasteride prevention was somewhat higher than the controls; however, long-term follow-up did not demonstrate an increase in prostate cancer mortality among men taking finasteride. Dutasteride, another 5α -reductase inhibitor, had similar effects. The FDA has reviewed the data and concluded that the reduction in risk is primarily in the group of pts with low-grade tumors whose risk from prostate cancer is unclear. One additional high-grade tumor emerges for every 3–4 low-grade tumors averted.

■ CERVICAL CANCER

Risk factors include early age at first intercourse, multiple sexual partners, smoking, and infection with human papillomavirus (HPV) types 16, 18, 45, and 56.

Interventions

Regular Pap testing (q 3 years beginning at age 21) can detect nearly all cases of the premalignant lesion called *cervical intraepithelial neoplasia (CIN)*. An alternative is combined Pap testing and HPV testing after age 30. If untreated, CIN can progress to carcinoma in situ and invasive cervical cancer. Surgical removal, cryotherapy, or laser therapy is used to treat the disease and is effective in 80%. Risk of recurrence is highest in women age >30, those with prior HPV infection, and those who have had prior treatment for the same condition. A vaccine (Gardasil) containing antigens of strains 6, 11, 16, and 18 has been shown to be 100% effective in preventing HPV infections from those strains. The vaccine is recommended for all females and males age 9–26 years and could prevent up to 70% of all cervical cancer. Risks of vaginal, vulvar, and anal cancer, and genital warts are also reduced. The vaccine is not effective after infection has been established.

■ HEAD AND NECK CANCER

Risk factors include smoking, alcohol consumption, and possibly HPV infection.

Interventions

Oral leukoplakia, white lesions of the oral mucosa, occur in 1–2 persons in 1000, and 2–3% of these pts go on to develop head and neck cancer. Spontaneous regression of oral leukoplakia is seen in 30–40% of pts. Retinoid treatment (13-*cis* retinoid acid) can increase the regression rate. Vitamin A induces complete remission in ~50% of pts. The use of retinoids in pts who have been diagnosed with head and neck cancer and received definitive local therapy has not produced consistent results. Initial studies claimed that retinoids prevented the development of second primary tumors, a common feature of head and neck cancer. However, large randomized studies did not confirm this benefit. Other studies are underway combining retinoids and NSAIDs with and without EGF receptor inhibitors.

PT EDUCATION IN EARLY DETECTION

Pts can be taught to look for early warning signals. The American Cancer Society has identified seven major warning signs of cancer:

- A change in bowel or bladder habits
- A sore that does not heal
- Unusual bleeding or discharge
- A lump in the breast or other parts of the body
- Chronic indigestion or difficulty in swallowing
- Obvious changes in a wart or mole
- Persistent coughing or hoarseness

209 Smoking Cessation



Over 480,000 individuals die prematurely each year in the United States from cigarette use: one out of every five deaths nationwide. Approximately 40% of smokers will die prematurely unless they are able to quit; risks of major diseases caused by cigarette smoking are listed in [Table 209-1](#).

APPROACH TO THE PATIENT

Nicotine Addiction

All pts should be asked whether they smoke, how much they smoke, how long they have smoked, their past experience with quitting, and whether they are currently interested in quitting; even those who are not interested should be encouraged and motivated to quit. Provide a clear, strong, and personalized message that smoking is an important health concern. A quit date should be negotiated within a few weeks of the visit, and a follow-up contact by office staff around the time of the quit date should be provided. Incorporation of cessation assistance into a practice requires a change of the care delivery infrastructure. Simple changes include:

- Adding questions about smoking and interest in cessation on pt-intake questionnaires
- Asking pts whether they smoke as part of the initial vital sign measurements made by office staff

TABLE 209-1 Relative Risks for Current Smokers of Cigarettes

AGE	35–44	45–64	65–74	≥75
Males				
Lung cancer	14.33	19.03	28.29	22.51
Coronary heart disease	3.88	2.99	2.76	1.98
Cerebrovascular disease	2.17	1.48	1.23	1.12
Other vascular diseases			7.25	4.93
Chronic obstructive pulmonary disease (COPD)			29.69	23.01
All causes	2.55	2.97	3.02	2.40
Females				
Lung cancer	13.30	18.95	23.65	23.08
Other tobacco-related cancers	1.28	2.08	2.06	1.93
Coronary heart disease	4.98	3.25	3.29	2.25
Cerebrovascular disease	2.27	1.70	1.24	1.10
Other vascular diseases			6.81	5.77
COPD			38.89	20.96
All causes	1.79	2.63	2.87	2.47
Relative risks for selected other cancers				
Other cancers	Male	Female		
Larynx	14.6	13		
Lip, oral cavity, pharynx	10.9	5.1		
Esophagus	6.8	7.8		
Bladder	3.3	2.2		
Kidney	2.7	1.3		
Pancreas	2.3	2.3		
Stomach	2	1.4		
Liver	1.7	1.7		
Colorectal	1.2	1.2		
Cervix		1.6		
Acute myeloid leukemia	1.4	1.4		

- Listing smoking as a problem in the medical record
- Automating follow-up contact with the pt on the quit date

TREATMENT

Nicotine Addiction

- Clinical practice guidelines suggest a variety of pharmacologic and nonpharmacologic interventions to aid in smoking cessation ([Table 209-2](#)).
- Numerous nicotine-replacement products exist, including over-the-counter nicotine patches, gum, and lozenges, as well as nicotine nasal and oral inhalers available by prescription; these products can be used for 3–6 months with a gradual step-down in dosage with increasing duration of abstinence.
- Prescription medications that have been shown to be effective include antidepressants such as bupropion (300 mg/d in divided doses for up to 6 months) and varenicline, a partial agonist for the nicotinic acetylcholine receptor (initial dose 0.5 mg daily increasing to 1 mg twice daily at day 8; treatment duration

TABLE 209-2 Clinical Practice Guidelines**Physician Actions**

Ask: Systematically identify all tobacco users at every visit

Advise: Strongly urge all smokers to quit

Identify smokers willing to quit

Assist the pt in quitting

Arrange follow-up contact

Effective Pharmacologic Interventions^a

First-line therapies

Nicotine gum (1.5)

Nicotine patch (1.9)

Nicotine nasal inhaler (2.3)

Nicotine oral inhaler (2.1)

Nicotine lozenge (2 mg 2.0, 4 mg 2.8)

Bupropion (2.0)

Varenicline (3.1)

Second-line therapies

Clonidine (2.1)

Nortriptyline (1.8)

Other Effective Interventions^a

Physician or other medical personnel counseling (10 min) (1.84)

Intensive group smoking cessation programs (at least 4–7 sessions of 20- to 30-min duration lasting at least 2 and preferably 8 weeks) (1.3)

Intensive individual counseling (1.7)

Clinic-based smoking status identification system (3.1)

Telephone counseling (1.6)

^aNumerical value following the intervention is the multiple for cessation success compared to no intervention.

up to 6 months). Antidepressants are more effective in pts with a history of depressive symptoms.

- Clonidine or nortriptyline may be useful for pts who have failed first-line therapies.
- Current recommendations are to offer pharmacologic treatment, usually with nicotine replacement therapy or varenicline, to all who will accept it and to provide counseling and other support as a part of the cessation attempt.

PREVENTION

Approximately 85% of individuals who will become cigarette smokers initiate the behavior during adolescence; prevention must begin early, preferably in the elementary school years. Physicians who treat adolescents should be sensitive to the prevalence of this problem and screen for tobacco use, reinforcing the fact that most adolescents and adults do not smoke, and explaining that all forms of tobacco are both addictive and harmful.

210 Women's Health



The most common causes of death in both men and women are heart disease and cancer, with lung cancer the top cause of cancer death, despite common misperceptions that breast cancer is the most common cause of death in women. These misconceptions perpetuate inadequate attention to modifiable risk factors in women, such as dyslipidemia, hypertension, and cigarette smoking. Furthermore, since women in the United States live on average about 5 years longer than men, the majority of the disease burden for many age-related disorders (e.g., hypertension, Alzheimer's disease [AD]) rests in women.

SEX DIFFERENCES IN HEALTH AND DISEASE

■ ALZHEIMER'S DISEASE (SEE ALSO CHAP. 185)

AD affects approximately twice as many women as men, due to larger numbers of women surviving to older ages and to sex differences in brain size, structure, and functional organization. The impact of postmenopausal hormone therapy on cognitive function and the development of AD is inconclusive.

■ CORONARY HEART DISEASE (SEE ALSO CHAPS. 121-123)

Coronary heart disease (CHD) presents differently in women, who are usually 10–15 years older than men with CHD and are more likely to have comorbidities, such as hypertension, congestive heart failure, and diabetes. Women more often have atypical symptoms, such as nausea, vomiting, indigestion, and upper back pain, and are less likely to recognize these and call 9-1-1. Physicians are less likely to suspect heart disease in women with chest pain and are less likely to perform diagnostic and therapeutic cardiac procedures in women. The conventional risk factors for CHD are the same in both men and women, though women receive fewer interventions for modifiable risk factors than do men. The prevalence of CHD is increasing in middle-aged women, at a time when the prevalence in men is unchanged or declining. The marked increase in CHD occurring after menopause or oophorectomy suggests that endogenous estrogens are cardioprotective. However, hormone replacement therapy in postmenopausal women was not shown to be cardioprotective in controlled trials such as the Women's Health Initiative and other randomized trials. Therapy with estrogen plus progestin therapy was associated with *increased* cardiovascular events. The discrepancy between endogenous and exogenous estrogen effects is poorly understood but may be related to deleterious effects of late re-exposure to estrogen after a period of estrogen deficiency.

■ DIABETES MELLITUS (SEE ALSO CHAP. 176)

The prevalence of type 2 diabetes mellitus (DM) is similar between men and women. Polycystic ovary syndrome and gestational DM are both common conditions in premenopausal women that carry an increased risk for type 2 DM. Premenopausal women with DM have identical rates of CHD to those of males.

■ HYPERTENSION (SEE ALSO CHAP. 119)

Hypertension, as an age-related disorder, is more common in women than in men after age 60. Antihypertensive drugs appear to be equally effective in women and men; however, women may experience more side effects.

■ AUTOIMMUNE DISORDERS (SEE ALSO CHAP. 161)

Most autoimmune disorders occur more commonly in women than in men; these include autoimmune thyroid and liver diseases, lupus, rheumatoid arthritis, scleroderma, multiple sclerosis, and idiopathic thrombocytopenic purpura. The mechanism for these sex differences remains obscure.

■ HIV INFECTION (SEE ALSO CHAP. 107)

Heterosexual contact with an at-risk partner is the fastest-growing transmission category of HIV, and women are more susceptible to HIV infection than men. Women account for about 50% of the 34 million persons infected with HIV-1 worldwide. Women with HIV have more rapid decreases in their CD4 cell counts than men do. Other sexually transmitted diseases, such as chlamydial infection and gonorrhea, are important causes of infertility in women, and papilloma virus infection predisposes to cervical cancer.

■ OBESITY (SEE ALSO CHAP. 175)

The prevalence of obesity is higher in women than in men, in part due to the unique risk factors of pregnancy and menopause. More than 80% of pts who undergo bariatric surgery are women. The distribution of body fat differs by sex, with a gluteal and femoral (gynoid) pattern in women and a central and upper body (android) pattern in men. The android distribution of fat carries a higher risk for metabolic syndrome, DM, and cardiovascular disease. Obesity increases a woman's risk for postmenopausal breast and endometrial cancer, in part because of adipose tissue aromatization of androgens to estrone.

■ OSTEOPOROSIS (SEE ALSO CHAP. 180)

Osteoporosis is much more prevalent in postmenopausal women than in age-matched men, since men accumulate more bone mass in their youth and lose bone more slowly than do women, in particular after age 50, when accelerated postmenopausal bone loss occurs in women. In addition, differences in calcium intake, vitamin D, and estrogen levels contribute to sex differences in bone formation and bone loss. Vitamin D insufficiency is present in a large proportion of elderly women living in Northern latitudes. Osteoporotic hip fracture is a major cause of morbidity and an important cause of mortality in elderly women.

■ PHARMACOLOGY

On average, women have lower body weights, smaller organs, higher percent body fat, and lower total-body water than men do. Gonadal steroids, menstrual cycle phase, and pregnancy can all affect drug metabolism and action. Women also take more medications than men do, including over-the-counter formulations and supplements. The greater use of medications, combined with biologic differences, may account for the reported higher frequency of adverse drug reactions in women.

■ PSYCHOLOGICAL DISORDERS (SEE ALSO CHAPS. 199 AND 201)

Depression, anxiety, and eating disorders (bulimia and anorexia nervosa) are more common in women than in men. Depression occurs in 10% of women during pregnancy and 10–15% of women during the postpartum period.

■ SLEEP DISORDERS (SEE ALSO CHAP. 58)

During sleep, women have an increased amount of slow-wave activity, differences in timing of delta activity, and an increase in the number of sleep spindles. They have a decreased prevalence of sleep apnea compared to men, a feature that may be related to lower androgen levels.

■ SUBSTANCE ABUSE AND TOBACCO (SEE ALSO CHAPS. 202-204)

Substance abuse is more common in men than women. However, women alcoholics are less likely to be diagnosed than men and are less likely to seek help. When they do seek help, it is more likely to be from a physician than from a treatment facility. Alcoholic women drink less than alcoholic men but exhibit the same degree of impairment. Alcohol abuse poses special risks to a woman, adversely affecting fertility and the health of the baby (fetal alcohol syndrome). Even moderate alcohol use increases the risk of breast cancer, hypertension, and stroke in women. More men than women smoke tobacco, but the prevalence of smoking is declining faster in men than women. The effects of smoking on pulmonary disease (COPD and cancer) and osteoporosis are more pronounced in women than in men.

■ VIOLENCE AGAINST WOMEN

Domestic violence is the most common cause of physical injury in women. More than one in three women in the United States have experienced rape, physical violence, and/or stalking by an intimate partner. Women may present with symptoms of chronic abdominal pain, headaches, substance abuse, and eating disorders, in addition to obvious manifestations such as trauma. Sexual assault is one of the most common crimes against women (reported by one in five women in the United States) and is more likely committed by a spouse, ex-spouse, or acquaintance than by a stranger.

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211 Adverse Drug Reactions



Adverse drug reactions are among the most frequent problems encountered clinically and represent a common cause for hospitalization. They occur most frequently in pts receiving multiple drugs and are caused by:

- Errors in self-administration of prescribed drugs (quite common in the elderly);
- Exaggeration of intended pharmacologic effect (e.g., hypotension in a pt given antihypertensive drugs);
- Concomitant administration of drugs with synergistic effects (e.g., aspirin and warfarin);
- Cytotoxic reactions (e.g., hepatic necrosis due to acetaminophen);
- Immunologic mechanisms (e.g., quinidine-induced thrombocytopenia, hydralazine-induced SLE);
- Genetically determined enzymatic defects (e.g., primaquine-induced hemolytic anemia in G6PD deficiency); or
- Idiosyncratic reactions (e.g., chloramphenicol-induced aplastic anemia).

Recognition

History is of prime importance. Consider the following:

- Nonprescription drugs and topical agents as potential offenders
- Previous reaction to identical drugs
- Temporal association between drug administration and development of clinical manifestations
- Subsidence of manifestations when the agent is discontinued or reduced in dose
- Recurrence of manifestations with cautious readministration (for less hazardous reactions)
- *Rare:* (1) biochemical abnormalities, e.g., red cell G6PD deficiency as cause of drug-induced hemolytic anemia; (2) abnormal serum antibody in pts with agranulocytosis, thrombocytopenia, or hemolytic anemia.

Table 211-1 lists a number of clinical manifestations of adverse effects of drugs. It is not designed to be complete or exhaustive. The table can be accessed via the following link: www.accessmedicine.com.

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TABLE 211-1 Clinical Manifestations of Adverse Reactions to Drugs**I. Multisystem manifestations****Anaphylaxis**

Cephalosporins
 Dextran
 Insulin
 Iodinated drugs or contrast media
 Lidocaine
 Penicillins
 Procaine

Angioedema

ACE inhibitors

Drug-induced lupus erythematosus

Cephalosporins
 Hydralazine
 Iodides
 Isoniazid
 Methyldopa
 Phenytoin

Procainamide
 Quinidine
 Sulfonamides
 Thiouracil

Fever

Aminosalicylic acid
 Amphotericin B
 Antihistamines
 Penicillins

Hyperpyrexia

Antipsychotics

Serum sickness

Aspirin
 Penicillins
 Propylthiouracil
 Sulfonamides

II. Endocrine manifestations**Addisonian-like syndrome**

Busulfan
 Ketoconazole

Galactorrhea (may also cause amenorrhea)

Methyldopa
 Phenothiazines
 Tricyclic antidepressants

Gynecomastia

Calcium channel antagonists
 Digitalis
 Estrogens
 Griseofulvin
 Isoniazid
 Methyldopa
 Phenytoin
 Spironolactone
 Testosterone

Sexual dysfunction

Beta blockers
 Clonidine
 Diuretics

Guanethidine
 Lithium
 Major tranquilizers
 Methyldopa
 Oral contraceptives
 Sedatives

Thyroid function tests, disorders of

Acetazolamide
 Amiodarone
 Chlorpropamide
 Clofibrate
 Colestipol and nicotinic acid
 Gold salts
 Iodides
 Lithium
 Oral contraceptives
 Phenothiazines
 Phenylbutazone
 Phenytoin
 Sulfonamides
 Tolbutamide

(Continued)

TABLE 211-1 Clinical Manifestations of Adverse Reactions to Drugs (Continued)

III. Metabolic manifestations

Hyperbilirubinemia

Rifampin

Hypercalcemia

Antacids with absorbable alkali

Thiazides

Vitamin D

Hyperglycemia

Chlorthalidone

Diazoxide

Encainide

Ethacrynic acid

Furosemide

Glucocorticoids

Growth hormone

Oral contraceptives

Thiazides

Hypoglycemia

Insulin

Oral hypoglycemics

Quinine

Hyperkalemia

ACE inhibitors

Amiloride

Cytotoxics

Digitalis overdose

Heparin

Lithium

Potassium preparations including salt substitute

Potassium salts of drugs

Spironolactone

Succinylcholine

Triamterene

Hypokalemia

Alkali-induced alkalosis

Amphotericin B

Diuretics

Gentamicin

Insulin

Laxative abuse

Mineralocorticoids, some glucocorticoids

Osmotic diuretics

Sympathomimetics

Tetracycline

Theophylline

Vitamin B12

Hyperuricemia

Aspirin

Cytotoxics

Ethacrynic acid

Furosemide

Hyperalimentation

Thiazides

Hyponatremia

1. Dilutional

Carbamazepine

Chlorpropamide

Cyclophosphamide

Diuretics

Vincristine

2. Salt wasting

Diuretics

Enemas

Mannitol

Metabolic acidosis

Acetazolamide

Paraldehyde

Salicylates

Spironolactone

IV. Dermatologic manifestations

Acne

Anabolic and androgenic steroids

Bromides

Glucocorticoids

Iodides

Isoniazid

Oral contraceptives

Alopecia

Cytotoxics

Ethionamide

(Continued)

TABLE 211-1 Clinical Manifestations of Adverse Reactions to Drugs (Continued)

Heparin	Hyperpigmentation
Oral contraceptives (withdrawal)	Bleomycin
Eczema	Busulfan
Captopril	Chloroquine and other antimalarials
Cream and lotion preservatives	Corticotropin
Lanolin	Cyclophosphamide
Topical antihistamines	Gold salts
Topical antimicrobials	Hypervitaminosis A
Topical local anesthetics	Oral contraceptives
Erythema multiforme or Steven Johnson syndrome	Phenothiazines
Barbiturates	Lichenoid eruptions
Chlorpropamide	Aminosalicylic acid
Codeine	Antimalarials
Penicillins	Chlorpropamide
Phenylbutazone	Gold salts
Phenytoin	Methyldopa
Salicylates	Phenothiazines
Sulfonamides	Photodermatitis
Sulfones	Captopril
Tetracyclines	Chlordiazepoxide
Thiazides	Furosemide
Erythema nodosum	Griseofulvin
Oral contraceptives	Nalidixic acid
Penicillins	Oral contraceptives
Sulfonamides	Phenothiazines
Exfoliative dermatitis	Sulfonamides
Barbiturates	Sulfonylureas
Gold salts	Tetracyclines, particularly demeclocycline
Penicillins	Thiazides
Phenylbutazone	Purpura (see also thrombocytopenia)
Phenytoin	Allopurinol
Quinidine	Ampicillin
Sulfonamides	Aspirin
Fixed drug eruptions	Glucocorticoids
Barbiturates	Rashes (nonspecific)
Captopril	Allopurinol
Phenylbutazone	Ampicillin
Quinine	Barbiturates
Salicylates	Indapamide
Sulfonamides	

(Continued)

TABLE 211-1 Clinical Manifestations of Adverse Reactions to Drugs (Continued)

Methyldopa	Phenylbutazone
Phenytoin	Phenytoin
Skin necrosis	Sulfonamides
Warfarin	Urticaria
Toxic epidermal necrolysis (bullous)	Aspirin
Allopurinol	Barbiturates
Barbiturates	Captopril
Bromides	Enalapril
Iodides	Penicillins
Nalidixic acid	Sulfonamides
Penicillins	

V. Hematologic manifestations

Agranulocytosis (see also Pancytopenia)

- Captopril
- Carbimazole
- Chloramphenicol
- Cytotoxics
- Gold salts
- Indomethacin
- Methimazole
- Oxyphenbutazone
- Phenothiazines
- Phenylbutazone
- Propylthiouracil
- Sulfonamides
- Tolbutamide
- Tricyclic antidepressants

Clotting abnormalities/hypothrombinemia

- Cefamandole
- Cefoperazone
- Moxalactam

Eosinophilia

- Aminosalicylic acid
- Chlorpropamide
- Erythromycin estolate
- Imipramine
- L-Tryptophan
- Methotrexate
- Nitrofurantoin
- Procarbazine
- Sulfonamides

Hemolytic anemia

- Aminosalicylic acid
- Cephalosporins
- Chlorpromazine
- Dapsone
- Insulin
- Isoniazid
- Levodopa
- Mefenamic acid
- Melphalan
- Methyldopa
- Penicillins
- Phenacetin
- Procainamide
- Quinidine
- Rifampin
- Sulfonamides

Hemolytic anemias in G6PD deficiency

See [Table 63-4](#)

Leukocytosis

- Glucocorticoids
- Lithium

Lymphadenopathy

- Phenytoin
- Primidone

Megaloblastic anemia

- Folate antagonists
- Nitrous oxide
- Oral contraceptives
- Phenobarbital
- Phenytoin

(Continued)

TABLE 211-1 Clinical Manifestations of Adverse Reactions to Drugs (Continued)

<p>Primidone Triamterene Trimethoprim</p> <p>Pancytopenia (aplastic anemia)</p> <p>Carbamazepine Chloramphenicol Cytotoxics Gold salts Mephenytoin Phenylbutazone Phenytoin Quinacrine Sulfonamides Trimethadione Zidovudine (AZT)</p> <p>Pure red cell aplasia</p> <p>Azathioprine Chlorpropamide Isoniazid Phenytoin</p>	<p>Thrombocytopenia (see also Pancytopenia)</p> <p>Acetazolamine Aspirin Carbamazepine Carbenicillin Chlorpropamide Chlorthalidone Furosemide Gold salts Heparin Indomethacin Isoniazid Methyldopa Moxalactam Phenylbutazone Phenytoin and other hydantoin Quinidine Quinine Thiazides Ticarcillin</p>
<p>VI. Cardiovascular manifestations</p>	
<p>Angina exacerbation</p> <p>Alpha blockers Beta blocker withdrawal Ergotamine Excessive thyroxine Hydralazine Methysergide Minoxidil Nifedipine Oxytocin Vasopressin</p> <p>Arrhythmias</p> <p>Adriamycin Antiarrhythmic drugs Atropine Anticholinesterases Beta blockers Digitalis Emetine Lithium Phenothiazines</p>	<p>Sympathomimetics Thyroid hormone Tricyclic antidepressants Verapamil</p> <p>AV block</p> <p>Clonidine Methyldopa Verapamil</p> <p>Cardiomyopathy</p> <p>Adriamycin Daunorubicin Emetine Lithium Phenothiazines Sulfonamides Sympathomimetics</p> <p>Fluid retention or congestive heart failure</p> <p>Beta blockers Calcium antagonists Estrogens</p>

(Continued)

TABLE 211-1 Clinical Manifestations of Adverse Reactions to Drugs (Continued)

<p>Indomethacin Mannitol Minoxidil Phenylbutazone Steroids</p> <p>Hypertension</p> <p>Clonidine withdrawal Corticotropin Cyclosporine Glucocorticoids Monoamine oxidase inhibitors with sympathomimetics NSAIDs Oral contraceptives Sympathomimetics Tricyclic antidepressants with sympathomimetics</p>	<p>Hypotension</p> <p>Calcium antagonists Citrated blood Diuretics Levodopa Morphine Nitroglycerin Phenothiazines Protamine Quinidine</p> <p>Pericarditis</p> <p>Emetine Hydralazine Methysergide Procainamide</p> <p>Thromboembolism</p> <p>Oral contraceptives</p>
VII. Respiratory manifestations	
<p>Airway obstruction</p> <p>Beta blockers Cephalosporins Cholinergic drugs NSAIDs Penicillins Pentazocine Streptomycin Tartrazine (drugs with yellow dye)</p> <p>Cough</p> <p>ACE inhibitors</p> <p>Pulmonary edema</p> <p>Contrast media Heroin Methadone Propoxyphene</p>	<p>Pulmonary infiltrates</p> <p>Acyclovir Amiodarone Azathioprine Bleomycin Busulfan Carmustine (BCNU) Chlorambucil Cyclophosphamide Melphalan Methotrexate Methysergide Mitomycin C Nitrofurantoin Procarbazine Sulfonamides</p>
VIII. Gastrointestinal manifestations	
<p>Cholestatic jaundice</p> <p>Anabolic steroids Androgens Chlorpropamide Erythromycin estolate Gold salts Methimazole</p>	<p>Nitrofurantoin Oral contraceptives Phenothiazines</p> <p>Constipation or ileus</p> <p>Aluminum hydroxide Barium sulfate</p>

(Continued)

TABLE 211-1 Clinical Manifestations of Adverse Reactions to Drugs (Continued)

Calcium carbonate	Verapamil
Ferrous sulfate	Zidovudine (AZT)
Ion exchange resins	Intestinal ulceration
Opiates	Solid KCl preparations
Phenothiazines	Malabsorption
Tricyclic antidepressants	Aminosalicilyc acid
Verapamil	Antibiotics (broad-spectrum)
Diarrhea or colitis	Cholestyramine
Antibiotics (broad-spectrum)	Colchicine
Colchicine	Colestipol
Digitalis	Cytotoxics
Magnesium in antacids	Neomycin
Methyldopa	Phenobarbital
Diffuse hepatocellular damage	Phenytoin
Acetaminophen (paracetamol)	Nausea or vomiting
Allopurinol	Digitalis
Aminosalicilyc acid	Estrogens
Dapsone	Ferrous sulfate
Erythromycin estolate	Levodopa
Ethionamide	Opiates
Glyburide	Potassium chloride
Halothane	Tetracyclines
Isoniazid	Theophylline
Ketoconazole	Oral conditions
Methimazole	1. Gingival hyperplasia
Methotrexate	Calcium antagonists
Methoxyflurane	Cyclosporine
Methyldopa	Phenytoin
Monoamine oxidase inhibitors	2. Salivary gland swelling
Niacin	Bretylium
Nifedipine	Clonidine
Nitrofurantoin	Guanethidine
Phenytoin	Iodides
Propoxyphene	Phenylbutazone
Propylthiouracil	3. Taste Disturbances
Pyridium	Biguanides
Rifampin	Captopril
Salicylates	Griseofulvin
Sodium valproate	Lithium
Sulfonamides	Metronidazole
Tetracyclines	Penicillamine
	Rifampin

(Continued)

TABLE 211-1 Clinical Manifestations of Adverse Reactions to Drugs (Continued)

<p>4. Ulceration Aspirin Cytotoxics Gentian violet Isoproterenol (sublingual) Pancreatin</p> <p>Pancreatitis Azathioprine Ethacrynic acid Furosemide</p>	<p>Glucocorticoids Opiates Oral contraceptives Sulfonamides Thiazides</p> <p>Peptic ulceration or hemorrhage Aspirin Ethacrynic acid Glucocorticoids NSAIDs</p>
IX. Renal/urinary manifestations	
<p>Bladder dysfunction Anticholinergics Disopyramide Monoamine oxidase inhibitors Tricyclic antidepressants</p> <p>Calculi Acetazolamide Vitamin D</p> <p>Concentrating defect with polyuria (or nephrogenic diabetes insipidus) Demeclocycline Lithium Methoxyflurane Vitamin D</p> <p>Hemorrhagic cystitis Cyclophosphamide</p> <p>Interstitial nephritis Allopurinol Furosemide Penicillins, esp. methicillin Phenindione Sulfonamides Thiazides</p> <p>Nephropathies Due to analgesics (e.g., phenacetin)</p> <p>Nephrotic syndrome Captopril Gold salts</p>	<p>Penicillamine Phenindione Probenecid</p> <p>Obstructive uropathy Extrarenal: methysergide Intrarenal: cytotoxics</p> <p>Renal dysfunction Cyclosporine NSAIDs Triamterene</p> <p>Renal tubular acidosis Acetazolamide Amphotericin B Degraded tetracycline</p> <p>Tubular necrosis Aminoglycosides Amphotericin B Colistin Cyclosporine Methoxyflurane Polymyxins Radioiodinated contrast medium Sulfonamides Tetracyclines</p>

(Continued)

TABLE 211-1 Clinical Manifestations of Adverse Reactions to Drugs (Continued)

X. Neurologic manifestations

Exacerbation of myasthenia

Aminoglycosides
Polymyxins

Extrapyramidal effects

Butyrophenones, e.g., haloperidol
Levodopa
Methyldopa
Metoclopramide
Oral contraceptives
Phenothiazines
Tricyclic antidepressants

Headache

Ergotamine (withdrawal)
Glyceril trinitrate
Hydralazine
Indomethacin

Peripheral neuropathy

Amiodarone
Chloramphenicol
Chloroquine
Chlorpropamide
Clofibrate
Demeclocycline
Disopyramide
Ethambutol
Ethionamide
Glutethimide
Hydralazine
Isoniazid
Methysergide
Metronidazole

Nalidixic acid
Nitrofurantoin
Phenytoin
Polymyxin, colistin
Procabazine
Streptomycin
Tolbutamide
Tricyclic antidepressants
Vincristine

Pseudotumor cerebri (or intracranial hypertension)

Amiodarone
Glucocorticoids, mineralocorticoids
Hypervitaminosis A
Oral contraceptives
Tetracyclines

Seizures

Amphetamines
Analeptics
Isoniazid
Lidocaine
Lithium
Nalidixic acid
Penicillins
Phenothiazines
Physostigmine
Theophylline
Tricyclic antidepressants
Vincristine

Stroke

Oral contraceptives

XI. Ocular manifestations

Cataracts

Busulfan
Chlorambucil
Glucocorticoids
Phenothiazines

Color vision alteration

Barbiturates
Digitalis
Methaqualone

Streptomycin
Thiazides

Corneal edema

Oral contraceptives

Corneal opacities

Chloroquine
Indomethacin
Vitamin D

(Continued)

TABLE 211-1 Clinical Manifestations of Adverse Reactions to Drugs (Continued)

<p>Glaucoma</p> <ul style="list-style-type: none"> Mydriatics Sympathomimetics <p>Optic neuritis</p> <ul style="list-style-type: none"> Aminosalicylic acid Chloramphenicol Ethambutol Isoniazid 	<ul style="list-style-type: none"> Penicillamine Phenothiazines Phenylbutazone Quinine Streptomycin <p>Retinopathy</p> <ul style="list-style-type: none"> Chloroquine Phenothiazines
XII. Ear manifestations	
<p>Deafness</p> <ul style="list-style-type: none"> Aminoglycosides Aspirin Bleomycin Chloroquine Erythromycin Ethacrynic acid 	<ul style="list-style-type: none"> Furosemide Nortriptyline Quinine <p>Vestibular disorders</p> <ul style="list-style-type: none"> Aminoglycosides Quinine
XIII. Musculoskeletal manifestations	
<p>Bone disorders</p> <p>1. Osteoporosis</p> <ul style="list-style-type: none"> Glucocorticoids Heparin <p>2. Osteomalacia</p> <ul style="list-style-type: none"> Aluminum hydroxide Anticonvulsants Glutethimide 	<p>Myopathy or myalgia</p> <ul style="list-style-type: none"> Amphotericin B Chloroquine Clofibrate Glucocorticoids Oral contraceptives <p>Myositis</p> <ul style="list-style-type: none"> Gemfibrozil Lovastatin
XIV. Psychiatric manifestations	
<p>Delirious or confusional states</p> <ul style="list-style-type: none"> Amantadine Aminophylline Anticholinergics Antidepressants Cimetidine Digitalis Glucocorticoids Isoniazid Levodopa Methyldopa Penicillins Phenothiazines Sedatives and hypnotics 	<p>Depression</p> <ul style="list-style-type: none"> Amphetamine withdrawal Beta blockers Centrally acting antihypertensives (reserpine, methyldopa, clonidine) Glucocorticoids Levodopa <p>Drowsiness</p> <ul style="list-style-type: none"> Antihistamines Anxiolytic drugs Clonidine Major tranquilizers Methyldopa Tricyclic antidepressants

(Continued)

TABLE 211-1 Clinical Manifestations of Adverse Reactions to Drugs (Continued)

Hallucinatory states	Schizophrenic-like or paranoid reactions
Amantadine	Amphetamines
Beta blockers	Bromides
Levodopa	Glucocorticoids
Meperidine	Levodopa
Narcotics	Lysergic acid
Pentazocine	Monoamine oxidase inhibitors
Tricyclic antidepressants	Tricyclic antidepressants
Hypomania, mania, or excited reactions	Sleep disturbances
Glucocorticoids	Anorexiant
Levodopa	Levodopa
Monoamine oxidase inhibitors	Monoamine oxidase inhibitors
Sympathomimetics	Sympathomimetics
Tricyclic antidepressants	

Source: Adapted from AJJ Wood: *HPIM-15*, pp. 432–436. For a more detailed discussion, see Roden DM: *Principles of Clinical Pharmacology*, Chap. 5, p. 33, *HPIM-18*; Wood AJJ: *Adverse Reactions to Drugs*, Chap. 71, p. 430, in *HPIM-15*.

Note: Page numbers followed by *f* or *t* denote figures or tables, respectively.

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