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, H_2 receptor blockers, omeprazole) of unproven benefit.
- Specific measures: *Varices:* octreotide (50-μg bolus, 50-μg/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:* ethinylestradiol/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 ≥51 μmol/L (≥3 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 glucuronosyltransferase activity. Results in mild unconjugated hyperbilirubinemia, almost always <103 μmol/L (<6 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

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 melenic 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 (± syncope, light-headedness, nausea, sweating, thirst).

SHOCK

BP <100 mmHg systolic usually indicates <30% reduction in blood volume (± 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; anticoagulant 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).

41 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 esophagogastroscopy 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.

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

6

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.

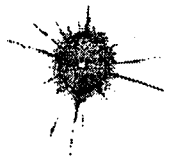
TABLE 33-1 Diagnoses of Pts Admitted to Hospital with Acute Chest Pain Ruled Not Myocardial Infarction

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

[a]In 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.

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.

- *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)

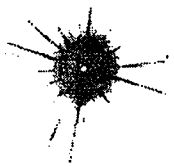
- **Clinical features:** High core temperature in association with an appropriate history (heat exposure, certain drug treatments) and dry skin, hallucinations, delirium, pupil dilation, muscle rigidity, and/or elevated levels of CPK
- **Diagnosis:** It can be difficult to distinguish fever from hyperthermia. 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, adrenocorticotropin hormone; CAD, coronary artery disease; COPD; chronic obstructive pulmonary disorder; EBV, Epstein-Barr virus; RA, rheumatoid arthritis; TSH, thyroid-stimulating hormone.

10

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° ± 0.4°C (98.2° ± 0.7°F), with diurnal variation (lower in A.M., higher in P.M.)
- *Fever:* An elevation of body temperature (>37.2°C/98.9°F in the morning and >37.7°C/99.9°F in the evening) in conjunction with an increase in the hypothalamic set point
- *Fever of unknown origin (FUO):* Temperatures >38.3°C (>101°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°C (>106.7°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. Vesiculobullous 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., meningococcemia, viral hemorrhagic fever, disseminated gonococcemia)
   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

12

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

13

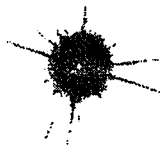
Anticoagulation Therapy for Noncardiogenic Stroke

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.

20 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

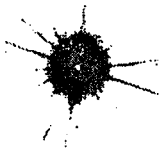
Sudden, severe headache, often with transient loss of consciousness at onset; vomiting is common. Bleeding may injure adjacent brain tissue and produce focal neurologic deficits. A progressive third nerve palsy, usually involving the pupil, along with headache, suggests posterior communicating artery 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.

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)

15

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:

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,

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 ≥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.

elevation (>100,000/μL) 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

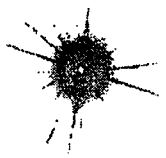
Used in some pts with thrombocytosis associated with myeloproliferative disorders with bleeding and/or thrombotic complications. Other treatments are generally used first. Plateletpheresis also enhances platelet yield from blood donors.

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.

21

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 methylnaltrexone (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	

22

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/μL (<20,000/μL in acute leukemia). One unit elevates the count by about 10,000/μL

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

24

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.

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.
- *Enteroaggregative 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 alkalinization 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 H_2S, 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 cavitary 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.

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:

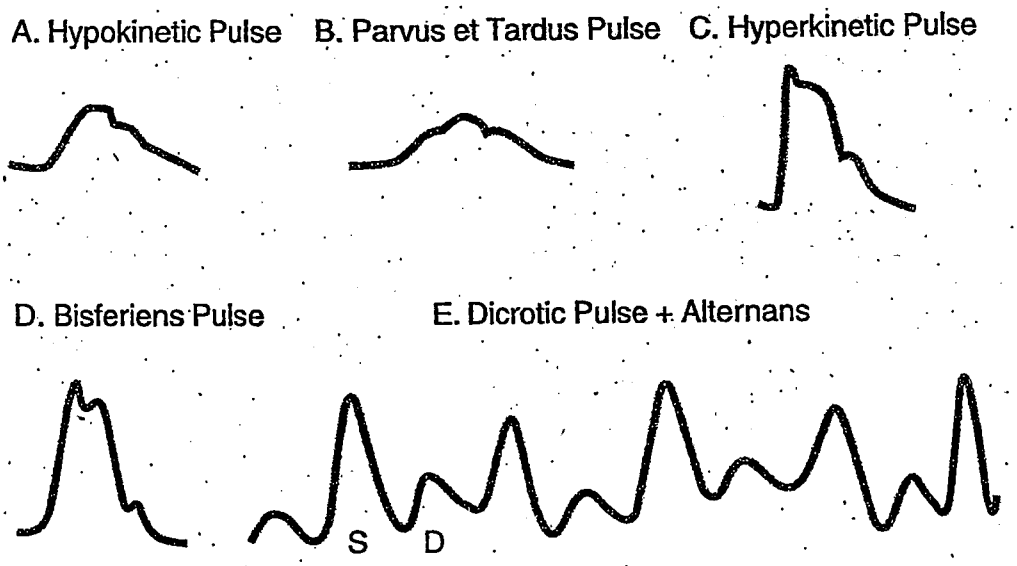


FIGURE 112-1 Carotid artery pulse patterns.

- *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)

S_1

Loud: MS, short PR interval, hyperkinetic heart, thin chest wall. *Soft:* Long PR interval, heart failure, mitral regurgitation, thick chest wall, pulmonary emphysema.

S_2

Normally A_2 precedes P_2 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* A_2: Systemic hypertension
- *Soft* A_2: Aortic stenosis
- *Loud* P_2: Pulmonary arterial hypertension
- *Soft* P_2: Pulmonic stenosis

S_3

Low-pitched, heard best with bell of stethoscope at apex, following S_2; normal in children; after age 30–35, indicates LV failure or volume overload.

S_4

Low-pitched, heard best with bell at apex, preceding S_1; reflects atrial contraction into a noncompliant ventricle; found in AS, hypertension, hypertrophic cardiomyopathy, and coronary artery disease (CAD).

Opening Snap (OS)

High-pitched; follows S_2 (by 0.06–0.12 s), heard at lower left sternal border and apex in MS; the more severe the MS, the shorter the S_2–OS interval.

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.

34

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 A_2, S_4. 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/m^2); sodium restriction; diet rich in fruits, vegetables, and low-fat dairy products; regular exercise; and moderation of alcohol consumption.

150 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.

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, ribbony 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 tbsp 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

[a]Criteria 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

[a]Available 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.

39

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.

40

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.

41

TREATMENT

Osteomalacia

In osteomalacia due to vitamin D deficiency [serum 25(OH)D <50 nmol/L (<20 ng/mL)], vitamin D_2 (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

42

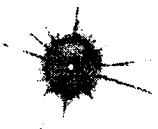
TREATMENT

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.

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—infects 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/μL, and most cases develop at counts of <100/μL.

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

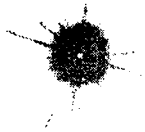
- Pts develop dyspnea, fever, and nonproductive cough.
  - HIV-infected pts often have an indolent course that presents as mild exercise intolerance or chest tightness without fever or cough. Over days to months, these pts develop the more typical symptoms of PCP.
  - Some pts with HIV infection and 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.

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.

108 *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.

45

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.

106 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.

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.

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

48

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, fenoldapam, 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

49

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 O_2 delivery, and reduce acidosis. Reduction in mean arterial pressure after institution of mechanical ventilation commonly occurs due to reduced venous return from positive

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 hypothyroidism 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 [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 [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 [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 [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.

57

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

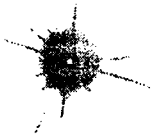
TABLE 1-1 Osmoregulation versus Volume Regulation

	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.

52

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 ≤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: weight/height^2 in kg/m^2) <18.5

ETIOLOGY

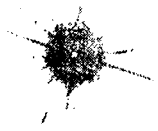
The major etiologies of malnutrition are starvation, stress from surgery or severe illness, and mixed mechanisms. Starvation results from decreased dietary intake (from poverty, chronic alcoholism, anorexia nervosa, fad diets, severe depression, neurodegenerative disorders, dementia, or strict vegetarianism; 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.

53

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.

54

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/μL (<20,000/μL in acute leukemia). One unit elevates the count by about 10,000/μL

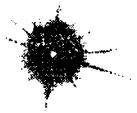
55

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/m^2 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."

- 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 O_2 saturation. Repeat while pt inhales 100% O_2; 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.

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.

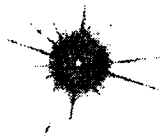
Bronchoscopy is often required to complete the evaluation. In massive hemoptysis, rigid bronchoscopy may be necessary.

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

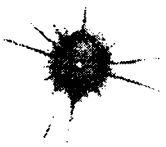
Soft tissue swelling of most or all regions of the body. Bilateral lower-extremity swelling, more pronounced after standing for several hours, and pulmonary edema are usually cardiac in origin. Periorbital edema noted on awakening often results from renal disease and impaired Na excretion. Ascites and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

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,

59

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

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 μmol/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).