A POCKET MANUAL OF DIFFERENTIAL DIAGNOSIS

Fifth Edition

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and appreciation

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Preface

In the practice of clinical medicine, physicians encounter a variety of symptoms, signs, and laboratory tests. Each clinical finding and test result is associated with a differential diagnosis—that is, a list of conditions or disease entities that may produce the given finding or result. Differential diagnoses for various clinical findings are available but are often scattered in a number of different references. Our book contains information gathered from many such sources, compiled in a compact, easily accessible form. It serves both as a convenient guide in the workup of clinical problems as well as a valuable teaching tool. Intended for medical students, physician assistants, house officers, and clinicians, this book helps make the process of medical diagnosis more efficient and comprehensive. It does not, however, serve as a substitute for the thoughtful, skillful integration of data obtained by careful history taking, physical examination, and judicious use of laboratory tests by each and every practitioner.

A *Pocket Manual of Differential Diagnosis*, Fifth Edition, has been thoroughly reviewed and updated. With each revision, we learn something new and enrich our personal knowledge through studying the explosion of information in the field of medicine. Each day brings new and exciting discoveries in medical science: new diagnostic tests for diseases, new methods of treatment, new pharmaceuticals, as well as the discovery of new side effects. An expanded section has been devoted to human immunodeficiency virus (HIV) infection covering new manifestations of HIV infection, including immune reconstitution syndrome. The infectious disease chapter has been revised, reflecting its importance in clinical medicine, the emergence of multidrug-resistant bacteria, and the unfortunate threat of bioterrorism. This chapter contains a comprehensive review of bacterial, viral, and fungal pathogens and their manifestations in both the primary care and health care settings. In fact, the advancement of discovery often outpaces the ability of this text to effectively keep up in some areas. Due to the rapid advancement of pharmaceuticals, the section on drugs has

been deleted from this text in deference to publications that are updated annually.

The text is divided into 12 chapters, ten of which are organized by organ system. The remaining two chapters discuss acid-base and electrolyte disorders, as well as infectious diseases. Each chapter contains multiple entries, representing symptoms, clinical signs, laboratory tests, radiologic findings, and disease processes. The differential diagnosis for each entry is listed, with the more common disease entities generally being listed first. Where possible, disease entities are organized by their pathophysiologic mechanisms. At the end of each entry, references are listed. These cover both general and subspecialty texts. A bibliography of general and subspecialty texts is also included at the end of each chapter.

We would like to express our thanks to all past and current contributors. We acknowledge the expert assistance of all who participated in the production of the manuscript, but especially Dr. Jill Adler, Paul Gasbarra, Matthew Klein, and Patrick Lane. Special thanks go to Denise Menefee and Ursula Ellis of the Deaconess Hospital Medical Library in Oklahoma City, OK. Their assistance in the research for this book was invaluable. We would also like to thank our editors Sonja Seigafuse, Nancy Winter, and Kerry Barrett at Lippincott Williams & Wilkins for their unfailing support in the process of bringing this manuscript to fruition. We appreciate our families' patience and forbearance during our hours of research and manuscript preparation. Most of all, we are grateful to our many patients who have been, and shall always remain, our finest teachers.

Contents

1

ACID-BASE AND ELECTROLYTE DISORDERS

1-A. Acid-Base Nomogram

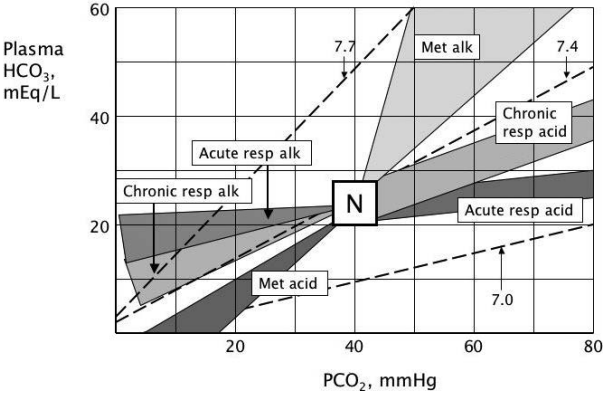

FIGURE 1-1. Redrawn from Shapiro JI, Kaehny WD. Pathogenesis and management of metabolic acidosis and alkalosis. In: Schrier RW, ed. *Renal and electrolyte disorders*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2003:122.

1-B. Metabolic Acidosis

Increased Anion Gap

Renal failure, acute or chronic
Ketoacidosis
    Diabetic
    Alcoholic
    Starvation
Lactic acidosis (see 1-E)
Toxins
    Aspirin
    Methanol
    Ethylene glycol
    Toluene
Massive rhabdomyolysis
Inborn errors of metabolism (e.g., maple syrup urine disease, methylmalonic aciduria)

Normal Anion Gap

Gastrointestinal loss
    Diarrhea
    Ileal loop, ureterosigmoidostomy
    Small bowel or pancreatic fistula or drainage
    Ion-exchange resins (e.g., cholestyramine)
    Calcium or magnesium chloride ingestion
Renal loss
    Renal tubular acidosis (see 5-F)
    Hypoaldosteronism
    Potassium-sparing diuretics
    Carbonic anhydrase inhibitors
Recovery phase of ketoacidosis
Rapid expansion of extracellular fluid volume with bicarbonate-free fluid (e.g., dilutional acidosis)

References

1. Shapiro JI, Kaehny WD. Pathogenesis and management of metabolic acidosis and alkalosis, p. 115. See Bibliography, 1.
2. Rose BD, p. 578. See Bibliography, 2.

1-C. Respiratory Acidosis

Neuromuscular Causes

Ingestion or overdose (e.g., tranquilizers, sedatives, anesthetics, anticholinesterases)

Cerebral, brainstem, or high spinal cord injury or infarct
Primary neuromuscular disease
- Guillain-Barré syndrome
- Myasthenia gravis
- Amyotrophic lateral sclerosis
- Poliomyelitis
- Botulism
- Tetanus

Myopathy involving respiratory muscles, especially:
- Muscular dystrophy
- Hypokalemic myopathy
- Familial periodic paralysis

Primary hypoventilation
Sleep apnea syndrome
Diaphragmatic paralysis

Airway Obstruction

Upper airway
- Laryngeal edema or spasm
- Tracheal edema, stenosis
- Obstructive sleep apnea

Lower airway
- Mechanical
  - Foreign body
  - Aspirated fluid (e.g., vomitus)
  - Neoplasm
- Bronchospasm
  - Acute
  - Chronic (e.g., chronic obstructive pulmonary disease)

Cardiopulmonary-Thoracic Causes

Cardiac arrest
Severe pneumonia
Severe pulmonary edema
Respiratory distress syndrome (infant or adult)
Restrictive lung disease (e.g., interstitial fibrosis)
Massive pulmonary embolism
Pneumothorax, hemothorax
Chest trauma
Kyphoscoliosis
Smoke inhalation
Inadequate mechanical ventilation

References

1. Rose BD, p. 647. See Bibliography, 2.
2. Kaehny WD. Pathogenesis and management of respiratory and mixed acid-base disorders, p. 154. See Bibliography, 1.

1-D. Anion Gap

Increased

Without acidosis
- Administration of sodium salts of organic compounds (e.g., citrate, lactate, acetate)
- High-dose penicillin or carbenicillin
- Respiratory or metabolic alkalosis
- Dehydration

With acidosis
- Renal failure, acute or chronic
- Ketoacidosis
  - Diabetic
  - Starvation
  - Alcoholic
- Lactic acidosis (see 1-E)
- Toxins
  - Aspirin
  - Methanol
  - Ethylene glycol
  - Toluene
- Inborn errors of metabolism (e.g., maple syrup urine disease, methylmalonic aciduria)

Decreased

Hypoalbuminemia
Hypernatremia, severe
Dilution of extracellular fluid
Multiple myeloma
Hyperviscosity
Bromide ingestion
Hypercalcemia, hypermagnesemia (severe)
Lithium toxicity

References

1. Rose BD, p. 578. See Bibliography, 2.
2. Emmett M, Narins RG. Clinical use of the anion gap. *Medicine.* 1977;56:38.

1-E. Lactic Acidosis

Associated with Impaired Tissue Oxygenation

Shock (e.g., hypovolemic, cardiogenic, septic)
Hypoxemia, respiratory failure
Anemia, severe

Occurring in Absence of Apparent Hypoxemia or Circulatory Insufficiency

Diabetes, uncontrolled
Hepatic failure
Renal failure
Malignancy, especially leukemia or lymphoma
Drugs, toxins
- Metformin
- Methanol
- Salicylates
- Human immunodeficiency virus (HIV) nucleoside reverse-transcriptase inhibitors (e.g., stavudine, zidovudine)
- Iron
- Strychnine
- Ethanol
- Cyanide
- Carbon monoxide

Seizures
Excessive muscular activity (e.g., excessive exercise)
Alkalosis, respiratory or metabolic
D-Lactic acidosis (secondary to intestinal bacterial overgrowth)
Congenital enzyme deficiency (e.g., glycogen storage disease)

References

1. Shapiro JI, Kaehny WD. Pathogenesis and management of metabolic acidosis and alkalosis, p. 115. See Bibliography, 1.
2. Rose BD, p. 578. See Bibliography, 2.
3. Kreisberg RA. Lactate homeostasis and lactic acidosis. *Ann Intern Med.* 1980;92:227.

1-F. Metabolic Alkalosis

Chloride-Responsive (Urine Cl^- <10 mEq/L)

Vomiting, nasogastric suction
Gastric drainage or fistula

Diuretics
Posthypercapnic state
Villous adenoma of colon
Congenital chloride diarrhea
Cystic fibrosis

Chloride-Resistant (Urine Cl^- >20 mEq/L)

Primary aldosteronism
Secondary aldosteronism
- Congestive heart failure
- Cirrhosis and ascites
- Malignant hypertension
- Adrenocorticotropic hormone (ACTH) or glucocorticoid excess (Cushing disease, Cushing syndrome, ectopic ACTH production)
- Bartter syndrome
- Gitelman syndrome
- Renin-secreting tumor (e.g., hemangiopericytoma)

Licorice ingestion
Excessive use of chewing tobacco
Severe potassium depletion
Congenital adrenal hyperplasia
Liddle syndrome

Miscellaneous

Administration of alkali or alkalinizing agents, especially in the presence of renal insufficiency:
- Alkalinizing agents (e.g., citrate, lactate)
- Antacids (milk-alkali syndrome)
- Massive transfusion of blood or plasma substitute

Nonparathyroid hypercalcemia (e.g., bone metastases, multiple myeloma)
Nonreabsorbable anionic antibiotics, large doses (e.g., penicillin, carbenicillin)
Glucose ingestion after starvation

References

1. Shapiro JI, Kaehny WD. Pathogenesis and management of metabolic acidosis and alkalosis, p. 115. See Bibliography, 1.
2. Rose BD, p. 551. See Bibliography, 2.

1-G. Respiratory Alkalosis

Central Causes

Voluntary hyperventilation
Anxiety, pain
Hypoxia
Fever
Salicylate toxicity
Head trauma
Brain tumor
Central nervous system infection
Cerebrovascular accident
Pregnancy
Recovery phase of metabolic acidosis

Cardiopulmonary Causes

Congestive heart failure
Pneumonia
Pulmonary embolism
Interstitial lung disease
Adult respiratory distress syndrome
High altitude

Other

Hepatic insufficiency
Sepsis (especially gram-negative)
Drugs
- Progesterone, medroxyprogesterone
- Xanthines (e.g., aminophylline)
- Catecholamines (massive amounts)
- Nicotine

Mechanical ventilation
Heat exposure (e.g., heatstroke)

References

1. Rose BD, p. 673. See Bibliography, 2.
2. Kaehny WD. Pathogenesis and management of respiratory and mixed acid-base disorders, p. 154. See Bibliography, 1.

1-H. Hypernatremia

Pure Water Loss

Inability to obtain or swallow water (e.g., coma, dementia, infancy)

Impaired thirst drive (e.g., hypothalamic lesion)
Increased insensible loss

Excessive Sodium Intake

Iatrogenic sodium administration
    Sodium bicarbonate (cardiopulmonary resuscitation, treatment of lactic acidosis)
Accidental or deliberate ingestion of large quantities of sodium
Seawater ingestion or drowning
Mineralocorticoid or glucocorticoid excess
    Primary aldosteronism
    Cushing syndrome
    Ectopic ACTH production

Loss of Water in Excess of Sodium (without Concomitant Water Intake)

Gastrointestinal loss (e.g., vomiting, diarrhea, intestinal fistula)
Renal loss
    Central diabetes insipidus
        Head trauma
        Posthypophysectomy
        Neoplasm
        Granulomatous disease (e.g., sarcoidosis, tuberculosis, Wegener granulomatosis, syphilis, histiocytosis)
        Central nervous system infection
        Vascular lesion (e.g., cerebrovascular accident, aneurysm, sickle cell disease, Sheehan syndrome)
        Congenital
    Impaired renal concentrating ability
        Osmotic diuresis
            Diabetic ketoacidosis
            Chronic renal failure, especially interstitial disease (e.g., polycystic disease, medullary cystic disease)
            Partial urinary tract obstruction, postobstructive diuresis
            Diuretic phase of acute renal failure
            Mannitol
            Tube feedings
            Infant formula (especially cow's milk)
        Excessive diuretic use
        Hypokalemia
        Hypercalcemia
        Decreased protein intake

Prolonged, excessive water intake
Sickle cell disease or trait
Multiple myeloma
Amyloidosis
Sarcoidosis
Sjögren syndrome
Nephrogenic diabetes insipidus, congenital

Drugs
- Alcohol
- Diuretics
- Lithium
- Demeclocycline
- Phenytoin
- Propoxyphene
- Sulfonylureas
- Amphotericin B
- Methoxyflurane
- Colchicine
- Vinblastine
- Foscarnet

Skin loss (e.g., burns, sweating)
Peritoneal dialysis

Essential Hypernatremia (Reset Osmostat)

References

1. Berl T, Schrier RW. Disorders of water metabolism, p. 1. See Bibliography, 1.
2. Ross EJ, Christie SBM. Hypernatremia. *Medicine.* 1969;48:441.

1-I. Hyponatremia

Factitious Hyponatremia (Normal Serum Osmolality)

Hyperglycemia
Hyperlipidemia
Hyperproteinemia
Hypertonic infusion of poorly reabsorbed solute (e.g., mannitol)

States with Decreased Extracellular Fluid Volume (Loss of Hypotonic Fluid Coupled with Water Intake)

Gastrointestinal loss (e.g., vomiting, diarrhea)
Third-space loss (e.g., burns, sweating, hemorrhagic pancreatitis)

Renal loss
- Diuretic use
- Renal salt-wasting (e.g., advanced chronic renal failure, interstitial disease, renal tubular acidosis)
- Osmotic diuresis
- Mineralocorticoid deficiency

States with Increased Extracellular Fluid Volume

Congestive heart failure
Cirrhosis and ascites
Nephrotic syndrome
Renal failure, acute or chronic

States with Normal or Slightly Increased Extracellular Fluid Volume

Syndrome of inappropriate antidiuretic hormone (SIADH)
- Central nervous system disease
  - Tumor
  - Trauma
  - Infection (meningitis, encephalitis, abscess)
  - Cerebrovascular accident (thrombosis or hemorrhage)
  - Guillain-Barré syndrome
  - Delirium tremens
  - Multiple sclerosis
- Pulmonary disease
  - Tumor
  - Pneumonia
  - Lung abscess
  - Tuberculosis
- Carcinoma (especially lung, pancreas, duodenum)
- Pain, stress (e.g., postoperative state)
- Acute psychosis
- Adrenal insufficiency
- Hypothyroidism
- Positive-pressure ventilation
- Porphyria

Drugs
- Antidiuretic hormone and analogs
- Nicotine
- Sulfonylureas (especially chlorpropamide)
- Narcotics (e.g., morphine)
- Barbiturates
- Isoproterenol
- Nonsteroidal anti-inflammatory drugs

Acetaminophen
Clofibrate
Carbamazepine
Antipsychotic agents (e.g., phenothiazines, haloperidol)
Antidepressants (e.g., amitriptyline, fluoxetine, sertraline)
Colchicine
Vincristine
Cyclophosphamide
Ifosfamide

Psychogenic polydipsia with massive water intake (>20–25 L/day)
Beer drinking (excessive) associated with malnutrition
Essential (reset osmostat)

References

1. Berl T, Schrier RW. Disorders of water metabolism, p. 1. See Bibliography, 1.
2. Rose BD, p. 696. See Bibliography, 2.

1-J. Hyperkalemia

Pseudohyperkalemia

Tourniquet use
Hemolysis (in vitro)
Leukocytosis (>100,000/mm^3)
Thrombocytosis (>500,000/mm^3)

Intracellular to Extracellular K^+ Shift

Acidosis
Heavy exercise
Beta-blocking agents
Insulin deficiency
Digitalis intoxication
Hyperkalemic periodic paralysis
Succinylcholine

K^+ Load (Especially in Presence of Renal Insufficiency)

K^+ supplements
K^+-rich foods
K^+-containing salt substitute
Intravenous K^+
K^+-containing drugs (e.g., potassium penicillin)
Transfusion of aged blood
Hemolysis
Gastrointestinal bleeding

Tumor lysis (especially with leukemia, lymphoma, myeloma)
Rhabdomyolysis or crush injury
Extensive tissue necrosis or catabolism

Decreased K^+ Excretion

Renal failure (acute or chronic)
Drugs
- K^+-sparing diuretics (spironolactone, triamterene, amiloride)
- Beta-blocking agents
- Nonsteroidal anti-inflammatory drugs
- Angiotensin-converting enzyme inhibitors
- Trimethoprim
- Pentamidine

Aldosterone deficiency (see 5-F, Renal Tubular Acidosis, Type IV)
Selective defect in renal K^+ excretion
- Pseudohypoaldosteronism
- Lupus erythematosus
- Sickle cell disease
- Obstructive uropathy
- Renal transplantation
- Congenital

References

1. Rose BD, p. 888. See Bibliography, 2.
2. Peterson LN, Levi M. Disorders of potassium metabolism, p. 171. See Bibliography, 1.

1-K. Hypokalemia

Extracellular to intracellular K^+ shifts
- Alkalosis
- Increased plasma insulin (e.g., treatment phase of diabetic ketoacidosis)
- Beta-adrenergic agonists
- Hypokalemic periodic paralysis
- Chloroquine intoxication

Decreased intake/absorption
- Poor dietary intake
- Geophagia

Gastrointestinal loss
- Vomiting, nasogastric suction
- Diarrhea, laxative or enema abuse

- Malabsorption
- Ureterosigmoidostomy, ileal loop
- Enteric fistula
- Villous adenoma

Renal loss
- Diuretic therapy
- Primary aldosteronism
- Secondary aldosteronism
  - Malignant hypertension
  - Renal artery stenosis
  - Congestive heart failure
  - Cirrhosis and ascites
  - ACTH or glucocorticoid excess (Cushing disease, Cushing syndrome, ectopic ACTH production)
  - Bartter syndrome
  - Gitelman syndrome
  - Liddle syndrome
  - Renin-secreting tumor (e.g., renal hemangiopericytoma)
- Licorice ingestion
- Excessive use of chewing tobacco
- Renal tubular acidosis
- Diuresis during recovery from obstruction or acute renal failure
- Osmotic diuresis
- Drugs and toxins
  - Carbenicillin, penicillin (large doses)
  - Amphotericin B
  - L-Dopa
  - Lithium
  - Thallium
- Hypomagnesemia
- Acute leukemia
- Congenital adrenal hyperplasia

Sweat loss
- Heavy exercise
- Heatstroke

States of rapid cellular synthesis
- Intravenous hyperalimentation
- Recovery from megaloblastic anemia
- Treatment of neutropenia with granulocyte colony-stimulating factor (GCSF)

References

1. Rose BD, p. 836. See Bibliography, 2.
2. Peterson LN, Levi M. Disorders of potassium metabolism, p. 171. See Bibliography, 1.

1-L. Hypercalcemia

Hemoconcentration (increased serum albumin)[1]
Hyperparathyroidism
- Primary
  - Parathyroid adenoma
  - Parathyroid hyperplasia
  - Parathyroid carcinoma
  - Multiple endocrine neoplasia
- Secondary (e.g., chronic renal failure)
- Ectopic

Malignancy
- Bony metastases
- Humoral factors (e.g., parathyroid hormone–related peptide, locally acting cytokines)
- Calcium-binding globulin (multiple myeloma)[1]

Medications
- Thiazides
- Lithium
- Theophylline

Immobilization [in association with rapid bone turnover states (e.g., adolescence or Paget disease)]
Milk-alkali syndrome
Vitamin D intoxication
Vitamin A intoxication
Granulomatous disease (especially sarcoidosis, tuberculosis)
Hypophosphatemia
Recovery from rhabdomyolysis-induced acute renal failure
Hyperthyroidism
Adrenal insufficiency
Acromegaly
Congenital (e.g., familial hypocalciuric hypercalcemia)

References

1. Popovtzer MM. Disorders of calcium, phosphorus, vitamin D, and parathyroid hormone activity, p. 216. See Bibliography, 1.

[1]Normal serum ionized calcium.

1-M. Hypocalcemia

- Hypoalbuminemia[1]
- Vitamin D deficiency states
  - Sunlight deficiency
  - Dietary deficiency
  - Malabsorption (see 4-G)
    - Post gastrectomy or intestinal bypass
    - Sprue, tropical and nontropical
    - Pancreatic insufficiency
    - Hepatobiliary disease with bile salt deficiency
    - Laxative abuse
  - Abnormal metabolism of vitamin D
    - Renal failure (acute and chronic)
    - Liver failure
    - Vitamin D–dependent rickets
    - Anticonvulsants, microsomal enzyme inducers
- Hypoparathyroidism
  - Congenital/familial (e.g., calcium-sensing receptor mutation)
  - Idiopathic (infantile- and adolescent-onset types)
  - Acquired
    - Surgical
    - Iron overload (e.g., after multiple transfusions)
    - Irradiation
    - Neoplasm
- Pseudohypoparathyroidism (types I and II)
- Hyperphosphatemia
  - Phosphate administration
    - Enemas, laxatives
    - Intravenous administration
    - Cow's milk in infant formula
  - Renal failure (chronic or acute)
  - Rhabdomyolysis
  - Tumor lysis syndrome
- Malignancy
  - Osteoblastic metastases (especially carcinoma of prostate, breast)
  - Malignancy with increased thyrocalcitonin levels (especially medullary carcinoma of thyroid)
- Magnesium depletion (see 1-Q)
- Drugs
  - Loop diuretics
  - Agents causing decreased bone resorption (e.g., dactinomycin, calcitonin, mithramycin)

Calcium-complexing agents [e.g., citrate, ethylenediaminetetraacetic acid (EDTA)]
Massive transfusion, plasma exchange
Acute pancreatitis
Healing phase of rickets, osteitis fibrosa
"Hungry bone" (postparathyroidectomy) syndrome
Hyperkalemic periodic paralysis, acute
Osteopetrosis
Neonatal tetany

Reference

1. Popovtzer MM. Disorders of calcium, phosphorus, vitamin D, and parathyroid hormone activity, p. 216. See Bibliography, 1.

[1]Normal serum ionized calcium.

1-N. Hyperphosphatemia

Decreased Excretion or Increased Load, or Both

Renal failure (acute or chronic)
Oral or intravenous phosphate
Phosphate-containing laxatives, enemas
Transfusion of stored blood
Acidosis (especially lactic acidosis or diabetic ketoacidosis)
Rhabdomyolysis
Tumor lysis syndrome
Hemolysis, resolving hematoma
Increased intestinal absorption (e.g., vitamin D intoxication)
Malignant hyperpyrexia
Phosphorus burns
Familial (rare)

Increased Renal Tubular Reabsorption

Hypoparathyroidism
Pseudohypoparathyroidism
Hyperthyroidism
Volume contraction
High atmospheric temperature
Postmenopausal state
Bisphosphonate therapy
Acromegaly
Juvenile hypogonadism
Tumoral calcinosis

Reference

1. Popovtzer MM. Disorders of calcium, phosphorus, vitamin D, and parathyroid hormone activity, p. 216. See Bibliography, 1.

1-O. Hypophosphatemia

Decreased Intake and Absorption and/or Increased Nonrenal Loss

Phosphate-binding antacids
Starvation, cachexia
Vomiting
Diarrhea, malabsorption
Hemodialysis

Transcellular Shift

Glucose infusion (with or without insulin administration)
Nutritional recovery syndrome
Alkalosis, respiratory
Androgens, anabolic steroids
Catecholamines (excessive secretion)
Infusion of:
- Bicarbonate
- Lactate
- Glucagon

Sepsis (especially gram-negative)
Thyrotoxicosis
Heatstroke
Gout, acute
Salicylate poisoning
Pregnancy
Myocardial infarction, acute
"Hungry bone" (postparathyroidectomy) syndrome

Increased Renal Excretion

Hyperparathyroidism, primary
Diuretic therapy
Volume expansion (including hyperaldosteronism)
Hypokalemia
Hypomagnesemia
Steroid therapy, Cushing syndrome
Estrogens, oral contraceptives
Acidosis (especially metabolic)

Renal transplantation
Renal tubular defects (e.g., Fanconi syndrome, vitamin D–resistant rickets)
Tumor phosphaturia (mesenchymoma, neurofibroma, pleomorphic sarcoma, sclerosing or cavernous hemangioma)

Multiple Mechanisms

Alcoholism and alcoholic withdrawal
Diabetic ketoacidosis
Liver disease, hepatic coma
Hyperalimentation
Vitamin D deficiency
Recovery from severe burns

Reference

1. Popovtzer MM. Disorders of calcium, phosphorus, vitamin D, and parathyroid hormone activity, p. 216. See Bibliography, 1.

1-P. Hypermagnesemia

Renal failure, acute and chronic
Increased magnesium load (especially in presence of renal insufficiency)
- Magnesium-containing laxatives, antacids, or enemas
- Treatment of eclampsia (mother and infant)
- Diabetic ketoacidosis

Increased renal magnesium reabsorption
- Hyperparathyroidism
- Familial hypocalciuric hypercalcemia
- Hypothyroidism
- Mineralocorticoid deficiency, adrenal insufficiency

Reference

1. Alfrey AC. Normal and abnormal magnesium metabolism, p. 278. See Bibliography, 1.

1-Q. Hypomagnesemia

Redistribution

Postparathyroidectomy
Correction of metabolic acidosis (especially diabetic ketoacidosis)

Intravenous glucose, hyperalimentation
Refeeding after starvation
Acute pancreatitis

Decreased Intake or Increased Extrarenal Loss, or Both

Alcoholism
Malnutrition, poor intake
Nasogastric suction
Diarrhea, malabsorption (especially involving distal ileum)
Small bowel resection
Intestinal or biliary fistula
Profuse sweating, burns
Lactation

Increased Renal Loss

Drugs
- Diuretics
- Aminoglycosides
- Cisplatin
- Amphotericin B
- Cyclosporine
- Pentamidine
- Foscarnet

Alcohol abuse
Diabetic ketoacidosis
Saline or osmotic diuresis
Postobstructive or postacute renal failure diuresis
Tubulointerstitial renal disease
Hypercalcemic states
Primary or secondary aldosteronism
Potassium depletion
Hypoparathyroidism
Hyperthyroidism
SIADH
Bartter syndrome, Gitelman syndrome
Inherited disorders

Reference

1. Alfrey AC. Normal and abnormal magnesium metabolism, p. 278. See Bibliography, 1.

Bibliography

1. Schrier RW, ed. *Renal and Electrolyte Disorders*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2003.
2. Rose BD. *Clinical Physiology of Acid-Base and Electrolyte Disorders*. 5th ed. New York: McGraw-Hill; 2001.
3. Kasper DS, et al., eds. *Harrison's Principles of Internal Medicine*. 16th ed. New York: McGraw-Hill; 2004.
4. Schrier RW, ed. *Diseases of the Kidney and Urinary Tract*. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.
5. Narins RG, ed. *Maxwell and Kleeman's Clinical Disorders of Fluid and Electrolyte Metabolism*. 5th ed. New York: McGraw-Hill; 1994.

2

CARDIOVASCULAR SYSTEM

2-A. Chest Pain

Skin and subcutaneous lesions [including adiposis dolorosa, thrombophlebitis of thoracoepigastric vein (Mondor disease)]
Breast lesions
- Fibroadenosis
- Chronic cystic mastitis
- Acute breast abscess or mastitis
- Carcinoma
- Trauma and hematoma

Musculoskeletal disorders
- Bruised or fractured rib
- Periostitis
- Periosteal hematoma
- Costochondritis (Tietze syndrome)
- Slipping costal cartilage
- Intercostal muscle "stitch" or cramp
- Intercostal myositis
- Pectoral or other muscular strain
- Shoulder girdle disorders (e.g., subacromial bursitis)
- Cervical disc herniation
- Dorsal spine osteoarthritis
- Thoracic outlet syndrome
- Fibromyalgia

- Neuralgia
  - Herpes zoster
  - Tabes dorsalis
  - Neurofibroma
  - Neoplasm
- Pericardial disease
  - Pericarditis (see 2-H)
  - Neoplasm
  - Congenital absence of left pericardium
- Mediastinal disease
  - Mediastinal emphysema
  - Neoplasm
  - Mediastinitis
- Cardiovascular disease
  - Coronary heart diseases
    - Acute coronary syndrome
    - Acute myocardial infarction
    - Angina pectoris
  - Aortic valvular disease
  - Hypertrophic cardiomyopathy
  - Cardiomyopathy (see 2-G)
  - Mitral valve prolapse
  - Acute aortic dissection
  - Thoracic aortic aneurysm
  - Myocarditis
  - Cardiac rupture
  - Ruptured sinus of Valsalva aneurysm
- Pleural or pulmonary disease
  - Pleuritis of any etiology (e.g., pneumothorax; see 11-K)
  - Tracheobronchitis
  - Pneumonia
  - Pulmonary hypertension (see 11-O)
  - Pulmonary thromboembolism
  - Pulmonary artery rupture
  - Neoplasm
    - Bronchogenic carcinoma
    - Metastatic tumor
    - Mesothelioma
    - Other parenchymal lesions
- Gastrointestinal disease
  - Esophageal lesions
    - Esophagitis
    - Esophageal spasm

- Mallory-Weiss syndrome
- Esophageal rupture
- Foreign body
- Carcinoma
- Zenker diverticulum
- Plummer-Vinson syndrome
- Hyperalgesia

Peptic ulcer disease (with or without perforation)
Gastric distention
Gastritis
- Biliary disease
- Acute cholecystitis
- Biliary colic

Distention of the liver
- Pancreatitis
- Subphrenic abscess
- Splenic infarct
- Splenic flexure syndrome

Thyroiditis
Psychogenic causes
- Hyperventilation
- Anxiety-panic disorders
- Depression
- Somatization disorders

References

1. Braunwald E. Examination of the patient. See Bibliography, 5.
2. Simel DL. Approach to the patient: history and physical examination. See Bibliography, 2.

2-B. Edema

Localized

Acute venous thrombosis
Chronic venous insufficiency
Baker cyst
Tumor invasion or compression of veins and/or lymphatics (e.g., superior vena cava syndrome)
Surgical or radiation damage
Inflammatory disease (e.g., cellulitis)
Allergic process (e.g., angioneurotic edema)
Physical or chemical trauma

Stings and bites
Immobilized or paralyzed limb
Congenital lymphedema
Filariasis

Generalized

Biventricular congestive heart failure (see 2-F)
Tricuspid stenosis and other valvular lesions
Right atrial myxoma
Cor pulmonale (e.g., obstructive sleep apnea) (see 11-M)
Pericardial disease (see 2-H, 2-I)
- Chronic constrictive pericarditis
- Pericardial effusion

Hypoalbuminemic states
- Hepatic cirrhosis
- Nephrotic syndrome
- Protein-losing enteropathy
- Malnutrition
- Severe chronic disease

Acute and chronic renal failure with volume overload
Myxedema
Pregnancy
Iatrogenic salt overload
- Enteral feeding
- Intravenous fluid administration
- Drugs
  - Sirolimus
  - Tamoxifen, letrozole (Femara), and similar drugs
  - Thiazolidiones (e.g., pioglitazone)
  - Estrogens
  - Corticosteroids
  - Minoxidil
  - Calcium channel blockers (e.g., nifedipine)
  - Nonsteroidal anti-inflammatory drugs

Trichinosis
Idiopathic and/or cyclic edema
Hereditary angioneurotic edema

References

1. Braunwald E. Examination of the patient. See Bibliography, 5.
2. Friedman HH. Edema, p. 1. See Bibliography, 1.

2-C. Palpitation

Palpitation without Arrhythmia

Noncardiac disorders
- Anxiety
- Exercise
- Anemia
- Fever
- Volume depletion
- Postural hypotension
- Thyrotoxicosis
- Menopausal syndrome
- Hypoglycemia
- Pheochromocytoma
- Aortic aneurysm
- Migraine syndrome
- Arteriovenous fistula
- Diaphragmatic flutter
- Drugs
  - Sympathomimetic agents
  - Monoamine oxidase (MAO) inhibitors
  - Digitalis
  - Nitrates
  - Theophylline
  - Atropine
  - Coffee, tea
  - Tobacco
  - Alcohol
  - Thyroid preparations

Cardiac disorders
- Aortic regurgitation
- Aortic stenosis
- Patent ductus arteriosus
- Ventricular septal defect
- Atrial septal defect
- Marked cardiomegaly
- Acute left ventricular failure
- Hyperkinetic heart syndrome
- Tricuspid insufficiency
- Pericarditis
- Prosthetic heart valve
- Electronic pacemaker

Palpitation with Arrhythmia (see 2-N)

Extrasystoles
Bradyarrhythmias
Tachyarrhythmias

References

1. Braunwald E. Examination of the patient. See Bibliography, 5.
2. Shander D. Palpitation and disorders of the heartbeat, p. 111. See Bibliography, 1.

2-D. Hypertension

Systolic and Diastolic

Pseudohypertension (e.g., wrong-sized cuff)
Primary (essential)
Renal causes (see 5-J, 5-L)
- Parenchymal
- Vascular
- Renoprival (after bilateral nephrectomy)
- Renin-producing tumor
- Liddle syndrome

Endocrine causes
- Obesity
- Acromegaly
- Hypothyroidism
- Hypercalcemia (e.g., hyperparathyroidism)
- Hypoglycemia
- Adrenal causes
  - Glucocorticoid-remediable aldosteronism (GRA; and other inherited syndromes)
  - Congenital adrenal hyperplasia
  - Cushing syndrome
  - Primary aldosteronism
  - Pheochromocytoma
  - Licorice

Extra-adrenal chromaffin tumors (e.g., carcinoid tumor)
Exogenous
- Oral contraceptives
- Estrogens
- Glucocorticoids
- Mineralocorticoids (e.g., licorice)
- Sympathomimetic agents
- Tyramine-containing foods and MAO inhibitors

Coarctation of aorta
Pregnancy-induced
Neurogenic causes
    Increased intracranial pressure (e.g., brain neoplasm)
    Intracranial hemorrhage
    Postoperative state
    Stress
    Acute porphyria
    Lead poisoning
    Quadriplegia (acute)
    Diencephalic syndrome
    Familial dysautonomia
    Bulbar polio
Increased intravascular volume
    Polycythemia vera
    Iatrogenic causes (e.g., perioperative, postresuscitative)
Burns
Sleep apnea
Psychogenic causes
Drug withdrawal
Other drugs
    Cocaine
    Cyclosporine
    Tacrolimus
    Erythropoietin
Vasculitis
    Sickle cell crisis

Systolic

Aortic rigidity (e.g., atherosclerosis)
Increased cardiac output or stroke volume, or both
    Aortic valvular regurgitation
    Fever
    Arteriovenous fistula, patent ductus arteriosus
    Paget disease
    Beriberi
    Thyrotoxicosis (endogenous or exogenous)
    Anemia
    Hyperkinetic circulation
        Anxiety
        Complete heart block

References

1. Friedman HH. Arterial hypertension, p. 53. See Bibliography, 1.
2. Kaplan NM. Systemic hypertension. See Bibliography, 5.
3. Victor R. Arterial hypertension. See Bibliography, 2.

2-E. Heart Murmurs (see also 2-M)

Systolic

Early systolic
- Physiologic (innocent)
- Small ventricular septal defect
- Large ventricular septal defect with pulmonary hypertension
- Severe acute mitral or tricuspid regurgitation
- Tricuspid regurgitation without pulmonary hypertension

Midsystolic
- Physiologic (innocent)
  - Vibratory murmur
  - Hyperkinetic states
  - Pulmonary ejection murmur
  - Aortic ejection murmur of old age
- Obstruction to left ventricular outflow
  - Valvular aortic stenosis
  - Supravalvular aortic stenosis
  - Hypertrophic cardiomyopathy
  - Aortic valve prosthesis

Aortic dilatation
- Murmurs of mitral regurgitation (occasionally)
- Aortic flow murmur in aortic regurgitation
- Coarctation of aorta
- Supraclavicular arterial bruit
- Obstruction to right ventricular outflow
  - Supravalvular pulmonary arterial stenosis
  - Pulmonic valvular stenosis
  - Subpulmonic (infundibular) stenosis
- Flow murmur of atrial septal defect
- Idiopathic dilatation of pulmonary artery

Pulmonary hypertension of any cause (occasionally)

Late systolic
- Mitral valve prolapse
- Tricuspid valve prolapse

Holosystolic
- Mitral regurgitation
- Tricuspid regurgitation secondary to pulmonary hypertension

- Ventricular septal defect
- Patent ductus arteriosus or aorticopulmonary window with pulmonary hypertension

Diastolic

Early diastolic
- Aortic regurgitation
- Pulmonic regurgitation associated with pulmonary hypertension, congenital or valvular disease

Middiastolic
- Mitral stenosis
- Mitral valve prosthesis
- Tricuspid stenosis
- Atrial myxoma
- Left atrial ball-valve thrombus
- Austin Flint murmur
- Increased diastolic atrioventricular flow
  - Hyperkinetic states
  - Mitral and tricuspid regurgitation
  - Left-to-right shunt (e.g., ventricular septal defect)
  - Acute rheumatic valvulitis (Carey-Coombs murmur)
  - Complete heart block
  - Anomalous pulmonary venous return
- Coronary artery stenosis

Presystolic or late diastolic
- Mitral stenosis
- Tricuspid stenosis
- Atrial myxoma
- Left-to-right shunt
- Complete heart block
- Severe pulmonic stenosis
- Severe aortic insufficiency (Austin Flint)

Continuous

Pseudomurmur (e.g., pericardial friction rub)
Coronary arteriovenous fistula
Patent ductus arteriosus
Surgically created aorticopulmonary fistula
Pulmonary embolism
Ruptured sinus of Valsalva aneurysm
Coarctation of aorta
Bronchial or intercostal artery collateral circulation
Anomalous left coronary artery

Intercostal arteriovenous fistula
Cervical venous hum
Mammary souffle
Aortic arch syndrome
Pulmonary artery branch stenosis or partial occlusion

References

1. Braunwald E. Approach to the patient with cardiovascular disease. See Bibliography, 5.
2. Braunwald E, Perloff JK. Physical examination of the heart and circulations. See Bibliography, 3.
3. Friedman HH. Heart murmurs, p. 70. See Bibliography, 1.

2-F. Congestive Heart Failure

Left Heart Failure

Hypertensive heart disease
Coronary artery disease
Left ventricular diastolic dysfunction
Acute myocardial infarction
Aortic and mitral valvular disease
Cardiomyopathy (see 2-G)
Pericardial disease (see 2-H, 2-I)
Arrhythmias
Congenital heart disease
Endocarditis
Cardiotoxic drugs (e.g., Adriamycin, Herceptin, cocaine, alcohol)
Myocarditis
Acute rheumatic fever
Traumatic heart disease
Thyrotoxicosis
Thiamine deficiency
Anemia
Arteriovenous fistula (e.g., Paget disease)
Neoplastic heart disease
Toxic shock syndrome
Pulmonary thromboembolism
Postcardioversion
Pregnancy
Left atrial thrombus
Salt-retaining drugs (e.g., NSAIDs)

Right Heart Failure[1]

Associated with pulmonary hypertension (see 11-O)
Pulmonary venous disease
Vascular disease
Without pulmonary hypertension
- Pulmonic stenosis
- Tricuspid stenosis (nonrheumatic)
- Tricuspid regurgitation not associated with pulmonary hypertension
- Decreased right ventricular compliance
- Ebstein anomaly
- Right atrial myxoma

Reference

1. Givertz MM, Colucci WS, Braunwald E. Clinical aspects of heart failure; pulmonary edema, high-output failure. See Bibliography, 5.
2. Massie BM. Heart failure: pathophysiology and diagnosis. See Bibliography, 2.

[1]See 12-N.

2-G. Cardiomyopathy[1]

Dilated

Congenital
- Familial
- Duchenne and Becker muscular dystrophy
- Facioscapulohumeral muscular dystrophy
- Limb-girdle muscular dystrophy
- Myotonic dystrophy
- Refsum disease
- Friedreich ataxia
- Fabry disease
- Hunter disease
- Gaucher disease
- Glycogen storage disease
- Hypertrophic pseudoxanthoma elasticum

Acquired
- Idiopathic
- Inflammatory
  - Infective myocarditis (e.g., Chagas disease, coxsackie virus)
  - Acquired immunodeficiency syndrome (AIDS)

- Noninfective
  - Collagen diseases
  - Giant cell myocarditis
  - Kawasaki disease
- Metabolic
  - Hypoxia
  - Nutritional
    - Fatty infiltration
    - Thiamine deficiency
    - Kwashiorkor
    - Pellagra
    - Scurvy
    - Hypervitaminosis D
    - Obesity
    - Selenium deficiency
    - Carnitine deficiency
  - Endocrine
    - Acromegaly
    - Thyrotoxicosis
    - Myxedema
    - Uremia
    - Cushing disease
    - Pheochromocytoma
    - Diabetes
    - Hypophosphatemia
    - Hypocalcemia
    - Gout
    - Porphyria
    - Oxalosis
    - Electrolyte imbalance
- Toxins, drugs
  - Alcohol
  - Disopyramide
  - Daunorubicin
  - Doxorubicin (Adriamycin)
  - Cyclophosphamide
  - Cocaine
  - Bleomycin
  - 5-Fluorouracil
  - Phosphate (poisoning)
  - Phenothiazines and antidepressants
  - Lithium
  - Carbon monoxide

- Emetine
- Chloroquine
- Acetaminophen, paracetamol
- Lead
- Arsenic
- Hydrocarbons
- Antimony
- Cobalt
- Snake or insect bites

Infiltrative
- Right ventricular dysplasia
- Collagen vascular disease
- Amyloidosis
- Hemochromatosis
- Neoplastic
- Sarcoidosis
- Whipple disease

Hematologic
- Leukemia
- Thrombotic thrombocytopenic purpura
- Sickle cell anemia
- Polycythemia vera

Hypersensitivity
- Methyldopa
- Penicillin
- Sulfonamides
- Tetracycline
- Phenindione
- Giant cell myocarditis
- Cardiac transplant rejection

Peripartum

Vasculitis

Physical agents
- Irradiation
- Trauma
- Heatstroke
- Hypothermia
- Chronic tachycardia

Restrictive

Endomyocardial
- Pseudoxanthoma elasticum
- Neoplasm

- Endocardial fibroelastosis
- Fatty infiltration
- Drugs
  - Serotonin
  - Ergotamine
  - Busulfan
  - Methysergide
  - Mercurials
  - Anthracycline
- Löffler endocarditis (hypereosinophilic syndrome)
- Endomyocardial fibrosis
- Carcinoid heart disease
- Whipple disease

Hypertrophic

Idiopathic hypertrophic cardiomyopathy

References

1. Wynne J, Braunwald E. The cardiomyopathies. See Bibliography, 5.

[1]The distinction between cardiomyopathy by functional impairment or etiology is not absolute, and overlap occurs frequently.

2-H Pericarditis[1]

- Idiopathic[2]
- Infection
  - Viral (e.g., AIDS)[2]
  - Bacterial[2]
  - Mycobacterial[2]
  - Mycoplasmal
  - Fungal[2]
  - Parasitic[2]
  - Spirochetal (e.g., Lyme disease)
- Acute myocardial infarction
- Uremia[2]
- Neoplasm[2]
  - Primary (e.g., mesothelioma)
  - Secondary (e.g., lung cancer)
- Aortic dissection with hemopericardium
- Connective tissue or hypersensitivity diseases[2]
  - Postmyocardial infarction (Dressler syndrome)
  - Postpericardiotomy

- Posttrauma (penetrating or blunt)
- Drugs
  - Penicillin
  - Methysergide
  - Daunorubicin and doxorubicin
  - Minoxidil
  - Dantrolene
  - Bleomycin
  - Cyclophosphamide
  - Cyclosporin
- Systemic lupus erythematosus
  - Idiopathic
  - Drug-related
    - Hydralazine
    - Procainamide
    - Phenytoin
    - Isoniazid
    - Methyldopa
- Mixed connective tissue disease
- Scleroderma
- Wegener granulomatosis
- Rheumatoid arthritis
- Polyarteritis nodosa
- Polymyositis
- Reiter syndrome
- Ankylosing spondylitis
- Serum sickness
- Acute rheumatic fever
- Catheter- or pacemaker-induced cardiac perforation
- Cardiopulmonary resuscitation
- Cardiothoracic surgery
- Cardioversion
- Pancreatic pericardial fistula
- Chylopericardium
- Pseudoaneurysm neptune
- Cholesterol pericarditis
  - Idiopathic
  - Rheumatoid arthritis
  - Hypercholesterolemia
  - Myxedema
- Talc or other foreign substance
- Sarcoidosis
- Postirradiation[2]

Esophageal rupture
Uncommon miscellaneous etiologies
- Congenital heart disease (e.g., atrial septal defect)
- Familial Mediterranean fever
- Right atrial myxoma
- Aortic dissection
- Degos disease
- Gaucher disease
- Myeloid metaplasia
- Amyloidosis
- Silicosis
- Giant cell arteritis
- Scorpion fish sting
- Pseudomyxoma peritonei
- Severe chronic anemia (e.g., thalassemia)
- Pancreatitis
- Whipple disease
- Acute gouty arthritis
- Associated with atrial septal defect
- Pulmonary thromboembolism
- Takayasu disease
- Mulibrey nanism[2]
- Nontraumatic hemopericardium
- Inflammatory bowel disease
- Behçet disease

References

1. LeWinter MM, Kabbani S. Pericardial diseases. See Bibliography, 5.
2. Manning WJ. Pericardial disease. See Bibliography, 2.

[1]See also 2-I.

[2]May be commonly associated with development of constrictive pericarditis.

2-I. Pericardial Effusion

Idiopathic

Pericarditis of any cause[1] (see 2-H)
Cancer
Congestive heart failure
Hypoalbuminemia
Cirrhosis

Nephrotic syndrome
Uremia, dialysis
Malnutrition
Chronic disease
Acute pancreatitis
Chylopericardium[1]
    Congenital, idiopathic
    Neoplasm (e.g., lymphoma)
    After cardiothoracic surgery
    Benign obstruction of thoracic duct
Hemopericardium[2]
    Trauma
        Blunt and/or penetrating
        Postsurgical
    Aortic dissection
    Anticoagulants
    Chemotherapeutic agents
    Myocardial infarction
    Cardiac rupture
    Aortic or pulmonary artery rupture
    Coagulopathy
    Uremia
Myxedema[1]

References

1. LeWinter MM, Kabbani S. Pericardial diseases. See Bibliography, 5.
2. Manning WJ. Pericardial disease. See Bibliography, 2.

[1]May be associated with chronic constrictive pericarditis.
[2]May be associated with acute cardiac tamponade.

2-J. Hypotension and Shock

Hypovolemia
    External losses
        Hemorrhage
        Gastrointestinal loss
        Fistulae
        Renal loss
            Diuretics
            Diabetes insipidus
            Osmotic diuresis (e.g., diabetes mellitus)

- Diuretic phase of acute renal failure
- Salt-losing nephropathy
- Postobstructive diuresis
- Cutaneous loss
  - Burns
  - Exudative lesions
  - Perspiration and insensible loss without replacement
- Internal losses
  - Hemorrhage (e.g., anticoagulant therapy)
    - Hemothorax
    - Hemoperitoneum
    - Retroperitoneal hemorrhage
    - Soft tissue injury
    - Fracture
  - Fluid sequestration
    - Ascites
    - Bowel obstruction or infarction
    - Peritonitis
    - Phlegmon (e.g., pancreatitis)
    - Budd-Chiari syndrome

Cardiovascular causes

- Arrhythmia (see 2-N)
- Regurgitant lesions
  - Acute mitral or aortic regurgitation (e.g., papillary muscle or chordae rupture)
  - Rupture of interventricular septum
  - Giant left ventricular aneurysm
- Obstructive lesions
  - Valvular stenosis
  - Hypertrophic cardiomyopathy
  - Atrial myxoma
  - Intracardiac or valvular thrombus (including prosthetic valve)
- Myopathy
  - Acute myocardial infarction
  - Contusion
  - Dilated or restrictive cardiomyopathy (see 2-G)
  - Ventricular wall defects and aneurysms
  - Other myocardial disorders (associated with low cardiac output) (see 2-F)
- Pericardial disease (see 2-H, 2-I)
  - Cardiac tamponade
  - Constrictive pericarditis

- Aortic lesions
  - Acute dissection
  - Coarctation
  - Rupture (e.g., trauma or aneurysm)
- Congenital heart disease
- Vena cava obstruction

Pleuropulmonary disease
- Pneumonia with bacteremia
- Tension pneumothorax
- Severe asthma
- Positive pressure ventilation
- Pulmonary embolism (including thrombus, amniotic fluid, air, tumor)
- Primary or secondary pulmonary hypertension
- Eisenmenger reaction

Infection
- Septicemia, including infected iatrogenic devices
- Specific infections (e.g., dengue fever)
- Toxic shock syndrome

Anaphylaxis

Endocrine disease
- Adrenal insufficiency
- Hypoglycemia or hyperglycemia
- Hypocalcemia or hypercalcemia
- Myxedema or thyroid storm
- Pheochromocytoma
- Pituitary failure including diabetes insipidus

Hypoxia

Severe acidosis or alkalosis

Nonbacterial sepsis syndrome

Hypothermia or hyperthermia

Hepatic failure

Drugs and toxins
- Drug overdose and poisoning (e.g., barbiturates)
- Antihypertensive agents
- Other vasodilators (e.g., nitroglycerin)
- Heavy metals
- Anesthesia (e.g., propofol)

Polycythemia vera

Sickle cell crisis

Hyperviscosity syndrome

Neuropathic causes
- Brainstem failure (e.g., stroke or neoplasm-induced herniation)
- Spinal cord dysfunction
- Autonomic insufficiency

References

1. Calkins H, Zipes DP. Hypotension and syncope. See Bibliography, 5.
2. Parillo JE. Approach to the patient with shock. See Bibliography, 2.

2-K. Cardiac Arrest (Sudden Cardiopulmonary Collapse)

Arrhythmia (with or without digitalis intoxication)
- Tachyarrhythmia
  - Ventricular fibrillation (e.g., prolonged QT syndromes)
  - Short couple torsades de pointe
  - Supraventricular tachycardia
  - Ventricular tachycardia
  - Wolff-Parkinson-White syndrome
- Bradyarrhythmia
  - Sinus bradycardia
  - Junctional rhythm
  - Atrioventricular block
  - Idioventricular rhythm
- Asystole

Upper airway obstruction
- Structural lesion
- Sleep apnea syndrome
- Foreign body

Acute and/or chronic respiratory failure with hypoxemia and/or hypercarbia (see 11-M)

Hypoxia of any cause (e.g., carbon monoxide poisoning)

Pulmonary hypertension

Smoke inhalation

Severe acidosis or alkalosis

Hypoglycemia

Syncope (see 10-D)

Addisonian crisis

- Drug overdose, allergy, adverse reaction or interaction
  - Narcotics
  - Insulin
  - Sedatives
  - Digitalis
  - Catecholamines
  - Quinidine
  - Cocaine
  - Disopyramide
  - Procainamide and other antiarrhythmics
  - Phenothiazines
  - Tricyclic antidepressants
  - Nitrates
  - Aminophylline
  - Propranolol
  - Warfarin
  - Penicillins
  - Sulfonamides
  - Antihypertensive agents
- Shock of any etiology (see also 2-J), especially
  - Cardiac causes
    - Severe coronary heart disease with or without myocardial infarction
    - Hypertensive heart disease
    - Chest trauma (commatio cordis)
    - Valvular disease (e.g., aortic stenosis; see 2-M)
    - Prosthetic valve dysfunction or thrombosis
    - Myocarditis and cardiomyopathy (see 2-G)
    - Cardiac rupture
    - Arrhythmogenic right ventricular dysplasia
    - Congenital heart disease including anomalous coronary artery anatomy
    - Mitral valve prolapse
    - Brugada syndrome
    - Primary conduction system or nodal disease
    - Intracardiac thrombosis or tumor
    - Nonatherosclerotic obstruction of coronary arteries
      - Embolus
      - Arteritis
      - Dissection (e.g., in pregnancy, Marfan)
      - Spasm
      - Congenital anomalies
      - Coronary artery ostia obstruction (e.g., syphilis)

Electrolyte abnormality (especially potassium, calcium, magnesium)
Hypothermia or hyperthermia
Electric shock
Drowning
Insect stings and bites
Neurologic disorders
- Stroke
- Hemorrhage
- Migraine
- Seizure
- Brainstem compression of any cause
- Infection
- Neoplasm

Sudden infant death syndrome
Liquid protein diet
Modified fast diet programs

References

1. Lerman BB. Ventricular arrhythmias and sudden death. See Bibliography, 2.
2. Myerburg RJ, Castellanos A. Cardiac arrest and sudden cardiac death. See Bibliography, 5.

2-L. Complications of Cardiopulmonary Resuscitation

Cerebral
- Hypoxic encephalopathy

Oronasopharyngeal
- Laceration
- Fractured teeth
- Epistaxis
- Laryngeal injury

Neck
- Spinal cord injury
- Vascular injury and hematoma

Lung and chest wall
- Pneumothorax and pneumomediastinum
- Subcutaneous emphysema
- Rib and sternal fractures
- Hemothorax
- Pulmonary contusion

- Atelectasis
  - Malpositioned endotracheal tube
  - Foreign body
  - Secretions
- Aspiration

Heart and pericardium
- Hemopericardium and cardiac tamponade
- Lacerated heart or coronary vessels
- Ruptured ventricle

Visceral injury
- Acute gastric dilatation
- Gastroesophageal, liver, or splenic laceration
- Mesenteric ischemia

Acute renal failure
Embolism to distal vessels with ischemia
Fat embolism
Volume overload
Metabolic alkalosis
- Sodium bicarbonate administration
- Posthypercapnic

Bacteremia

Reference

1. Myerburg RJ, Castellanos A. Cardiac arrest and sudden cardiac death. See Bibliography, 5.

2-M. Valvular Disease[1]

Aortic Valve

Stenosis
- Valvular
  - Congenital
  - Rheumatic
  - Calcific (senile) (e.g., Paget disease, end-stage renal disease)
  - Atherosclerotic
  - Rheumatoid
  - Ochronosis
- Supravalvular
- Subvalvular

Regurgitation
- Congenital
  - Bicuspid aortic valve

- Isolated
- Associated with:
  - Coarctation
  - Ventricular septal defect
  - Patent ductus arteriosus
- Tricuspid aortic valve
  - Isolated
  - Associated with:
    - Ventricular septal defect
    - Valvular aortic stenosis
    - Supravalvular aortic stenosis
    - Subvalvular aortic stenosis
    - Congenital aneurysm of sinus of Valsalva
    - Cusp fenestrations
- Quadricuspid aortic valve

Acquired

- Aortic dilation or distortion
- Valvular
  - Rheumatic heart disease
  - Bacterial endocarditis
  - Calcific aortic valve disease
  - Atherosclerosis
  - Traumatic valve rupture, including iatrogenic
  - Dissection of the aorta
  - Post–aortic valve surgery
    - Postvalvulotomy
    - Leakage around prosthesis
    - Endocarditis
  - Miscellaneous
    - Ankylosing spondylitis
    - Reiter syndrome
    - Rheumatoid arthritis
    - Whipple disease
    - Crohn disease
    - Jaccoud arthropathy
    - Systemic lupus erythematosus
    - Scleroderma
    - Myxomatous degeneration
    - Pseudoxanthoma elasticum
    - Mucopolysaccharidoses
    - Osteogenesis imperfecta
    - Cusp fenestrations
  - Hypertension

- Senile dilatation
- Cystic medial necrosis with or without Marfan syndrome
- Takayasu disease
- Relapsing polychondritis
- Syphilis
- Ankylosing spondylitis
- Psoriatic arthritis
- Ulcerative colitis with arthritis
- Reiter syndrome
- Giant cell arteritis
- Ehlers-Danlos syndrome
- Hypertension
- Cogan syndrome
- Behçet syndrome
- Osteogenesis imperfect
- Associated with bicuspid valves

Mitral Valve

- Stenosis
  - Congenital
  - Rheumatic
  - Carcinoid syndrome
  - Marantic endocarditis
  - Systemic lupus erythematosus
  - Lutembacher syndrome
  - Amyloidosis
  - Rheumatoid arthritis
  - Hunter-Hurler disease
  - Fabry disease
  - Methysergide
  - Whipple disease
- Regurgitation
  - Congenital
    - Isolated mitral regurgitation
    - Hypertrophic cardiomyopathy
    - Connective tissue disorders
      - Ehlers-Danlos syndrome
      - Hurler syndrome
      - Marfan syndrome
      - Pseudoxanthoma elasticum
      - Osteogenesis imperfecta associated with bicuspid valve

- Atrioventricular cushion defect
- Endocardial fibroelastosis
- Parachute mitral valve complex
- Hypoplastic left heart syndrome
- Anomalous left coronary artery from pulmonary artery
- Congenital mitral stenosis
- Corrected transposition of great vessels with or without Ebstein malformation
- Supravalvular ring of left atrium

Acquired

- Coronary heart disease
- Rheumatic (acute or chronic)
- Mitral valve prolapse syndrome
- Papillary muscle dysfunction
  - Coronary heart disease with or without myocardial infarction
  - Neoplasm
  - Myocardial abscess
  - Granulomas
  - Sarcoidosis
  - Amyloidosis
- Ruptured or abnormal chordae tendineae (e.g., idiopathic myxomatous degeneration)
- Bacterial endocarditis
- Calcified mitral annulus
  - Idiopathic systemic hypertension
  - Aortic stenosis
  - Diabetes
  - Chronic renal failure with secondary hyperparathyroidism
- Left ventricular dilatation or aneurysm (e.g., dilated cardiomyopathy)
- Aortic valve disease
- Prosthetic valve disruption
- Trauma
- Post–cardiac surgery
- Rheumatoid arthritis
- Ankylosing spondylitis
- Scleroderma
- Systemic lupus erythematosus
- Left atrial myxoma
- Spontaneous rupture

- Carcinoid syndrome
- Giant left atrium
- Kawasaki disease
- Hypereosinophilic syndrome

Pulmonic Valve

- Stenosis
  - Congenital
    - Valvular stenosis
    - Valvular dysplasia (e.g., Noonan syndrome)
    - Tetralogy of Fallot
    - Supravalvular aortic stenosis syndrome
  - Acquired
    - Intrinsic valvular lesions
      - Rheumatic disease
      - Carcinoid syndrome
      - Endocarditis
      - Primary neoplasm
    - Extrinsic lesions
      - Neoplasm
      - Aortic or septal aneurysm
      - Sinus of Valsalva aneurysm
      - Constrictive pericarditis
- Regurgitation
  - Congenital
    - Absent pulmonic valve
    - Isolated pulmonic regurgitation
    - Associated with:
      - Tetralogy of Fallot
      - Ventricular septal defect
      - Pulmonic valvular stenosis
      - Idiopathic dilatation of pulmonic valve
  - Acquired
    - Valve ring dilatation secondary to pulmonary hypertension of any cause (see 2-F, Right Heart Failure)
    - Pulmonary artery dilatation, idiopathic
    - Bacterial endocarditis
    - Post–pulmonic valve surgery
    - Rheumatic disease
    - Trauma
    - Syphilis
    - Carcinoid syndrome

Marfan syndrome
Induced by pulmonary artery catheter

Tricuspid Valve

Stenosis
- Rheumatic heart disease (acute and chronic)
- Carcinoid syndrome
- Fibroelastosis
- Tricuspid atresia
- Endomyocardial fibrosis

Regurgitation
- Right ventricular dilatation of any cause (e.g., mitral stenosis)
- Pulmonary hypertension (see 2-F, Right Heart Failure)
- Rheumatic heart disease
- Right ventricular papillary muscle dysfunction
- Myxomatous valve and chordae (usually in association with mitral valve prolapse with or without atrial septal defect)
- Trauma
- Bacterial endocarditis
- Carcinoid syndrome
- Ebstein anomaly
- Common atrioventricular canal
- Ventricular septal aneurysm
- Right atrial myxoma
- Constrictive pericarditis
- Endomyocardial fibrosis
- Methysergide
- Systemic lupus erythematosus
- Radiation injury
- Thyrotoxicosis
- Isolated lesion
- After surgical excision
- Marfan syndrome
- Rheumatoid arthritis

References

1. Bonow RO, Braunwald E. Valvular heart disease. See Bibliography, 5.
2. Carabello BA. Valvular heart disease. See Bibliography, 2.

[1]See also 2-E.

2-N. Arrhythmias

Premature Beats

Extrasystole
- Sinus (rare)
- Atrial
- Atrioventricular junctional
- Ventricular

Parasystole
Capture beat
Reciprocal beat
Better atrioventricular conduction (e.g., 3:2), interrupting poorer (e.g., 2:1)
Supernormal conduction during advanced atrioventricular block
Rhythm resumption after inapparent bigeminy

Bradycardia (<60 beats/min)

Sinus bradycardia
Atrioventricular junctional rhythm
Sinus arrhythmia
Wandering atrial pacemaker
Sinoatrial block (second and third degree)
Sinus pause or arrest
Nonconducted atrial or ventricular bigeminy
Hypersensitive carotid sinus syndrome
Atrioventricular block (second and third degree)
Supraventricular tachyarrhythmias with high-grade atrioventricular block (rare)
Escape rhythms (resulting from bradycardia of any cause)
- Atrioventricular junctional
- Idioventricular

References

1. Miller JM. Diagnosis of cardiac arrhythmias. See Bibliography, 5.
2. Shander D. Palpitation and disorders of the heartbeat, p. 117. See Bibliography, 1.
3. Wagner GS. Abnormal rhythms, p. 236. See Bibliography, 4.

TABLE 2-1. Tachycardia (Ventricular Rate >100 Beats/Min)

	Atrial Rate	Ventricular Rate	Ventricular Response to Carotid Sinus Massage
Normal QRS (<0.10 sec)			
Regular rhythm			
Sinus tachycardia	100–200 (usually <160)	100-200 (usually <160)	Gradual slowing with return to previous rate
Atrioventricular (AV) nodal re-entry	140–250	140–250	No effect or abrupt termination
Atrial tachycardia with block	140–250	Variable (usually 75–200)	May abruptly and transiently decrease ventricular rate; generally contraindicated
Atrial flutter	250–320	Variable (usually 75–175)	May transiently slow ventricular rate, revealing flutter waves
Paroxysmal AV junctional tachycardia	100–180	100–180	No effect or abrupt termination
Nonparoxysmal AV junctional tachycardia	Depends on atrial mechanism	70–150	No effect or gradual slowing with return to previous rate; generally contraindicated

Reciprocating tachycardias using an accessory Wolff-Parkinson-White syndrome pathway	150–250	150–250	No effect or abrupt termination
Ventricular tachycardia	Equal to or less than ventricular rate	60–250 (usually >150 and may be slightly irregular)	Atrial rate may slow; no effect on ventricular rate
Irregular rhythm			
Atrial fibrillation	350–600	Variable	Transient decrease in ventricular rate
Paroxysmal atrial tachycardia with variable block	140–250	Variable	May abruptly and transiently decrease ventricular rate; generally contraindicated
Atrial flutter with variable block	250–300	Variable	Transient slowing of ventricular rate, revealing flutter waves
Multifocal atrial tachycardia	100–200	100–200	No effect or gradual slowing

TABLE 2-2. Causes of the Eight Basic Rhythm Patterns

- Regular rhythm at normal rates
  - Normal sinus rhythm
  - Accelerated junctional rhythm
  - Accelerated idioventricular rhythm
  - Atrial flutter with 4:1 conduction
  - Atrial tachycardia with block
- Early beats
  - Extrasystole
  - Parasystole
  - Capture beats
  - Intermittent improved conduction during heart block
  - Rhythm resumption after inapparent bigeminy
- Pauses
  - Nonconducted premature atrial contractions (PACs) (most common)
  - Second-degree atrioventricular (AV) block (types I and II)
  - Second-degree sinoatrial (SA) exit block
  - Concealed conduction
  - Concealed junctional extrasystoles
- Bradycardia
  - Sinus bradycardia
  - Nonconducted atrial bigeminy
  - Second- and third-degree AV block
  - Second- and third-degree SA block
- Bigeminy
  - PACs and premature ventricular contractions (PVCs)
  - 3:2 SA and AV block
  - Atrial tachycardia or flutter with alternate 4:1 and 2:1 conduction
  - Nonconducted atrial trigeminy
  - Reciprocal beating
  - Concealed junctional extrasystoles
- Chaos
  - Atrial fibrillation
  - Atrial flutter with variable conduction
  - Multifocal atrial tachycardia
  - Wandering pacemaker
  - Multifocal PVCs
  - Parasystoles
  - Combinations of the above

TABLE 2-2. (continued)

Regular tachycardia
Sinus tachycardia
Paroxysmal atrial tachycardia
Atrial flutter
Ectopic atrial tachycardia
Junctional tachycardia
Ventricular tachycardia

Adapted from Marriott HJL. *Practical Electrocardiography*. 7th ed. Baltimore: Williams & Wilkins; 1983.

TABLE 2-3. Differentiation of Aberrant Ventricular Condition from Ventricular Ectopy

Characteristics favoring aberrant ventricular conduction
Right bundle-branch block with R′ > R
Rate >170
Initial QRS vector same as conducted QRS
QRS duration <140 msec
Normal axis
Preceding P′
Ashman phenomenon
Characteristics favoring ventricular ectopy
Left axis deviation
QRS >140 msec
Monophasic or diphasic in V1
Fusion or capture beats
Rate <170
Atrioventricular dissociation
R > R′ in V1
Concordant precordial pattern

References

1. Ahtar M. Cardiac arrhythmias with superventricular origin. See Bibliography, 2.
2. Lerman BB. Ventricular arrhythmias and sudden death. See Bibliography, 2.
3. Olgin JE. Specific arrhythmias: diagnosis and treatment. See Bibliography, 5.

2-O. Electrocardiographic Abnormalities

QRS Interval, Prolonged

Bundle-branch blocks
Nonspecific intraventricular conduction delay
Aberrant ventricular conduction
Ectopic ventricular rhythm (e.g., ventricular parasystole)
Drug effect (e.g., quinidine or procainamide)
Electrolyte abnormalities (hyperkalemia, hypokalemia, hypercalcemia, hypermagnesemia)
Pre-excitation (Wolff-Parkinson-White syndrome)
Left ventricular enlargement
Peri-infarction block
Hypothermia

QRS Low Voltage

Anasarca
Pneumothorax
Pleural effusion
Pericardial effusion
Obesity
Emphysema
Hypothyroidism
Infiltrative myocardial disease of amyloid

ST Segment Changes

Elevation
- Normal variant (e.g., early repolarization)
- Artifact
- Myocardial infarction
- Prinzmetal angina
- Ventricular aneurysm
- Type 1-C antiarrhythmic drugs
- Trauma, ventricular
- Reciprocal changes
- Pericarditis
- Postcardioversion
- Hyperkalemia (rarely)
- Bundle-branch block
- Brugada pattern
- Acute cor pulmonale (e.g., pulmonary thromboembolism)
- Myocarditis
- Neoplastic heart disease

- Stroke, intracranial hemorrhage
- Hypertrophic cardiomyopathy
- Hypothermia
- Cocaine abuse
- Hypercalcemia

Depression
- Nonspecific abnormality (e.g., anxiety, shock)
- Drugs
  - Digitalis
  - Tricyclic antidepressants
  - Lithium
- Bundle-branch block
- Left or right ventricular strain
- Electrolyte abnormalities (hyperkalemia or hypokalemia)
- Subendocardial ischemia or infarction
- Mitral valve prolapse
- Tachycardia
- Myocarditis or cardiomyopathy
- Reciprocal changes
- Cerebral or subarachnoid injury
- Pancreatitis or other acute intra-abdominal catastrophe
- Pulmonary thromboembolism
- Hypothyroidism

QT Interval

Prolonged
- Electrolyte abnormalities (hypocalcemia, hypokalemia, "QU" prolongation)
- Complete heart block
- Mitral valve prolapse
- Left ventricular enlargement
- Myocardial infarction and ischemia
- Myocarditis and cardiomyopathy
- Diffuse myocardial disease
- Cerebral or subarachnoid injury, including surgical
- Drugs (e.g., quinidine, procainamide, phenothiazines, sotalol, amiodarone, terfenadine, tricyclic antidepressants)
- Hypothermia (Osburn wave)
- Heritable anomaly
- Alkalosis

Shortened
- Electrolyte abnormalities (hypercalcemia, hyperkalemia, hypermagnesemia)
- Digitalis
- Acidosis

T-Wave Changes

Peaking
- Normal variant
- Nonspecific abnormality
- Electrolyte abnormalities (hyperkalemia, hypocalcemia, hypomagnesemia)
- Acute myocardial ischemia or infarction
- Reciprocal effect in strictly posterior myocardial infarction
- Left ventricular enlargement
- Anemia
- Cerebrovascular disease
- Mitral or aortic regurgitation

Inversion
- Normal
- Early repolarization
- Juvenile T-wave pattern
- Left bundle-branch block, Wolff-Parkinson-White
- Nonspecific abnormality
- Myocardial ischemia or infarction
- Myocarditis
- Pericarditis
- Apical cardiomyopathy (Yamaguchi syndrome)
- Ventricular strain
- Acute or chronic cor pulmonale
- Cerebral or subarachnoid injury
- Drugs (e.g., quinidine, phenothiazines)
- Electrolyte abnormalities (hypokalemia, hypomagnesemia)
- Complete atrioventricular block
- Vagotomy
- After tachycardia
- Idiopathic global T-wave pattern

Q Waves, Abnormal

Myocardial infarction
Ischemia (transient)
Dextrocardia or dextroversion

Hypertrophic cardiomyopathy
Reversal of right and left arm leads (lead I)
Ventricular enlargement
Acute and chronic cor pulmonale (e.g., pulmonary embolism, chronic obstructive pulmonary disease)
Pre-excitation (Wolff-Parkinson-White syndrome)
Cardiac surgery
Spontaneous pneumothorax (especially left)
Cardiomyopathy and myocarditis (e.g., hypertrophic cardiomyopathy; see 2-G)
Localized destructive myocardial disease (e.g., neoplasm)
Left bundle-branch block
Left anterior division block
Normal variant (rare)
Tachycardia (transitory)
Critical illness (e.g., pancreatitis, shock)

References

1. Goldschlager N. Electrocardiography. See Bibliography, 5.
2. Shander D. Palpitation and disorders of the heartbeat, p. 111. See Bibliography, 1.
3. Wagner GS. Abnormal rhythms, p. 236. See Bibliography, 4.

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1. Friedman HH. *Problem-Oriented Medical Diagnosis*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2001.
2. Goldman L, Ausielo D. *Cecil Textbook of Medicine*. 22nd ed. Philadelphia: WB Saunders; 2004.
3. Kasper DL, Braunwald E, Fauci AS, Hauser SL, et al., eds. *Harrison's Principles of Internal Medicine*. 16th ed. New York: McGraw-Hill; 2005.
4. Wagner DS. *Marriott's Practical Electrocardiography*. 10th ed. Philadelphia: Lippincott Williams & Wilkins, 2001.
5. Zipes DP, Libby P, Bonow RO, Braunwald E. *Braunwald's Heart Disease—A Text Book of Cardiovascular Medicine*. 7th ed. Philadelphia: WB Saunders; 2005.

3

ENDOCRINE/METABOLIC SYSTEM

3-A. Hypothermia

Congestive heart failure
Drugs and intoxicants
- Alcohol
- Anesthetics, general
- Antidepressants
- Antithyroid agents
- Barbiturates
- Benzodiazepines
- Cancer chemotherapy
- Clonidine
- Hypnotics/sedatives
- Lithium
- Marijuana
- Neuromuscular blockers
- Opiates
- Phenothiazines
- Tranquilizers

Endocrine disorders
- Adrenal insufficiency
- Diabetic ketoacidosis
- Hypoglycemia
- Hypopituitarism
- Hypothyroidism

- Environmental exposure (especially in neonates; premature or low birth weight babies; the elderly; or persons who are mentally impaired, unconscious, immobilized, drugged, debilitated, under anesthesia, wearing inadequate clothing, or exhausted)
  - Accidental
    - Cold water immersion
    - Sports related
    - Occupational
    - Wet clothing
  - Iatrogenic
    - Administration of cold blood or intravenous fluids
    - Iced saline gastric lavage
    - Peritoneal dialysis
- Hepatic failure
- Increased cutaneous blood flow
  - Burns
  - Erythrodermas (including toxic epidermal necrolysis and psoriasis)
- Malnutrition
- Myocardial infarction
- Neurologic disorders
  - Central [hypothalamic and central nervous system (CNS) dysfunction; note: the hypothermia may be paroxysmal]
    - Anorexia nervosa
    - Brain tumors
    - Cerebrovascular accidents, paralysis, paresis
    - Encephalopathy
    - Episodic spontaneous hypothermia with hyperhidrosis (including those with agenesis of the corpus callosum—Shapiro syndrome)
    - Head trauma
    - Other hypothalamic lesions (e.g., infarction, midbrain lesions, sarcoidosis)
    - Parkinson disease
    - Prolonged cardiopulmonary resuscitation
    - Seizure
    - Spontaneous periodic hypothermia (paroxysmal hypothermia—nearly always with evidence

of injury to the preoptic area of the hypothalamus)
Wernicke encephalopathy
Peripheral
Diabetic autonomic neuropathy
Spinal cord transection above T1
Pancreatitis
Prolonged surgery
Respiratory failure
Sepsis
Shock
Uremia

References

1. Danzl DF. Hypothermia and frostbite, p. 122. See Bibliography, 1.
2. Yoder E. Disorders due to heat and cold, p. 628. See Bibliography, 5.

3-B. Weight Gain

Cessation of cigarette smoking
Congenital disorders (e.g., Prader-Willi syndrome and pseudohypoparathyroidism)
Depression
Disturbances of hypothalamic satiety centers
Encephalitis
Trauma
Tumors
Drugs
Antidepressants
Monoamine oxidase inhibitors
Selective serotonin uptake inhibitors
Tricyclic antidepressants
Antiepileptics
Carbamazepine
Gabapentin
Valproate
Antihistamines
Antihypertensives
Alpha-adrenergic blockers
Beta-adrenergic blockers
Clonidine

- Antipsychotics
  - First-generation antipsychotics
    - Haloperidol
    - Loxapine
    - Phenothiazines
  - Second-generation (atypical) antipsychotics
    - Aripiprazole
    - Clozaril
    - Olanzapine
    - Quetiapine
    - Risperidone
- Glucocorticoids (pharmacologic doses)
- Highly active antiretroviral therapy
- Hypoglycemic agents
  - Insulin
  - Meglitinides
  - Sulfonylureas
  - Thiazolidinediones
- Megestrol acetate
- Oral contraceptives
- Progestational agents

Endocrine disorders
- Acromegaly
- Cushing syndrome
- Hypothyroidism
- Insulinoma
- With treatment of diabetes mellitus
- With treatment of thyrotoxicosis

Exogenous obesity
Increased body fluid (see 2-B)

Reference

1. Jensen MD. Obesity, pp. 1342–1343.
See Bibliography, 5.

3-C. Weight Loss

Ankylosing spondylitis
Bilateral lesions of the lateral hypothalamus (hypothalamic anorexia)
Decreased food intake/malnutrition
- Abdominal angina
- Anorexia of aging
- Chronic/recurrent nausea/vomiting

- Dementia/Alzheimer disease
- Esophageal disease/dysphagia
- Medications
  - Angiotensin-converting enzyme inhibitors (distortion of taste)
  - Antibiotics
  - Antidepressants
  - Digoxin
  - Levodopa
  - Metformin
  - Nonsteroidal anti-inflammatory agents
  - Sedatives
  - Theophylline
- Obstructive disease (including pyloric obstruction due to chronic peptic ulcer disease)
- Oral disease (e.g., loose dentures, poor or absent teeth)
- Pain
- Poor social situation
- Postantrectomy (especially Billroth II) or gastrectomy
- Poverty
- Unpalatable diets

Endocrine disorders
- Adrenal insufficiency
- Diabetes mellitus
- Diabetic neuropathic cachexia
- Hypercalcemia
- Panhypopituitarism
- Pheochromocytoma
- Thyrotoxicosis

Extensive exercise

Infection, especially:
- Amebic abscess
- Bacterial endocarditis
- Chronic suppurative pleuropulmonary disease
- Cryptosporidiosis
- Fungal diseases
- Giardiasis
- Human immunodeficiency virus (HIV)
- *Mycobacterium avium* pulmonary infections
- Parasitic infestations
- Paraspinal/epidural abscess
- Tuberculosis
- Visceral leishmaniasis

Maldigestion/malabsorption
- Inflammatory bowel disease
- Pernicious anemia

Malignancy, especially:
- Biliary
- Breast
- Gastrointestinal
- Glucagonoma
- Hepatic
- Leukemia
- Lymphoma
- Myeloma
- Pancreatic
- Pulmonary
- Somatostatinoma

Myelofibrosis
Myotonic dystrophy
Neuromuscular disorders
Parkinson disease
Pink disease (mercury poisoning in children)
Psychiatric disease
- Alcoholism
- Anorexia nervosa
- Anxiety disorders
- Bulimia
- Conversion disorders
- Depression
- Manipulative behaviors
- Psychosis/paranoia
- Schizophrenia
- Substance abuse

Severe chronic organ failure
- Heart failure (cardiac cachexia)
- Hepatic disease
- Pulmonary disease
- Renal failure

Stroke
Systemic lupus erythematosus

References

1. Reife CM. Weight loss, p. 234. See Bibliography, 1.
2. Baron RB. Protein-energy malnutrition, p. 1315. See Bibliography, 5.

3-D. Thyrotoxicosis

Thyrotoxicosis with High or Normal Radioactive Iodine Uptake

Abnormal thyroid stimulator
- Human chorionic gonadotropin (HCG)
  - Gestational transient thyrotoxicosis (typically in association with hyperemesis)
  - Tumors secreting HCG
    - Choriocarcinoma
    - Hydatidiform mole
    - Embryonal cell carcinoma of the testis
- Thyroid-stimulating hormone (TSH)
  - Resistance to thyroid hormone (often tachycardic)
  - TSH-secreting pituitary adenoma
- Thyroid-stimulating immunoglobulins
  - Amiodarone-induced thyrotoxicosis type I [usually the radioactive iodine (RAI) uptake is low]
  - Graves disease
  - Hashitoxicosis
  - Interferon-induced Graves disease
  - Interleukin-2–induced Graves disease
  - Neonate of mother with Graves disease

Autonomous thyroid function
- Constitutive activation of TSH receptors (autosomal dominant)
- Toxic adenoma
- Toxic multinodular goiter

Infarction of a thyroid adenoma

Postaspiration thyrotoxicosis (after needle aspirate of thyroid cyst)

TSH hyperresponsiveness (autosomal dominant)

Thyrotoxicosis with a Low Radioactive Iodine Uptake

Excessive thyroidal production of thyroid hormone
- Iodine-induced thyrotoxicosis (the "Jod-Basedow" phenomenon)
  - Amiodarone-induced thyrotoxicosis type I (rarely the RAI uptake may be normal or elevated)
  - Other iodine-containing drugs (including kelp tablets and certain cough preparations)
  - Iodine-containing x-ray contrast agents

Extrathyroidal sources of thyroid hormone
- Ectopic thyroid tissue
  - Metastatic differentiated thyroid cancer (usually follicular carcinoma)
  - Struma ovarii
- Hormone ingestion
  - "Hamburger thyrotoxicosis"
  - Iatrogenic
  - Thyrotoxicosis factitia

Inflammation of the thyroid
- Drug-induced thyroiditis
  - Amiodarone-induced thyrotoxicosis type II
  - Interferon-α
  - Interleukin-2
- Postpartum thyroiditis
- Radiation thyroiditis
- Silent (painless) thyroiditis
- Subacute (De Quervain, granulomatous) thyroiditis

Postparathyroidectomy thyrotoxicosis (transient—2 weeks)

References

1. Burman KD. Hyperthyroidism, p. 416. See Bibliography, 2.
2. Braverman LE, Utiger RD. Introduction to thyrotoxicosis, p. 454. See Bibliography, 4.

3-E. Hypothyroidism

Primary Hypothyroidism

Destruction of the thyroid gland
- External-beam radiation therapy to the head/neck
- RAI (may be transient)
- Replacement of thyroid tissue
  - Infiltrative diseases
    - Amyloidosis
    - Cystinosis
    - Hemochromatosis
    - Kaposi sarcoma
    - Lymphoma of the thyroid
    - Metastases to the thyroid
    - Riedel thyroiditis
    - Sarcoidosis and other granulomatous diseases
    - Scleroderma
- Surgery (total or subtotal thyroidectomy) (may be transient)

- Thyroiditis
  - Acute (suppurative) thyroiditis [bacterial, mycobacterial, fungal, parasitic, gummatous, *Pneumocystis carinii* infection in acquired immunodeficiency syndrome (AIDS)]
  - Chronic
    - Atrophic thyroiditis
    - Hashimoto thyroiditis (including after Graves disease)
  - Due to drug therapy
    - Amiodarone
    - Interferon-α
    - Interleukin-2
    - Lymphokine-activated killer cell therapy
  - Transient
    - Postpartum thyroiditis
    - Silent (painless) thyroiditis
    - Subacute (De Quervain, granulomatous) thyroiditis
- Generalized resistance to thyroid hormone
- Inhibition of thyroid hormone synthesis or accelerated disappearance from the circulation
  - Exposure to exogenous goitrogens (see 3-I)
  - Inherited defects of thyroid hormone synthesis
  - Iodine deficiency
  - Multiple hepatic hemangiomas (infants)
  - Selenium deficiency (usually with concomitant iodide deficiency)
  - Thalidomide
  - Thyroid agenesis, dysgenesis, or ectopy
- Thyroid growth-blocking antibodies
- Transplacental passage of antithyroid drugs, chemicals, or agents
- TSH hyporesponsiveness
  - Pseudohypoparathyroidism type Ia
  - TSH receptor abnormalities
  - TSH receptor–blocking antibodies

Secondary (Pituitary) or Tertiary (Hypothalamic) Hypothyroidism

- After withdrawal of thyroid hormone therapy in euthyroid patients (transient)
- Pituitary/hypothalamic disease (see 3-T)
- Thyroid-releasing hormone deficiency or insensitivity

TSH synthetic defect
Treatment with bexarotene and other retinoid X receptor–selective ligands

Increased Requirement for Oral Levothyroxine

Decreased gastrointestinal absorption of levothyroxine tablets
- Drugs that interfere with levothyroxine absorption
  - Aluminum hydroxide–containing antacids
  - Bile acid sequestrants
  - Calcium
  - Ciprofloxacin
  - Ferrous sulfate and ferrous fumarate
  - Raloxifene
  - Sodium polystyrene sulfonate
  - Sucralfate

Increased levothyroxine metabolism
- Carbamazepine
- Phenobarbital
- Phenytoin
- Rifampin

Increased levothyroxine requirement by an unknown mechanism
- Lovastatin
- Sertraline

Levothyroxine malabsorption
- Celiac disease and other malabsorption syndromes
- Large quantities of fiber, bran, or soy

References

1. Shapiro LE, Surks MI. Hypothyroidism, p. 446. See Bibliography, 2.
2. Braverman LE, Utiger RD. Introduction to hypothyroidism, p. 698. See Bibliography, 4.

3-F. Serum Thyroxine

Elevated Total Thyroxine but Normal Free Thyroxine

Increased affinity of serum binding proteins for thyroxine (T_4)
- Increased affinity of albumin for T_4
  - Familial dysalbuminemic hyperthyroxinemia (total T_4 and free T_4 index elevated, but free T_4 normal) (note: a familial dysalbuminemic hypertriiodothyroninemia has also been described)

- Increased affinity of transthyretin for T_4
  - Familial increase in transthyretin binding (autosomal dominant) (total T_4 and free T_4 index elevated, but free T_4 normal)
- Increased serum concentration of binding proteins for T_4
  - Increased thyroid-binding globulin (TBG) concentration
    - Estrogens (oral but not transdermal)
    - Drugs (small increases in TBG)
      - Clofibrate
      - Fluorouracil
      - Heroin
      - Methadone
      - Perphenazine
      - Raloxifene (very little effect)
      - Tamoxifen (small effect)
    - Increased endogenous estrogen production
      - Estrogen-secreting adrenal or testicular tumors
      - Pregnancy
    - Inherited increase in TBG
    - Liver disease
      - Chronic active hepatitis
      - Primary biliary cirrhosis
      - Infectious hepatitis
  - Increased T_4 binding to autoantibodies to T_4

Elevated Total and Free Thyroxine

- Thyrotoxicosis (see 3-D)
- Iatrogenic (excessive doses of oral levothyroxine)
- Amphetamines (large doses)
- Antibodies that interfere with the thyroid hormone assay
  - Autoantibodies to T_4 and triiodothyronine (T_3)
  - Human antimouse antibodies
- Generalized resistance to thyroid hormone
- High altitude
- Inhibition of binding of T_4 to thyroid-binding proteins (increases free T_4 but not total T_4)
  - Enoxaparin
  - Heparin
- Inhibition of peripheral conversion of T_4 to T_3
  - 5′-Deiodinase inhibition
  - Amiodarone
  - Neonatal period
  - Nonthyroidal illness (including acute psychiatric illness)

Decreased Total Thyroxine but Normal Free Thyroxine

- Decreased levels of serum thyroid-binding proteins
  - Acromegaly
  - Cirrhosis
  - Cushing syndrome
  - Drugs
    - Androgens and anabolic steroids
    - Asparaginase
    - Chlorpropamide
    - Colestipol combined with niacin
    - Danazol
    - Large doses of adrenocorticotropic hormone (ACTH) or glucocorticoids (chronic)
    - Salsalate
    - Sulfonamides
  - Inherited decrease in serum levels of TBG
  - Malnutrition
  - Protein loss (e.g., nephrotic syndrome)
  - Nonthyroidal illness
  - Testosterone-secreting adrenal or ovarian tumors
- Decreased affinity of serum-binding proteins for T_4
  - Decreased affinity of TBG for T_4
    - Inherited TBG that has decreased affinity for T_4
    - Nonthyroidal illness
  - Decreased affinity of transthyretin for T_4
    - Familial amyloid polyneuropathy
    - Nonthyroidal illness
- Displacement of T_4 from serum-binding sites
  - Drugs
    - Furosemide (oral doses >100 mg or large intravenous doses)
    - Salicylates (in high doses)

Decreased Total and Free Thyroxine

- Hypothyroidism (see 3-E)
- Increased hepatic metabolism of T_4 (TSH usually remains normal)
  - Carbamazepine
  - Phenobarbital
  - Phenytoin
  - Rifampin

Severe nonthyroidal illness
Ingestion of T_3 alone

References

1. Toft AD, Beckett GJ. Measuring serum thyrotropin and thyroid hormone and assessing thyroid hormone transport, pp. 335–340. See Bibliography, 4.
2. Weiss RE, Wu SY, Refetoff S. Diagnostic tests of the thyroid. See Bibliography, 6.

3-G. Serum Thyroid-Stimulating Hormone

Elevated Serum Thyroid-Stimulating Hormone

Primary hypothyroidism (see 3-E)
    Overt (low free T_4)
    Subclinical (normal free T_4)
Addison disease
Drugs
    Domperidone (acutely)
    Metoclopramide (acutely)
Heterophile antibodies interfering with the TSH assay
Pulsatile TSH secretion, nocturnal
    TSH surge
Recovery from nonthyroidal illness
Resistance to thyroid hormone
TSH-secreting pituitary tumors

Low Serum Thyroid-Stimulating Hormone

Thyrotoxicosis (see 3-D)
    Overt (low free T_4)
    Subclinical (normal free T_4)
    T_3 toxicosis (with normal free T_4)
After treatment of thyrotoxicosis, before the axis recovers from suppression
Drugs
    Bromocriptine (acutely)
    Dopamine
    Glucocorticoids (acutely)
Nonthyroidal illness
Secondary (pituitary) and tertiary (hypothalamic) hypothyroidism (see 3-E)

References

1. Toft AD, Beckett GJ. Measuring serum thyrotropin and thyroid hormone and assessing thyroid hormone transport, pp. 336, 338, 341. See Bibliography, 4.
2. Weiss RE, Wu SY, Refetoff S. Diagnostic tests of the thyroid, pp. 1924–1925. See Bibliography, 6.

3-H. Radioactive Iodine Uptake

Factors Causing Increased Uptake

- Reflecting increased hormone synthesis
  - Certain types of thyrotoxicosis (see 3-D)
  - Excessive hormone losses
    - Chronic diarrhea states
    - Nephrosis
    - Soybean ingestion
  - Response to glandular hormone depletion
    - Rebound after suppression of TSH
    - Recovery phase of silent, subacute, or other transient destructive thyroiditis
    - Rebound phase after withdrawal of iodide or other antithyroid drugs (if TSH is elevated)
- Not reflecting increased hormone synthesis
  - Iodine deficiency
    - Dietary
    - Excessive loss
      - Dehalogenase defect
      - Pregnancy (RAI contraindicated)
    - Hashimoto thyroiditis (if TSH is elevated)
    - Inherited disorders of thyroid hormone synthesis (except for iodide-trapping defects)
    - Lithium administration

Factors Causing Decreased Uptake

- Reflecting decreased hormone synthesis
  - Primary hypofunction
    - Drugs
      - Major effect
        - Glucocorticoids (in large doses, acutely)
        - Para-aminobenzoic acid
        - Perchlorate
        - Salicylates (>5 g/day)
        - Sulfonamides

- Sulfonylureas
- Thalidomide
- Thiocyanate
- Thionamides
  - Carbimazole
  - Methimazole
  - Propylthiouracil
- Minor effect (small increases in TSH)
  - Aminoglutethimide
  - Ethionamide
  - Resorcinol (topical)
- Hashimoto thyroiditis (end stage)
- Some hormone biosynthetic defects (especially defects in iodide trapping)
- Status post thyroidectomy, radioiodine, or external radiotherapy to the head/neck
- Transient thyroiditis (active phase)
  - Postpartum thyroiditis (RAI contraindicated if breast feeding)
  - Silent (painless) thyroiditis
  - Subacute (De Quervain, granulomatous) thyroiditis
- Secondary hypofunction
  - Exogenous thyroid hormone
  - Secondary (pituitary) or tertiary (hypothalamic) hypothyroidism

Not reflecting decreased hormone synthesis

- Certain types of thyrotoxicosis (see 3-D)
- Increased nonradioactive iodide exposure
  - Cardiac or renal failure with iodide retention
  - Increased dietary iodide
  - Pharmacologic iodide exposure
    - Amiodarone
    - Other iodine-containing drugs (e.g., kelp tablets, certain cough preparations, topical)
    - Iodine-containing x-ray contrast agents
  - Rapid hormone release due to very severe hyperthyroidism (rare)

References

1. McDougall R. In vivo radionuclide tests and imaging, p. 314. See Bibliography, 4.
2. Weiss RE, Wu SY, Refetoff S. Diagnostic tests of the thyroid, p. 1902. See Bibliography, 6.

3-I. Goiter/Neck Mass

Diffuse Goiter

- Euthyroid or hypothyroid
  - Cigarette smoking (thiocyanate)
  - Increased intrinsic growth potential
  - Exposure to thyroid growth factors
    - Excess TSH
      - Chemicals
        - Cobalt
        - Flavonoids (polyphenols) (e.g. topical resorcinol)
        - Organochlorines
      - Cytokines (e.g., insulin-like growth factor-1, epidermal growth factor)
      - Defects in thyroid hormone synthesis (inherited)
      - Drugs
        - Amiodarone
        - Aminoglutethimide
        - *p*-Aminosalicylic acid
        - Antithyroid drugs
          - Carbimazole
          - Methimazole
          - Propylthiouracil
        - Ethionamide
        - Iodine excess (long term)
        - Lithium carbonate
        - Nicardipine
        - Para-aminobenzoic acid
        - Perchlorate
        - Tumor necrosis factor-α
  - Infiltration
    - Amyloidosis
    - Thyroiditis
      - Acute (suppurative) thyroiditis
      - Hashimoto thyroiditis
      - Riedel thyroiditis
      - Silent (painless) thyroiditis
      - Subacute (De Quervain, granulomatous) thyroiditis
    - Sarcoidosis
  - Ingestion of goitrogens (these rarely cause goiter unless patient is iodine deficient)
    - *Brassica* genus (broccoli, brussels sprouts, cabbage, cauliflower, kale, rape, rutabagas, swedes, turnips)

- Cyanoglucosides (bamboo shoots, cassava, lima beans, maize, sweet potatoes)
- Kelp
- Soybean milk/soybean flour

Iodine deficiency
Neonatal
- Maternal antithyroid drug therapy
- Maternal iodine therapy

Pregnancy
Protein calorie malnutrition
Resistance to thyroid hormone
Selenium deficiency (usually with concomitant iodine deficiency)
Thyroid growth immunoglobulins

Hyperthyroid
Excessive stimulation by HCG
- Gestational transient thyrotoxicosis (usually with hyperemesis)
- Tumors secreting HCG
  - Choriocarcinoma
  - Embryonal cell carcinoma of the testis
  - Hydatidiform mole

Graves disease
Hashitoxicosis
Neonatal (mother with Graves disease)
Resistance to thyroid hormone (tachycardia)
Silent (painless) thyroiditis
Subacute thyroiditis
TSH-secreting pituitary tumor

Multinodular Goiter

Multiple adenomas
Nontoxic nodular goiter (same causes as euthyroid or hypothyroid; see 3-I)
Toxic multinodular goiter

Nongoiter Neck Masses

Branchial cleft cyst
Cystic hygroma
Thyroglossal duct cyst

References

1. Davis PJ, Davis FB. Nontoxic goiter, pp. 367–369. See Bibliography, 2.
2. Hermus AR, Huysmans DA. Pathogenesis of nontoxic diffuse and nodular goiter. pp. 873–877. See Bibliography, 4.
3. Hegedüs L, Gerber H, Bonnema SJ. Multinodular goiter, pp. 2115–2118. See Bibliography, 6.

3-J. Solitary Thyroid Nodule

Thyroid Lesions

Colloid nodule (also called hyperplastic nodule or adenomatous nodule)
Ectopic normal or tumoral tissue within the thyroid
- Parathyroid
- Thymic

Follicular adenoma (including Hurthle cell adenoma)
Focal or asymmetric thyroiditis
- Acute (suppurative) thyroiditis (including *Pneumocystis carinii* infection in AIDS)
- Hashimoto thyroiditis (asymmetric)
- Riedel struma
- Subacute (De Quervain, granulomatous) thyroiditis

Malignancy
- Anaplastic carcinoma
- Carcinosarcoma
- Follicular carcinoma
- Hemangioendothelioma
- Lymphoma
- Malignant form of histiocytosis X
- Malignant hemangioendothelioma
- Medullary carcinoma
- Metastases to the thyroid from other primaries
- Mixed papillary-follicular carcinoma
- Papillary carcinoma
- Paraganglioma
- Sarcoma, angiosarcoma, fibrosarcoma
- Squamous cell carcinoma

Miscellaneous
- Agenesis of one lobe
- Asymmetric multinodular goiter
- Compensatory hyperplasia after hemithyroidectomy

Focal granulomatous disease (e.g., sarcoidosis)
Hematoma
Simple cyst

Nonthyroid Lesions

Branchial cleft cyst and other epithelial cysts
Carotid aneurysm
Cystic hygroma
Dermoid
Fibrosis (including postradiation)
Hemangioma
Laryngocele/bronchocele
Lipoma
Lymph node
Parathyroid adenoma
Parathyroid cyst
Teratoma
Thyroglossal duct cyst

References

1. Kaplan MM. Clinical evaluation and management of solitary thyroid nodules, p. 997. See Bibliography, 4.
2. Pacini F, DeGroot LJ. Thyroid neoplasia, pp. 2148, 2156. See Bibliography, 6.

3-K. Hypercortisolism

Acute or chronic physical illness
Alcoholism
Apparent hypercortisolism due to interference with testing
Fenofibrate [interferes with urinary free cortisol high-performance liquid chromatography (HPLC) but not radioimmunoassay (RIA) or HPLC-mass spectrometry (MS)/MS]
Depression
Elevated levels of cortisol-binding globulin
Congenital
Estrogens
Pregnancy
Generalized glucocorticoid resistance
Pulsatile cortisol secretion (normal)
Cushing syndrome
ACTH-dependent Cushing syndrome
Pituitary tumor secreting ACTH (usually intrasellar, but occasionally ectopic)

- Ectopic ACTH production
  - Appendicular carcinoma
  - Carcinoids
  - Cystadenoma of the pancreas
  - Enthesioneuroblastoma (olfactory neuroblastoma)
  - Epithelial carcinoma of the thymus
  - Medullary carcinoma of the thyroid
  - Melanoma
  - Oat cell carcinoma of the lung
  - Other cancers, rarely (ovarian, breast, prostate, gallbladder, gastrointestinal)
  - Pancreatic islet cell carcinoma
  - Paraganglioma
  - Pheochromocytoma
  - Pulmonary tumorlets (nests of neuroendocrine cells)
  - Squamous cell carcinomas
    - Cervix
    - Larynx
    - Lung
- Ectopic corticotropin-releasing hormone (CRH)–secreting tumor
  - Bronchial carcinoid
  - Gangliocytoma
  - Medullary carcinoma of the thyroid
  - Oat cell carcinoma of the lung
  - Prostatic carcinoma
  - Pheochromocytoma

- ACTH-independent Cushing syndrome
  - Adrenal hyperplasias causing Cushing syndrome
    - Bilateral macronodular hyperplasia
      - ACTH dependent (the existence of this entity has been disputed)
      - ACTH independent
        - Due to abnormal expression of receptors for gastrointestinal peptide, luteinizing hormone (LH)/HCG, vasopressin, catecholamines, serotonin, estradiol, interleukin-1) (can cause adrenal adenoma as well as bilateral hyperplasia)
        - Etiology unknown

- Bilateral micronodular dysplasia
  - With atrophy of intervening nonnodular cortex
    - Primary pigmented nodular adrenal disease
      - Familial (autosomal dominant, with or without the Carney complex)
      - Sporadic
  - With hyperplasia of intervening nonnodular cortex (including McCune-Albright syndrome, with activating mutation in the G-protein linked to adenyl cyclase)
- Nodular adrenal hyperplasia secondary to abnormal production of 21-deoxycortisol

Factitious (surreptitious ingestion of glucocorticoids)
Iatrogenic (glucocorticoid therapy, including parenteral, topical, nasal, and inhaled corticosteroids)
Ingestion of Klack solution
Primary adrenal tumor
- Adenoma
- Carcinoma

References

1. Schteingart GE. Cushing syndrome, pp. 724–729. See Bibliography, 2.
2. Stewart PM. The adrenal cortex, pp. 511–515. See Bibliography, 3.
3. Cavagnini F, Giraldi FP. Adrenal causes of hypercortisolism, pp. 2365–2370. See Bibliography, 6
4. Malchoff DM, Malchoff CD. Generalized Glucocorticoid resistance, pp. 2389–2390. See Bibliography, 6.

3-L. Adrenal Insufficiency

Primary

Autoimmune/idiopathic
- Autoimmune polyendocrine syndrome type I
- Autoimmune polyendocrine syndrome type II
- Sporadic

Congenital/genetic
- ACTH resistance syndromes
  - Mutations in *MCR-2*
  - Triple A syndrome
- Adrenal aplasia or hypoplasia
- Adrenoleukodystrophy/adrenomyelodystrophy
- Congenital adrenal hyperplasias

- Hereditary unresponsiveness to ACTH (familial glucocorticoid deficiency)
- Drugs
  - Inhibition of cortisol biosynthesis
    - Aminoglutethimide
    - Metyrapone
    - *o,p*-Dichlorodiphenyldichloroethane (mitotane)
    - Drugs that cause adrenal insufficiency in patients under stress or with limited pituitary or adrenal reserve
      - Etomidate (effect can last for several days)
      - Ketoconazole
      - Spironolactone
      - Suramin
      - Trilostane
  - Acceleration of cortisol metabolism (usually causing adrenal insufficiency only in patients with limited pituitary or adrenal reserve, or patients on replacement glucocorticoid therapy)
    - Barbiturates
    - Phenytoin
    - Rifampin
- Iatrogenic
  - Irradiation
  - Bilateral adrenalectomy
- Infectious
  - AIDS
    - *Cryptococcus*
    - Cytomegalovirus
    - Lymphoma
    - Metastatic Kaposi sarcoma
    - *Mycobacterium avium* complex
    - Toxoplasmosis
    - Tuberculosis
  - Fungal
  - Syphilis
  - Tuberculosis
- Infiltrative
  - Amyloidosis
  - Hemochromatosis
  - Sarcoidosis
- Neoplastic
  - Leukemic infiltration
  - Lymphoma
  - Metastatic cancer

Vascular
- Bilateral adrenal hemorrhage and/or infarction
  - Anticoagulants
  - Antiphospholipid syndrome
  - Arteritis
  - Coagulopathy
  - Emboli
  - Hypotension
  - Interleukin-2 therapy
  - Intravascular lymphoma
  - Neonatal
  - Postadrenal venography
  - Pregnancy
  - Sepsis (especially Waterhouse-Friderichsen syndrome)
  - Surgery
  - Thrombosis
  - Trauma

Secondary (Pituitary) or Tertiary (Hypothalamic)

After removal of ACTH-secreting pituitary tumor
After removal of cortisol-secreting adrenal tumor
After withdrawal of drugs that suppress ACTH
- ACTH
- Glucocorticoids
- Megestrol acetate

Hypothalamic/pituitary disease (see 3-T)
Isolated ACTH deficiency (including *POMC* gene mutations and processing defects)

References

1. Stewart PM. The adrenal cortex, p. 526. See Bibliography, 3.
2. Ten S, New M, Maclaren N. Addison's disease 2001. *J Clin Endocrinol Metab.* 2001;86:2909–2922.

3-M. Adrenal Masses/Hyperplasia

Unilateral or Bilateral Adrenal Masses

Adrenal adenomas
Adrenal carcinomas
Adrenal cysts
Adrenal hyperplasia
Amyloidosis

Angiosarcoma
Fibrous histiocytoma
Ganglioneuromas
Ganglioneuroblastoma
Hemangioma
Hamartomas
Hemorrhage
Infection (echinococcosis, cryptococcosis, paragonimiasis)
Leiomyoma
Leiomyosarcoma
Lipoma
Metastasis from other cancers
Myelolipomas
Neurofibroma
Nodular hyperplasia
Pheochromocytomas
Pseudoadrenal masses (e.g., arising from kidney, pancreas, spleen, lymph nodes, and vessels)
Schwannoma
Teratocarcinoma
Teratoma
Xanthomatosis

Bilateral Masses/Hyperplasia

Functional
- ACTH-dependent Cushing syndrome
- Congenital adrenal hyperplasia
- Pheochromocytoma
- Conn syndrome, hyperplastic variety
- Micronodular adrenal disease
- Hemorrhage
- Idiopathic
- Infections (tuberculosis, fungal)
- Infiltrative (leukemia, lymphoma)
- Metastases (bilateral)
- Replacement (amyloidosis)

References

1. Cook DM, Loriaux DL. The incidental adrenal mass. In: Mazzaferri EL, et al., eds. *Advances in endocrinology and metabolism*. Volume 5. St. Louis: Mosby; 1994:152, 160.
2. Copeland PM. The incidentally discovered adrenal mass: an update. *Endocrinologist*. 1999;416.

3-N. Erectile Dysfunction

- Drug induced
  - Antiadrenergic
    - Benztropine
    - Guanethidine
    - Phenoxybenzamine
    - Phentolamine
    - Prazosin
    - Propranolol
    - Thioridazine
  - Antiandrogen
    - Cimetidine (in high doses)
    - Cyproterone acetate
    - Estrogens
    - Finasteride
    - Flutamide
    - Ketoconazole
    - Progestins
    - Spironolactone
  - Anticholinergic
    - Atropine
    - Disopyramide
    - Ganglionic blocking agents
    - Tricyclic antidepressants
  - CNS depressants
    - Alpha-methyldopa
    - Barbiturates
    - Benzodiazepines
    - Butyrophenones
    - Carbamazepine
    - Clonidine
    - Ethanol
    - Fluoxetine
    - Opiates
    - Phenothiazines
    - Phenytoin
    - Primidone
    - Reserpine
  - Other drugs
    - Amphetamines
    - Cocaine
    - Marijuana
    - Monoamine oxidase inhibitors

- Selective serotonin reuptake inhibitors
- Thiazides

Endocrine
- Cushing syndrome (see 3-K)
- Diabetes mellitus
- Feminizing adrenal or testicular tumors
- Hyperprolactinemia (see 3-S)
- Hypogonadism (see 3-O)
- Hypopituitarism (see 3-T)
- Hypothyroidism (see 3-E)
- Thyrotoxicosis (see 3-D)

Endurance factors
- Anemia
- Angina
- Congestive heart failure
- Hepatic failure
- Postmyocardial infarction
- Pulmonary insufficiency
- Sleep disorders
- Systemic illnesses
- Uremia

Genitourinary
- Cystitis
- Genital malignancy
- Hydrocele
- Hypospadias
- Micropenis and other congenital deformities
- Pelvic fracture
- Penectomy
- Penile trauma
- Peyronie disease
- Phimosis
- Priapism
- Prostate irradiation
- Prostatitis
- Ruptured urethra
- Scleroderma
- Seminal vesiculitis
- Urethral stricture
- Urethritis

Neurologic
- Amyotrophic lateral sclerosis
- Arachnoiditis

- Autonomic neuropathy
- Bicycle rider's palsy
- Friedreich ataxia
- General paresis
- Herniated disc
- Multiple sclerosis
- Neurosyphilis (general paresis, tabes dorsalis)
- Parkinsonism
- Peripheral neuropathy
- Pernicious anemia (subacute combined degeneration)
- Shy-Drager syndrome
- Spinal cord disease
- Tabes dorsalis
- Temporal lobe disorders
- Transverse myelitis

Psychogenic

Surgical

- Abdominal perineal resection
- Aortoiliac surgery
- External sphincterotomy
- Pelvic or retroperitoneal lymphadenectomy
- Perineal prostatectomy
- Perineal prostatic biopsy
- Rectosigmoid surgery
- Sympathectomy
- Vascular surgery (abdominal aortic aneurysm repair)

Vascular

- Aneurysm
- Aortoiliac arteriosclerosis
- Arterial dysplasia
- Arteritis
- Embolism
- Hypertension
- Leriche syndrome
- Priapism
- Thrombosis

References

1. Cunningham GR, Hershkowitz M. Erectile dysfunction, pp. 1161–1162 and 1166–1168. See Bibliography, 2.
2. Braunstein GD. Testes, p. 503. See Bibliography, 8.

3-O. Male Hypogonadism

Primary

Acquired
- Adult seminiferous tubule failure
- Amyloidosis
- Autoimmune destruction
- Congenital adrenal hyperplasia
- Cryptorchidism
- Drugs
  - Chemotherapy
  - Ethanol
  - Ketoconazole
  - Marijuana
  - Spironolactone
- Granulomatous disease (especially leprosy)
- Leukemia
- Mumps
- Polyarteritis nodosa
- Surgery (castration)
- Testicular radiation
- Testicular trauma

Developmental
- Congenital anorchia
- Decreased responsiveness to testosterone (male pseudohermaphroditism)
  - Incomplete androgen insensitivity syndrome
  - 5α-Reductase deficiency
- Enzymatic defects of testosterone biosynthesis
- Functional prepubertal castrate (vanishing testes syndrome)
- Klinefelter syndrome
- LH-resistant testes
- Myotonic dystrophy
- Persistent müllerian duct syndrome
- Sertoli cell–only syndrome
- Ullrich-Noonan syndrome (male Turner syndrome)
- XY/XO mixed gonadal dysgenesis
- XX male
- XYY syndrome

Secondary (Pituitary) or Tertiary (Hypothalamic)

Hypopituitarism (see 3-T)
Constitutional delay of puberty
Cushing syndrome (see 3-K)

Estrogen-secreting tumors
Exposure to estrogen in embalming compounds
Hemochromatosis
Hyperprolactinemia (see 3-S)
Idiopathic hypogonadotropic hypogonadism (may be adult onset)
Isolated gonadotropin deficiency
- Hypogonadotropic eunuchoidism
  - Adrenal hypoplasia congenita
  - Inherited immunologically active, biologically inactive LH
  - Kallmann syndrome
  - Mutations in the gonadotropin-releasing hormone receptor
  - Predominant LH deficiency, "fertile eunuch" syndrome
  - Variant form (isolated follicle-stimulating hormone deficiency)
- Specific genetic syndromes
  - Bardet-Biedl syndrome
  - Börjeson-Forssman-Lehman syndrome
  - CNS anomalies, genital hypoplasia, and ear anomalies and/or deafness (CHARGE) syndrome
  - Fröhlich syndrome
  - Laurence-Moon syndrome
  - Lowe syndrome
  - Martsolf syndrome
  - Möbius syndrome
  - Multiple lentigines (leopard syndrome)
  - Prader-Labhart-Willi syndrome
  - Rothmund-Thomson syndrome
  - Rud syndrome
  - Steroid sulfatase deficiency

Morbid obesity
Pituitary dwarfism
Ramelteon therapy
Severe illness (acute or chronic)
Uremia
Withdrawal of androgen therapy (temporary)

Combined Primary and Secondary

Aging
Cirrhosis
Sickle cell disease

References

1. Plymate SR. Male hypogonadism, p. 1126. See Bibliography, 2.
2. Tung DS, Cunningham GR. Androgen deficiency in men. *Endocrinologist*. 2007;17:101–115.

3-P. Gynecomastia

Acromegaly
Chest wall trauma (including hip spica cast)
Drugs
- Amiodarone
- Amphetamines
- Androgens (aromatizable)
  - Testosterone enanthate
  - Testosterone propionate
- Angiotensin-converting enzyme inhibitors
- Antineoplastics (especially alkylating agents and cisplatin)
- Busulfan
- Calcium channel blockers
- Cimetidine
- Clomiphene
- Cyproterone acetate
- D-penicillamine
- Diazepam
- Diethylpropion
- Digitalis preparations
- Estrogens, phytoestrogens
- Ethionamide
- Etomidate
- Finasteride
- Flutamide
- Gonadotropins
- Haloperidol
- Heroin
- Isoniazid
- Ketoconazole
- Marijuana
- Methyldopa
- Metronidazole
- Omeprazole
- Phenothiazines
- Phenytoin
- Progestogens

- Ranitidine
- Reserpine
- Spironolactone
- Sulindac
- Theophylline
- Tricyclic antidepressants

Hyperprolactinemia (see 3-S)
HIV infection
Idiopathic gynecomastia
Increased estrogen production
Increased availability of estrogen precursors
- Congenital adrenal hyperplasia
  - 21-Hydroxylase deficiency
  - 11-Hydroxylase deficiency
  - Increased peripheral aromatase activity
    - Hereditary
    - Neoplasia
      - Fibrolamellar hepatocellular carcinoma
      - Testicular carcinomas
    - Obesity
- Thyrotoxicosis
- True hermaphroditism

Klinefelter syndrome
Male hypogonadism (see 3-O)
Myotonic dystrophy
Neoplasms
- Secreting estrogens or estrogenic precursors
  - Feminizing adrenal tumors
  - Testicular tumors (especially Leydig cell tumors, Sertoli cell tumors, choriocarcinomas, and germinal epithelial tumors)
- Secreting gonadotropins
  - Gonadotropin-secreting pituitary adenomas
- Secreting HCG
  - Nontesticular tumors
    - Gynecomastia reported with elevated HCG
      - Adenocarcinoma of the stomach
      - Carcinoma of the lung (especially bronchogenic carcinoma)
      - Carcinoma of the pancreas
      - Hepatoma, hepatoblastoma
      - Renal cell carcinoma
      - Undifferentiated mediastinal carcinoma

- Detectable HCG reported without gynecomastia (yet)
  - Biliary tract
  - Breast
  - Colon/rectal
  - Esophagus
  - Insulinoma
  - Leukemia
  - Liver sarcoma
  - Lymphoma
  - Medullary carcinoma of the thyroid
  - Melanoma
  - Multiple myeloma
  - Ovarian
  - Pheochromocytoma
  - Sarcomas
  - Small intestine
- Testicular tumors
  - Germ cell tumors of the testis (embryonal carcinomas, choriocarcinomas, teratomas, rarely seminomas)
- Secreting prolactin
  - Pituitary prolactinomas

Persistent pubertal macromastia
- Physiologic
  - Normal physical finding
  - Neonatal
  - Pubertal
  - Senescent

Pseudogynecomastia
- Obesity
- Benign or malignant breast tumor

Psychological stress

Spinal cord injury

Systemic diseases (especially recovery from chronic disease)
- Cirrhosis
- Hepatitis
- HIV infection
- Poorly controlled diabetes mellitus
- Pulmonary tuberculosis
- Refeeding gynecomastia (after starvation)
- Uremia and dialysis

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2. Hershkovitz E, Leiberman E. Gynecomastia: a review. *Endocrinologist.* 2002;12:321–332.
3. Santen RJ. Gynecomastia, pp. 3286–3287. See Bibliography, 6.

3-Q. Amenorrhea

Hypothalamic and Pituitary Causes

Adrenal insufficiency
Androgen excess (see 8-D)
Chronic debilitating diseases (e.g., liver disease, uremia, regional ileitis)
Congenital hypothalamic hypogonadism
  Idiopathic
  With anosmia or hyposmia (Kallmann syndrome)
Cushing syndrome
Defects in gonadotropin synthesis
Estrogen-secreting ovarian or adrenal tumors
Gonadotropin-secreting pituitary tumors
HCG-secreting tumors
Hypopituitarism (see 3-T)
Hypothalamic-pituitary dysfunction due to factors extrinsic to the hypothalamus and pituitary
  Anovulation
    Hypothyroidism
    Obesity
    Perimenopause
    Polycystic ovary syndrome
  Hyperprolactinemia (see 3-S)
  Lactation
  Nutritional
    Acute weight loss
    Malnutrition (including anorexia nervosa)
    Underweight
  Postpill amenorrhea
  Pregnancy
  Pseudocyesis
  Strenuous exercise
  Stress
  Thyrotoxicosis
  Idiopathic delayed puberty
  Secretion of biologically inactive gonadotropin

Ovarian Causes

Acquired (premature ovarian failure)
- Autoimmune
- Chemotherapy
- Idiopathic (premature ovarian failure)
- Myotonic dystrophy
- Postinfection
  - Mumps oophoritis
  - Severe pelvic inflammatory disease
- Radiation
- Surgical castration
- Trauma

Congenital
- Congenital thymic aplasia
- Galactosemia
- Gonadal agenesis
- Gonadal dysgenesis (including Turner syndrome)
- Ovarian enzymatic deficiency
  - 17α-Hydroxylase deficiency
  - 17,20-Lyase deficiency
- Resistant ovary syndrome (Savage syndrome)
- Sex chromosome mosaicism
- Trisomy X
- True hermaphroditism
- XY gonadal dysgenesis

Menopause

Uterine and Outflow Tract Abnormalities

Female pseudohermaphroditism
- Congenital adrenal hyperplasia
- Exposure to maternal androgens in utero

Hysterectomy

Male pseudohermaphroditism
- 5α-Reductase deficiency
- Androgen insensitivity syndrome
- Enzymatic defects in testosterone biosynthesis

Müllerian agenesis

Müllerian anomalies
- Absence or anomalies of vagina, cervix, endometrium, or endometrial cavity
- Imperforate hymen
- Labial agglutination or fusion

Trauma (including surgical)
- Cervical stenosis
- Sclerosis of the uterine cavity (Asherman syndrome)
  - Abortion
  - After uterine surgery (caesarian section, metroplasty, myomectomy)
  - Repeated or overzealous uterine curettage
  - Severe, generalized pelvic infections
  - Tuberculous endometritis
  - Uterine schistosomiasis
- Vaginal stenosis

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2. Speroff L, Fritz MA. Amenorrhea, pp. 418–445. See Bibliography, 7.

3-R. Galactorrhea/Nipple Discharge

Galactorrhea
- Hyperprolactinemia (see 3-S)
- Normoprolactinemic galactorrhea
  - Idiopathic galactorrhea with menses
  - Post–oral contraceptive galactorrhea

Pseudogalactorrhea
- Intramammary lesions
  - Benign
    - Fibrocystic disease
    - Intraductal papilloma
  - Malignant neoplasm

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1. Goldenberg IS. Nipple discharge. *Postgrad Med.* 1981;70:116–117.
2. Santen RJ. Benign breast disorders, pp. 3068–3069. See Bibliography, 6.

3-S. Hyperprolactinemia

Addison disease
Antiprolactin autoantibodies
Chronic renal failure

- Cirrhosis
- Drugs
  - Alpha-methyl-para tyrosine
  - Amphetamines
  - Androgens
  - Antidepressants
    - Dibenzoxazepine antidepressants (e.g., amoxapine)
    - Tricyclic antidepressants
  - Antihypertensives
    - Alpha-methyldopa
    - Reserpine
    - Verapamil
  - Cimetidine
  - Benzodiazepines
  - Cocaine
  - Cyproterone acetate
  - Domperidone
  - Estrogen (estrogens cause hyperprolactinemia in pregnancy, but typical doses in contraceptive pills and postmenopausal replacement are usually not associated with hyperprolactinemia)
  - Isoniazid
  - Monoamine oxidase inhibitors
  - Meprobamate
  - Metoclopramide
  - Neuroleptics
    - First generation
      - Azophenothiazines
      - Benzisoxazoles
      - Butyrophenones
      - Dibenzothiazepines
      - Dihydroindolones
      - Phenothiazines
      - Thioxanthenes
    - Second generation (atypical antipsychotics)
      - Molindone
      - Olanzapine
      - Quetiapine
      - Risperidone
  - Opiates
  - Ramelteon
- Empty sella syndrome
- Hypoglycemia

- Hypothalamic destruction (see 3-T)
- Hypothyroidism (primary only)
- Idiopathic hyperprolactinemia
- Intravascular lymphoma
- Macroprolactinemia
- Neural stimulation
  - Due to disorders of the chest wall and thorax
    - Atopic dermatitis
    - Bronchiectasis/chronic bronchitis
    - Bronchogenic tumors
    - Burns
    - Chest wall lesions, scars, trauma
    - Herpes zoster of the chest
    - Mastectomy/mammoplasty
    - Neoplasms of the chest wall
    - Thoracotomy/thoracoplasty
    - Tight garments
  - Due to nipple stimulation
    - Chronic inflammatory disease
    - Mechanical stimulation of the nipples
  - Due to psychogenic factors
    - Pseudocyesis
    - Posttrauma
    - Stress
  - Due to spinal cord disease
    - Cervical ependymoma
    - Cervical spinal cord lesions
    - Extrinsic tumors
    - Syringomyelia
    - Tabes dorsalis
  - Major surgery and anesthesia, especially oophorectomy
  - Seizures
- Neuraxis irradiation
- Physiologic causes of hyperprolactinemia
  - Exercise
  - Intercourse
  - Newborn
  - Postpartum (nonnursing: days 1–7; nursing: with suckling)
  - Pregnancy
  - Sleep
- Pituitary stalk section (e.g., pituitary tumors compressing the stalk)
- Polycystic ovary syndrome

Pseudohypoparathyroidism
Pseudotumor cerebri
Rathke pouch cyst
Refeeding after starvation
Sarcoidosis
Trauma
Tuberculosis
Tumors secreting prolactin or placental lactogen
    Acromegaly
    Bronchogenic carcinoma
    Chorioepithelioma
    Hydatidiform mole
    Hypernephroma
    Prolactinoma
    Uterine leiomyoma

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3. Molitch ME. Medication-induced hyperprolactinemia. *Mayo Clin Proc*. 2005;80:1050–1057.

3-T. Pituitary/Hypothalamic Insufficiency

Acquired during birth
    Asphyxia
    Breech delivery
    Intracranial hemorrhage or thrombosis
Chronic renal failure (TSH, gonadotropin deficiency)
Congenital
    Tumors
        Diencephalic syndrome
    Developmental
        Absence of anterior pituitary
        Anencephaly
        Basal encephalocele
        Cleft lip and palate
        Combined pituitary hormone deficiency (mutations in genes for pituitary transcription factors) (TSH, growth hormone, and prolactin deficiency)
        Ectopic anterior pituitary

- Holoprosencephalic syndromes
- Optic nerve hypoplasia
- Single central incisor

Iatrogenic
- Radiation therapy to the head, neck, hypothalamus, or pituitary
- Surgery on the pituitary gland or hypothalamus
- Vincristine

Idiopathic
- Congenital
- Familial
- Sporadic
- Necrotizing infundibulohypophysitis

Immunologic
- Lymphocytic hypophysitis

Infectious
- AIDS
  - Cytomegalovirus
  - Herpes simplex type 2 encephalitis
- Brucellosis
- Encephalitis
- Fungal infections
- Infected Rathke cleft cyst
- Malaria
- Meningitis
- Pyogenic abscess
- Septic cavernous sinus
- Syphilis
- Tay-Sachs disease
- Tuberculosis

Infiltrative
- Amyloidosis
- Hemochromatosis
- Histiocytosis X
- Idiopathic granulomatous hypophysitis
- Leukemia
- Lipid storage diseases
- Sarcoidosis
- Tay-Sachs disease
- Wegener granulomatosis

Injury
- Acute epidural and subdural hematoma
- Head trauma (especially basilar skull fractures)
- Subarachnoid hemorrhage

- Invasive
  - Aneurysm of the intracranial internal carotid artery
  - Arteriovenous anomalies
  - Basal encephalocele
  - Craniopharyngioma
  - Empty sella syndrome
  - Metastases to the pituitary or hypothalamus (especially breast, lung, and melanoma)
  - Pituitary adenoma
  - Parasellar and hypothalamic tumors (e.g., glioma, meningioma, pinealoma, lymphoma)
  - Rathke cleft cyst
  - Third ventricle cyst
- Infarction
  - Arteriosclerosis
  - Cavernous sinus thrombosis
  - Collagen vascular disease
  - Diabetes mellitus
  - Eclampsia
  - Intravascular lymphoma
  - Pituitary apoplexy
  - Sheehan syndrome
  - Sickle cell anemia (disease and trait)
  - Temporal arteritis
- Isolated
  - Isolated ACTH deficiency
  - Isolated gonadotropin deficiency
    - Biologically inactive LH
    - Kallmann syndrome
  - Isolated growth hormone deficiency
    - Biologically inactive/subactive growth hormone
    - Deprivational dwarfism
    - Growth hormone neurosecretory defect
  - Isolated prolactin deficiency
  - Isolated thyrotropin (TSH) deficiency
    - Abnormal TSH β-subunit secretion
  - Isolated vasopressin deficiency

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1. Pinzone JJ. Hypopituitarism, p. 178. See Bibliography, 2.
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3-U. Diabetes Insipidus

Nephrogenic (See 5-B)

Central

Gestational diabetes insipidus (placental vasopressinase production)
Congenital malformations
- Holoprosencephaly
- Hypogenesis or ectopia of the pituitary
- Midline craniofacial defects
- Septo-optic dysplasia

Iatrogenic
- Surgery (hypophysectomy)
- Irradiation

Idiopathic
- Familial
  - Isolated
    - Autosomal dominant
    - Autosomal recessive
    - Deletion chromosome 7q
    - X-linked recessive
    - Wolfram syndrome [also known as DIDMOAD syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, deafness, atonia of bladder and ureters)] (autosomal recessive)
- Sporadic (one third have circulating antibodies to vasopressin-producing cells)

Infection
- Actinomycosis
- AIDS
  - CNS herpes
  - CNS lymphoma
  - Cytomegalovirus
  - *Toxoplasma gondii*
- Blastomycosis
- Brain abscess
- Brucellosis
- Chronic meningitis
- Diphtheria
- Encephalitis
- Landry–Guillain-Barré syndrome

- Measles
- Meningitis
- Mumps
- Scarlet fever
- Syphilis
- Toxoplasmosis
- Tuberculosis

Infiltrative
- Amyloidosis
- Eosinophilic granuloma
- Histiocytosis X
- Lupus erythematosus
- Sarcoidosis
- Scleroderma
- Wegener granulomatosis
- Xanthoma disseminatum

Invasive
- Basal encephalocele
- Craniopharyngioma
- Lymphoma, leukemia
- Metastases to the hypothalamus and pituitary from other primaries
- Pituitary tumors
- Primary CNS tumors (e.g., meningioma, dysgerminoma)

Miscellaneous
- Circulating antibodies to vasopressin (secondary to Pitressin injection)
- Collagen vascular disease
- Empty sella syndrome (rarely)
- Fat embolus
- Hydrocephalus
- Lymphocytic hypophysitis
- Suprasellar and intrasellar cysts

Toxins
- Snake venom
- Tetrodotoxin

Traumatic
- Birth trauma
- Head injury (closed and penetrating)
- Post–transcranial or –transsphenoidal surgery

Vascular
- Aneurysm of the intracranial internal carotid artery
- Aortocoronary bypass

Cardiopulmonary arrest
Hypertensive encephalopathy
Hypoxic encephalopathy
Intraventricular hemorrhage
Pituitary apoplexy
Ruptured cerebral aneurysm
Sheehan syndrome
Shock/hemorrhage
Sickle cell crisis
Thrombosis
Thrombotic thrombocytopenic purpura
Vasculitis

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1. Robertson GL. Disorders of the neurohypophysis, p. 2099. See Bibliography, 1.
2. Baylis PH, Thompson CJ. Diabetes insipidus and hyperosmolar syndromes, p. 286. See Bibliography, 2.

3-V. Hyperlipidemia

Type I (Chylomicrons)

Primary
- Familial apolipoprotein C-II deficiency
- Familial lipoprotein lipase deficiency
- Inherited circulating lipoprotein inhibitor

Secondary
- Dysglobulinemias (lupus, lymphoma, myeloma, Waldenström macroglobulinemia)
- Glycogen storage disease, type I
- High-dose glucocorticoids
- Severe untreated diabetes mellitus
- Tamoxifen therapy

Type IIA (Low-Density Lipoproteins) and IIB (Low-Density Lipoproteins + Very Low–Density Lipoproteins)

Primary
- IIA only
  - Familial defective apolipoprotein B100 [reduced affinity of low-density lipoprotein (LDL) for its receptor]
  - Familial hypercholesterolemia
    - Defective LDL receptors
    - Deficiency of LDL receptors

- LDL internalization defect
- Polygenic hypercholesterolemia

IIA and IIB
- Familial combined hyperlipidemia

Secondary

IIA only
- Acute intermittent porphyria
- Anorexia nervosa
- Cholestasis
- Dysglobulinemias (lupus, lymphoma, monoclonal gammopathy, myeloma, Waldenström macroglobulinemia)
- Drugs
  - Carbamazepine
  - Cyclosporine
  - Glucocorticoids
  - Progestogens
  - Thiazides
- Excess dietary cholesterol
- Hepatoma
- Hypothyroidism
- Liver disease
  - α_1-Antitrypsin deficiency
  - Biliary atresia
  - Extrahepatic biliary obstruction
  - Primary biliary cirrhosis
- Nephrotic syndrome
- Werner syndrome

IIB only
- Ateliotic dwarfism
- Diabetes mellitus (moderate)
- Familial hypercholesterolemia (rarely)
- Glucocorticoids
- Nephrotic syndrome
- Sitosterolemia

IIA and IIB
- Biliary obstruction
- Cushing syndrome
- Diabetes mellitus (uncontrolled)
- Glucocorticoids (low dose)
- Hypothyroidism
- Nephrotic syndrome
- Pregnancy
- Thiazides

Type III (Intermediate-Density Lipoproteins)

Primary
- Familial dysbetalipoproteinemia
- Apolipoprotein E deficiency
- Apolipoprotein E_2 homozygotes
- Other apolipoprotein E variants
- Hepatic lipase deficiency

Secondary
- Beta-blockers
- Diabetes mellitus
- Dysglobulinemias (lupus, lymphoma, monoclonal gammopathy, myeloma, Waldenström macroglobulinemia)
- Hypothyroidism (rarely)
- Obesity
- Thiazides
- Uremia

Type IV (Very Low–Density Lipoproteins)

Primary
- Familial apolipoprotein C-II deficiency
- Familial combined hyperlipidemia
- Familial hypertriglyceridemia
- Familial lipoprotein lipase deficiency
- Lecithin-cholesterol acyltransferase (LCAT) deficiency
- Fish-eye disease (milder variant of LCAT deficiency)
- Sporadic hypertriglyceridemia
- Tangier disease

Secondary
- Acromegaly
- Alcohol
- Cushing syndrome
- Diabetes mellitus (moderate)
- Drugs
  - Beta-blockers (but not those with intrinsic sympathomimetic activity)
  - Bile acid–binding resins
  - Estrogen or oral contraceptive therapy
  - Furosemide
  - Glucocorticoids
  - HIV protease inhibitors
  - Isotretinoin
  - Thiazides

- Dysglobulinemias (lupus, lymphoma, monoclonal gammopathy, myeloma, Waldenström macroglobulinemia)
- Glycogen storage disease, type I
- Hepatitis, acute
- Hypopituitarism (ateliotic dwarfism)
- Ileal bypass surgery
- Lipodystrophy (congenital or acquired)
- Nephrotic syndrome
- Obesity
- Pancreatitis
- Pregnancy
- Renal failure
- Sepsis
- Stress

Type V (Chylomicrons and Very Low–Density Lipoproteins)

Primary
- Familial apolipoprotein C-II deficiency
- Familial combined hyperlipidemia (rare)
- Familial hypertriglyceridemia (severe form)
- Familial lipoprotein lipase deficiency

Secondary
- Alcohol (rare)
- Diabetes mellitus (moderate or severe)
- Dysglobulinemias (lupus, lymphoma, myeloma, Waldenström macroglobulinemia)
- Estrogen or oral contraceptive therapy (rarely)
- Glycogen storage disease, type I (rarely)
- High-dose glucocorticoids
- Hypopituitarism (ateliotic dwarfism)
- Hypothyroidism
- Isotretinoin therapy
- Lipodystrophy (congenital or acquired)
- Nephrotic syndrome
- Pregnancy
- Uremia

Lipoprotein (a) Excess

- Acromegaly
- Familial
- Growth hormone
- Hypothyroidism

Inflammation
Menopause
Nephrosis
Orchidectomy
Renal insufficiency

Low High-Density Lipoprotein Levels

Primary
- Apolipoprotein A_1 variants
- Cerebrotendinous xanthomatosis
- Familial apolipoprotein A-I and C-III deficiency
- Familial apolipoprotein A-I, C-III, and A-IV deficiency
- Familial apolipoprotein A-I Milano
- Familial hypoalphalipoproteinemia
- Fish-eye disease
- High-density lipoprotein deficiency with planar xanthomas
- LCAT deficiency
- Tangier disease

Secondary
- Cigarette smoking
- Diabetes mellitus, type 2
- Drugs
  - Anabolic steroids
  - Beta-blockers
  - Probucol
- Gaucher disease
- Low-fat diet
- Malnutrition
- Obesity
- Physical inactivity
- Puberty in boys

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1. Rader DJ, Hobbs HH. Disorders of lipoprotein metabolism, p. 2294. See Bibliography, 1.
2. Mahley RW, Weisgraber KH, Farese RV Jr. Disorders of lipid metabolism, p. 1669. See Bibliography, 3.

3-W. Hypoglycemia

Fasting Hypoglycemia

Overutilization of glucose
- Autoimmune
  - Anti-idiotypic antibodies to anti-insulin antibodies
  - Anti-insulin antibodies

- Anti-insulin receptor antibodies (stimulating) (including type B extreme insulin resistance)
- Deficiency of enzymes of fat oxidation and ketogenesis
- Drug-induced overutilization (factitious or iatrogenic)
  - Clarithromycin added to sulfonylureas
  - Excessive doses of hypoglycemic agents, oral or injectable
    - Exenatide
    - Meglitinides
    - Sitagliptin
    - Sulfonylureas
    - Vildagliptin
  - Insulin (including inhaled insulin)
  - Metformin accompanied by
    - Deficient caloric intake
    - Ethanol
    - Strenuous exercise
    - Other glucose-lowering agents (insulin, sulfonylureas, meglitinides)
    - Vacor (acutely)
- Extrapancreatic tumors
  - Adrenocortical carcinomas
  - Bulky mesenchymal tumors
  - Carcinoidlike tumors
  - Gastrointestinal carcinomas
  - Hepatomas
  - Lymphomas/leukemias
  - Melanoma
  - Other (teratoma, kidney, ovary)
- Insulin excess
  - Discontinuation of total parenteral nutrition (transient)
  - Erythroblastosis fetalis (transient)
  - Infants of diabetic mothers (transient)
  - Pancreatic beta-cell disorders
    - Adenomatosis Beckwith-Wiedemann syndrome
    - Factitious (surreptitious use of insulin, sulfonylureas, or meglitinides)
    - Insulinoma
    - Islet cell hyperplasia
    - Leprechaunism
    - Nesidioblastosis
  - Small cell carcinoma of the cervix
- Prolonged exercise (less likely in trained athletes)

- Underproduction of glucose
  - Congestive heart failure
  - Deficiencies of insulin counterregulatory hormones
    - Adrenal hyporesponsiveness of small for gestational age babies
    - Adrenal insufficiency
    - Epinephrine deficiency (infants)
    - Glucagon and epinephrine deficiency (type 1 diabetics)
    - Growth hormone deficiency (children; adults after prolonged fasting)
    - Hypopituitarism (less common in those older than age 6 years) (see 3-T)
    - Hypothalamic sarcoidosis (deficient catecholamine and glucagon secretion)
    - Hypothyroidism (see 3-E)
  - Drug- or toxin-induced hypoglycemia
    - Angiotensin-converting enzyme inhibitors
    - Acetaminophen
    - Acetazolamide
    - Beta-blockers
    - Chloramphenicol
    - Chloroquine
    - Chlorpromazine
    - Chromium
    - Cimetidine
    - Clofibrate (potentiates sulfonylureas)
    - Coumarin derivatives
    - Disopyramide
    - Doxepin
    - Ethylenediaminetetraacetic acid
    - Encainide
    - Ethanol (blood alcohol levels may not be elevated when patient is hypoglycemic)
    - Fenoterol
    - Fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin)
    - Guanethidine
    - Haloperidol
    - Hypoglycin (unripe ackee fruit ingestion, “Jamaican vomiting illness”)
    - Imipramine
    - Indomethacin

- Isoproterenol
- Lidocaine
- Lithium
- Mebendazole
- Methimazole (autoimmune insulin syndrome)
- Monoamine oxidase inhibitors
- Oxytetracycline
- Para-aminobenzoic acid
- Para-aminosalicylic acid
- Penicillamine (autoimmune insulin syndrome)
- Pentamidine
- Perhexiline
- Phenindione
- Potassium para-aminobenzoate
- Probenecid
- Propoxyphene (in chronic renal failure)
- Quinidine (in treatment of cerebral malaria)
- Quinine (intravenous, in treatment of cerebral malaria)
- Ranitidine
- Ritodrine
- Salicylates (children, and topical application for psoriasis in chronic renal failure patients)
- Sulfadiazine
- Sulfonamides
- Terbutaline

Falciparum malaria (children)
Disorders of gluconeogenesis
- Genetic disorders of amino acid metabolism
- Fructose-1,6-bisphosphatase deficiency
- Phosphoenolpyruvate carboxykinase deficiency
- Pyruvate carboxykinase deficiency

Disorders of glycogen synthesis and breakdown
- Glycogen storage diseases (types I, III, and VI)
- Glycogen synthase deficiency

Hepatic dysfunction (severe)
Hypothermia
Idiopathic hypoglycemia of infancy and childhood
Kidney transplantation, in children
Lactic acidosis
Removal of pheochromocytoma
Reye syndrome
Sepsis

- Substrate deficiency
  - Ackee fruit ingestion
  - Fasting hypoglycemia of pregnancy (late)
  - Ketotic hypoglycemia of infancy
  - Severe malnutrition (including anorexia nervosa and extreme food faddism)
- Transient neonatal hypoglycemia (felt secondary to inadequate substrate or enzyme function)
  - Maternal toxemia
  - Prematurity
  - Respiratory distress
  - Small for gestational age
  - Smaller of twins
- Type I glucose transporter defect, inherited (in children—normal plasma glucose but low cerebrospinal fluid glucose)
- Uremia

Reactive Hypoglycemia[1]

- Induced by glucose
  - Alimentary
    - Gastrojejunostomy
    - Partial or total gastrectomy
    - Peptic ulcer disease
    - Pyloroplasty
    - Rapid gastric emptying
    - Thyrotoxicosis
    - Vagotomy
  - Early type 2 diabetes mellitus (uncommon)
  - Endocrine deficiencies
    - Adrenal insufficiency
    - Hypothyroidism
  - Functional/idiopathic/spontaneous reactive hypoglycemia
  - Insulinoma (occasionally)
- Induced by other substrates
  - Galactosemia
  - Hereditary fructose intolerance
  - Leucine-induced hypoglycemia

Factors Causing Increased Frequency of Hypoglycemia in Previously Compensated Diabetic Patients

- Adrenal insufficiency
- Anti-insulin antibodies (as a result of exposure to exogenous insulin)

Autoimmune (see 3-W)
Decreased caloric intake
Development of hypoglycemic unawareness
Drugs and toxins (see 3-W)
Ethanol
Hypopituitarism (see 3-T)
Hypothyroidism (see 3-E)
Increased exercise
Renal failure
Weight loss

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2. Cryer PE. Hypoglycemia, p. 2180. See Bibliography, 1.

[1]Twenty-five percent of normal controls have been reported to have symptomatic hypoglycemia during 5-hour oral glucose tolerance tests. Consider a diagnosis of "pseudohypoglycemia" or "postprandial syndrome" (postprandial adrenergic symptoms with concomitant normal plasma glucose levels).

3-X. Hyperglycemia

Inadequate dietary preparation for glucose tolerance test
Impaired glucose tolerance or impaired fasting glucose
Gestational diabetes
Type 1 diabetes (B-cell destruction, usually leading to absolute insulin deficiency)
  Idiopathic
  Immune mediated
Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
Other specific types
  Diseases of the exocrine pancreas
    Cystic fibrosis
    Fibrocalculous pancreatopathy (tropical or J-type diabetes due to malnutrition; the true existence of this disorder is under debate)
    Hemochromatosis
    Neoplasia
    Pancreatectomy

- Pancreatitis, acute, chronic, or recurrent (usually with exocrine insufficiency)
- Pancreatic trauma

Drug or toxin induced

- ACTH
- Alpha-adrenergic agents
- Asparaginase
- Atypical (second-generation) antipsychotics
- Barium
- Benzodiazepines
- Beta-adrenergic agonists
- Cadmium
- Calcium channel blockers
- Chlorpromazine
- Clonidine
- Danazol
- Dapsone
- Diazoxide
- Dichlorodiphenyltrichloroethane (DDT)
- Diuretics (by causing potassium depletion)
- Epinephrine
- Estrogens, including oral contraceptives
- Ethanol
- Ethacrynic acid
- Fluoride
- Furosemide
- Ganciclovir
- Gatifloxacin
- Glucagon
- Glucocorticoids
- Growth hormone
- Histaminergic blockers
- Indomethacin
- α-Interferon
- Lithium
- Nicotinic acid
- Norepinephrine
- Octreotide
- Opiates
- Oxymetholone
- Pentamidine (after initial hypoglycemia)
- Phenothiazines
- Phenytoin

- Plicamycin
- Prazosin
- Protease inhibitors
- Rifampin
- Salicylates
- Somatostatin
- Sympathomimetic agents
- Tacrolimus
- Thalidomide
- Thiazides
- Thyroid hormone
- Trimethoprim-sulfamethoxazole
- Vacor
- Zinc

Endocrinopathies
- Increased counterregulatory hormones due to stress

Disorders of increased counterregulatory hormone production
- Acromegaly
- Carcinoid syndrome
- Cushing syndrome
- Glucagonoma
- Hyperaldosteronism (hypokalemia)
- Hyperprolactinemia
- Pheochromocytoma
- Somatostatinoma
- Thyrotoxicosis
- VIPoma

Genetic defects in insulin action
- Leprechaunism
- Lipoatrophic diabetes
- Rabson-Mendenhall syndrome
- Type A insulin resistance

Genetic defects of B-cell function
- Maturity-onset diabetes of the young types 1–6 (autosomal dominant)
- Mitochondrial DNA

Infections
- Congenital rubella
- Cytomegalovirus

Uncommon forms of immune-mediated diabetes
- Anti-insulin receptor antibodies
- “Stiff-man” syndrome

Syndromes associated with increased risk of hyperglycemia
- Acute intermittent porphyria
- Alström syndrome
- Ataxia telangiectasia
- Cockayne syndrome
- Down syndrome
- Friedreich ataxia
- Glycogen storage disease, type I
- Hermann syndrome
- Huntington chorea
- Isolated growth hormone deficiency
- Klinefelter syndrome
- Laurence-Moon-Biedl syndrome
- Leprechaunism
- Lipodystrophic syndromes
- Machado disease
- Mutant insulins (e.g., insulin Chicago)
- Myotonic dystrophy
- Panhypopituitary dwarfism
- Prader-Willi syndrome
- Turner syndrome
- Werner syndrome
- Wolfram (DIDMOAD) syndrome

Factors Causing Worsening of Previously Compensated Diabetes

Decreased exercise
Drugs and toxins (see 3-X, Drug or toxin induced)
Endocrinopathies (see 3-X, Endocrinopathies)
Increased caloric intake
Infection
Myocardial infarction
Pregnancy
Stroke
Surgery
Trauma
Weight gain

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4

GASTROINTESTINAL AND HEPATIC SYSTEM

4-A. Nausea and Vomiting[1]

Central Nervous System Disorders

Increased intracranial pressure
- Head trauma
- Central nervous system neoplasms
- Meningitis, encephalitis
- Hydrocephalus
- Pseudotumor cerebri
- Subarachnoid hemorrhage
- Epidural/subdural hematoma
- Reye syndrome

Vestibular or middle ear disease
- Motion sickness
- Benign positional paroxysmal vertigo
- Ménière disease
- Acoustic neuroma
- Labyrinthitis
- Ear infections

Eye disorders
- Glaucoma
- Refractive error
- Eye trauma

Vascular causes
- Migraine headache
- Migraine equivalent

- Cocaine-induced headache
- Cerebral arteritis

Psychiatric causes
- Cyclical vomiting syndrome
- Psychogenic vomiting
- Self-induced (anorexia, bulimia)
- Concealed vomiting
- Erotic vomiting
- Conditioned reflexes
- Drug withdrawal
- Rumination syndrome

Gastrointestinal Disorders

Mechanical intestinal obstruction (see 4-I)

Inflammatory
- Gastroesophageal reflux disease
- Peptic ulcer disease
- Gastritis
- Alkaline gastritis
- Crohn disease
- Eosinophilic gastroenteritis
- Graft-versus-host disease
- Pneumatosis intestinalis
- Intestinal ischemia
- Gastrointestinal sarcoidosis

Mass effect
- Pancreatic pseudocyst
- Carcinoma/lymphoma of gastrointestinal tract or pancreaticobiliary system
- Abdominal carcinomatosis
- Duodenal hematoma
- Prior gastric surgery
- Intussusception
- Enterocele
- External compression due to genitourinary tumors

Visceral pain
- Referred pain
- Pancreatitis
- Cholecystitis
- Biliary stricture
- Choledocholithiasis
- Appendicitis
- Esophageal rupture/Boerhaave syndrome

- Abdominal trauma
- Peritonitis
- Perforation

Functional intestinal obstruction
- Gastroparesis
  - Diabetes
  - Scleroderma
  - Amyloidosis
  - Metabolic
  - Postoperative (postvagotomy)
  - Postviral
  - Idiopathic
  - Medication induced (i.e., narcotics)
- Pseudo-obstruction
  - Chronic idiopathic intestinal pseudo-obstruction
  - Colonic pseudo-obstruction (Ogilvie syndrome)
- Adynamic ileus
- Gastric motility disorders
- Irritable bowel syndrome
- Nonulcer dyspepsia

Pregnancy

Nausea and vomiting of pregnancy
Hyperemesis gravidarum
Acute fatty liver of pregnancy

Infections

Acute infections (especially children)
Systemic infections and sepsis
Food poisoning
Bacterial/viral gastroenteritis
Helicobacter pylori infection
Hepatitis
Epidemic vomiting (Norwalk, Hawaii agent, etc.)
Intestinal or biliary parasitic infestations
Gastric herpes, cytomegalovirus (CMV) (immunocompromised host)
Acquired immunodeficiency syndrome (AIDS)

Endocrine and Metabolic Disorders

Diabetic ketoacidosis
Metabolic acidosis

Uremia
Hypercalcemia
Hyponatremia
Hypothyroidism
Hyperthyroidism
Hyperparathyroidism
Adrenal insufficiency
Pituitary adenomas

Genitourinary Disorders
Pyelonephritis
Obstructive uropathy
Renal calculi
Salpingitis
Endometritis
Endometriosis

Drugs
Chemotherapeutic agents
Antiarrhythmics
Antibiotics
Anticholinergic drugs
Cardiac glycosides (digitalis)
Ergot alkaloids
Estrogens, oral contraceptives
Theophylline
Colchicine
Narcotics
Ipecac
Potassium chloride

Toxins
Alcohol
Carbon monoxide
Carbon tetrachloride
Heavy metals
Illicit drugs

Other
Acute myocardial infarction
Congestive heart failure
Radiation sickness
Radiation therapy

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[1]The causes of nausea and vomiting are innumerable; this list is not intended to include them all. The important categories of disorders with vomiting as a major symptom are listed, and several examples of each are given.

4-B. Dysphagia, Odynophagia

Oropharyngeal (Transfer) Dysphagia

- Inflammation/infection
  - Herpes stomatitis
  - Monilial stomatitis
  - Viral or bacterial pharyngitis
  - Vincent angina
  - Retropharyngeal abscess
  - Peritonsillar abscess
  - Mumps
  - Stevens-Johnson syndrome
- Structural abnormalities
  - Intrinsic
    - Postcricoid web
    - Zenker diverticulum
    - Upper esophageal stricture
    - Upper esophageal tumors
    - Head and neck tumors
    - Postsurgical change
    - Postradiation change
    - Foreign body
    - Congenital anomalies
  - Extrinsic
    - Dental anomalies
    - Cervical osteophyte
    - Thyromegaly
    - Cricopharyngeal bar
    - Cervical lymphadenopathy
    - Vascular anomalies

- Neurologic disorders
  - Central nervous system disorders
  - Cerebrovascular accident
  - Parkinson disease
  - Brainstem tumors
  - Alzheimer disease
  - Depression
  - Tardive dyskinesia and dystonia
  - Stiff-man syndrome
  - Cerebral palsy
  - Motor neuron disease (e.g., amyotrophic lateral sclerosis)
  - Multiple sclerosis
  - Poliomyelitis
  - Huntington chorea
  - Syringobulbia
  - Tabes dorsalis
  - Spinocerebellar degeneration
  - Cranial nerve diseases
  - Recurrent laryngeal nerve palsy
  - Cranial nerve injury
  - Rabies
  - Diphtheria
  - Peripheral neuropathies
  - Diabetic neuropathy
  - Lead poisoning
- Neuromuscular diseases
  - Myasthenia gravis
  - Botulism
- Skeletal muscle diseases
  - Muscular dystrophies
    - Oculopharyngeal dystrophy
    - Myotonic dystrophy
  - Polymyositis
  - Dermatomyositis
  - Connective tissue diseases
    - Scleroderma
    - Lupus erythematosus
    - Behçet disease
    - Mixed connective tissue disease
    - Rheumatoid arthritis
  - Metabolic myopathies
    - Hyperthyroidism
    - Hypothyroidism
  - Amyloidosis

- Drug induced
  - Tardive dyskinesia
  - Steroid myopathy
  - Mucositis secondary to chemotherapy
- Other causes
  - Cricopharyngeal dysfunction
  - Xerostomia
    - Medication induced
    - Sjögren syndrome
    - Radiation induced

Esophageal Dysphagia

- Caustic ingestion
- Inflammation/infection
  - Reflux esophagitis
  - Bile reflux esophagitis
  - Radiation esophagitis
  - Caustic ingestion
  - Medication-induced esophagitis
  - Esophageal trauma
  - Esophageal infection
    - CMV
    - Herpes simplex virus (HSV)
    - Idiopathic human immunodeficiency virus (HIV) ulcers
    - Esophageal moniliasis
  - Esophageal Crohn disease
  - Eosinophilic esophagitis
  - Esophageal sarcoidosis
  - Graft-versus-host disease
  - Behçet syndrome
  - Necrotizing esophagitis
- Structural abnormalities
  - Intrinsic
    - Esophageal stricture
    - Esophageal carcinoma
    - Carcinoma of the gastric cardia
    - Esophageal benign tumor
    - Esophageal web (Plummer-Vinson or Patterson-Kelly syndrome)
    - Esophageal ring (e.g., Schatzki ring)
    - Midesophageal diverticulum
    - Epiphrenic diverticulum
    - Esophageal pseudodiverticulosis

- Paraesophageal hernia
- Esophageal foreign body
- Extrinsic
  - Vascular ring
  - Cervical osteophyte
  - Carcinoma of the lung
  - Mediastinal lymphoma
  - Mediastinal tuberculosis
  - Pulmonary abscess
  - Empyema
  - Enlarged right atrium
  - Pericardial effusion
  - Enlarged aorta (dysphagia aortica)
  - Anomalous right subclavian artery (dysphagia lusoria)
- Motility disorders
  - Primary
    - Achalasia
    - Nonspecific esophageal motility disorder
    - Nutcracker esophagus
    - Hypertensive lower esophageal sphincter
    - Diffuse esophageal spasm
  - Secondary
    - Scleroderma and other connective tissue diseases
    - Polymyositis
    - Dermatomyositis
    - Diabetes mellitus
    - Amyloidosis
    - Hyperthyroidism
    - Hypothyroidism
    - Chagas disease
    - Pseudoachalasia
    - Chronic idiopathic intestinal pseudo-obstruction
    - Alcoholism
    - Paraneoplastic syndrome

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4-C. Abdominal Pain[1]

Abdominal Disorders

- Inflammatory disorders
  - Peritoneum
    - Peritonitis (chemical or bacterial; see 4-J)
    - Subdiaphragmatic abscess
    - Familial Mediterranean fever
  - Hollow viscera
    - Gastritis
    - Duodenitis
    - Peptic ulcer disease
    - Gastroenteritis
    - Cholecystitis
    - Bacterial cholangitis
    - Vasculitis
    - Intestinal perforation
    - Meckel diverticulum
    - Appendicitis
    - Crohn disease
    - Colitis (idiopathic and infectious)
    - Diverticulitis
  - Solid viscera
    - Pancreatitis (see 4-K)
    - Hepatitis (see 4-O)
    - Pyelonephritis
    - Abscess (hepatic, splenic, pancreatic, perinephric, psoas)
    - Mesenteric lymphadenitis
- Mechanical disorders
  - Hollow viscera
    - Intestinal obstruction
      - Adhesions
      - Incarcerated hernia
      - Enterocele
    - Intussusception
    - Cecal or sigmoid volvulus
    - Biliary tract obstruction (stones, strictures, malignancy)
    - Ureteral obstruction
    - Sphincter of Oddi dysfunction

- Solid viscera
  - Acute capsular distention
  - Acute splenomegaly
  - Acute hepatomegaly (i.e., hepatitis, hepatic congestion)
  - Nephrolithiasis
- Abdominal wall
  - Abdominal wall contusion
  - Abdominal wall hematoma

Neoplasms
- Pancreatic tumors
- Gastric tumors
- Hepatic tumors, primary or metastatic
- Ampullary/duodenal tumors
- Colonic tumors
- Small intestinal tumors
- Abdominal wall tumors

Vascular disorders
- Intra-abdominal bleeding
- Ischemic colitis
- Mesenteric artery insufficiency or thrombosis
- Mesenteric venous thrombosis
- Budd-Chiari syndrome
- Infarction (especially liver, spleen)
- Omental ischemia
- Abdominal aortic aneurysm

Functional disorders
- Irritable bowel syndrome
- Nonulcer dyspepsia
- Sphincter of Oddi dysfunction
- Functional constipation
- Functional abdominal pain syndrome

Pelvic Disorders

Inflammatory disorders
- Pelvic inflammatory disease
- Tubo-ovarian disease
- Mittelschmerz
- Endometritis
- Endometriosis
- Salpingitis
- Fitz-Hugh-Curtis syndrome
- Cystitis

- Seminal vesiculitis
- Epididymitis

Mechanical disorders
- Ovarian cyst/torsion
- Ectopic pregnancy
- Distended bladder
- Omental torsion

Neoplasms
- Cervical
- Ovarian
- Uterine
- Bladder
- Prostate

Extra-abdominal Disorders

Thoracic
- Esophagitis
- Esophageal spasm
- Esophageal rupture (Boerhaave syndrome)
- Myocardial infarction or ischemia
- Pericarditis
- Myocarditis
- Endocarditis
- Congestive heart failure
- Pneumonia
- Pulmonary embolism or infarction
- Pneumothorax
- Empyema
- Pleuritis
- Costochondritis

Neurologic
- Radiculitis
  - Herpes zoster (shingles)
  - Degenerative arthritis
  - Herniated intervertebral disc
  - Spinal or peripheral nerve tumors
- Causalgia
- Tabes dorsalis
- Abdominal epilepsy

Hematologic
- Leukemia
- Lymphoma
- Sickle cell anemia

- Hemolytic anemia
- Henoch-Schönlein purpura

Toxins
- Insect bite
- Snake bite
- Lead poisoning

Metabolic disorders
- Uremia
- Diabetes mellitus
- Diabetic ketoacidosis
- Acute adrenal insufficiency (Addison disease)
- Porphyria cutanea tarda
- Hypercalcemia
- Hyperparathyroidism
- Hypertriglyceridemic pancreatitis
- Hereditary angioneurotic edema

Psychiatric disorders
- Depression
- Anxiety disorders
- Schizophrenia
- Factitious abdominal pain
- Munchausen syndrome

Miscellaneous/Rare Causes

Migraine with abdominal pain
Hereditary angioedema
Omental infarction following abdominal surgery
Anterior abdominal wall hematoma or neuroma
Acute glaucoma
Narcotic withdrawal
Heat stroke
Unexplained intractable abdominal pain

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[1]See also 4-D.

4-D. Characteristic Location of Abdominal Pain Associated with Various Diseases[1]

Diffuse

Gastroenteritis
Peritonitis
Pancreatitis
Leukemia
Sickle cell crisis
Early appendicitis (may be periumbilical)
Mesenteric adenitis
Mesenteric thrombosis
Abdominal aortic aneurysm
Intussusception
Colitis
Intestinal obstruction
Inflammatory bowel disease
Metabolic, toxic, bacterial causes

Epigastric

Reflux esophagitis
Peptic ulcer disease
Pancreatitis
Gastritis
Cholecystitis
Myocardial ischemia
Pericarditis
Abdominal wall hematoma

Right Upper Quadrant

Cholecystitis
Choledocholithiasis
Hepatitis
Hepatic neoplasms or metastases
Hepatic abscess
Hepatomegaly resulting from congestive heart failure
Ruptured hepatic cyst or neoplasm
Budd-Chiari syndrome (hepatic vein obstruction)
Peptic ulcer
Pancreatitis
Retrocecal appendicitis
Renal pain
Herpes zoster

Pulmonary infarction
Pleuritis

Left Upper Quadrant

Gastritis
Peptic ulcer disease
Pancreatitis
Splenomegaly or splenic rupture
Infarction, aneurysm
Renal pain
Herpes zoster
Myocardial ischemia
Pericarditis
Pneumonia
Empyema
Pulmonary infarction
Pleuritis

Right Lower Quadrant

Appendicitis
Neutropenic enteritis/colitis
Intestinal obstruction
Crohn disease
Diverticulitis
Cholecystitis
Perforated ulcer
Leaking aortic aneurysm
Abdominal wall hematoma
Ectopic pregnancy
Ovarian cyst or torsion
Salpingitis
Mittelschmerz
Endometriosis
Ureteral colic
Renal pain
Seminal vesiculitis
Psoas abscess

Left Lower Quadrant

Diverticulitis
Intestinal obstruction
Colon cancer
Appendicitis

Leaking aortic aneurysm
Inflammatory bowel disease
Abdominal wall hematoma
Splenomegaly
Ectopic pregnancy
Mittelschmerz
Ovarian cyst or torsion
Salpingitis
Endometriosis
Ureteral colic
Renal pain
Seminal vesiculitis
Psoas abscess
Irritable bowel syndrome

4-E. Constipation

Behavioral/Psychiatric Factors

Low-residue diet
Chronic laxative and/or enema abuse
Immobility
Reduced food intake
Encopresis
Psychosis
Depression
Eating disorders
Obsessive/compulsive disorders

Functional Constipation

Idiopathic constipation
Irritable bowel syndrome
Colonic inertia
Outlet delay, anismus
Fecal impaction
Pseudo-obstruction

Gastrointestinal Disorders

Colonic extraluminal obstruction
- Intra-abdominal or pelvic tumors
- Chronic volvulus
- Hernias
- Rectal prolapse
- Ascites

- Late pregnancy
- Adhesions

Colonic luminal obstruction
- Carcinoma of the colon or rectum
- Benign colonic tumors
- Recurrent diverticulitis
- Diverticular stricture
- Colonic stricture
- Chronic ulcerative colitis
- Eosinophilic colitis
- Chronic amebiasis
- Lymphogranuloma venereum
- Syphilis
- Tuberculosis
- Ischemic colitis
- Endometriosis
- Postsurgical abnormalities
- Intussusception
- Sigmoidocele
- Corrosive enemas

Anorectal disorders
- Proctitis (especially ulcerative)
- Hemorrhoids
- Fissures and fistulas (e.g., Crohn disease)
- Perianal abscess
- Rectal prolapse
- Anterior mucosal prolapse
- Anal atresia or malformation
- Anal stenosis
- Solitary rectal ulcer syndrome
- Internal intussusception
- Hereditary internal anal sphincter myopathy
- Carcinoma of the rectum or anus
- Ulcerative proctitis
- Lymphogranuloma venereum
- Postsurgical
- Descending perineum syndrome
- Rectocele

Endocrine/Metabolic Causes

Hypothyroidism
Hypercalcemia
Porphyria cutanea tarda

Pheochromocytoma
Panhypopituitarism
Diabetes mellitus
Uremia
Hypokalemia
Heavy metal poisoning
Pregnancy
Glucagonoma
Pseudohypoparathyroidism

Neuromuscular Disorders

Parkinson disease
Cerebral palsy
Cerebrovascular accident
Brain tumors
Senile dementia
Multiple sclerosis
Tabes dorsalis
Spinal lesions
Aganglionic megacolon (Hirschsprung disease)
Neurofibromatosis
Multiple endocrine neoplasia type 2b
Diabetic autonomic neuropathy
Chagas disease
Familial visceral myopathy
Muscular dystrophies
Likongo syndrome (hindgut dysgenesis)
Scleroderma
Amyloidosis
Hypoganglionosis and hyperganglionosis
Intestinal pseudo-obstruction
Dermatomyositis

Drugs

Antacids
    Calcium carbonate
    Aluminum hydroxide
Opiates
Anticholinergics
Anticonvulsants
Tricyclic antidepressants
Ganglionic blockers
Phenothiazines

Ferrous sulfate
Antihypertensives
    Diuretics
    Clonidine
    Calcium channel blockers
Barium sulfate
Bismuth compounds
Ion exchange resins
Antispasmodics
Antidepressants
Antipsychotics
Calcium supplements
Sucralfate
Cholestyramine
Monoamine oxidase (MAO) inhibitors
Analgesics
Vinca alkaloids

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4-F. Diarrhea

Acute Diarrhea

Infections
    Viral gastroenteritis (adenovirus, Norwalk agent, rotavirus, etc.)
    Bacterial
        Invasive (e.g., *Shigella*, *Salmonella*, *Campylobacter*, *Escherichia coli*, *Yersinia*)
        Toxigenic (e.g., *Staphylococcus*, *E. coli*, *Clostridium difficile*, *Vibrio* spp., toxic shock syndrome, ciguatera toxin)
    Mycobacterial (e.g., *Mycobacterium avium* complex)
    Food poisoning
        Staphylococcus aureus
        Bacillus cereus
        Clostridium perfringens

- Protozoal (e.g., amebiasis, giardiasis, *Cryptosporidium*, *Cyclospora*, microsporidia, *Isospora belli*)
- Fungal (e.g., *Histoplasma*, *Cryptococcus*, *Candida*)
- Viral (e.g., CMV, HSV, adenovirus)
- AIDS enteropathy

Stress induced

Food allergy (rare)

Dietary indiscretion (e.g., prunes, unripe fruit, rhubarb, olestra)

Gastrointestinal disorders

- Partial bowel obstruction
- Fecal impaction
- Diverticulitis
- Appendicitis
- Ischemic bowel disease
- Initial attack of ulcerative colitis or Crohn disease

Systemic/extraintestinal disorders

- Uremia
- Carcinoid syndrome
- Zollinger-Ellison syndrome
- Thyrotoxicosis
- Addisonian crisis
- Pelvic inflammation

Drugs/toxins (partial list)

- Laxatives (poorly absorbable sugars, fiber)
- Antibiotics
- Magnesium-containing antacids/products
- Colchicine
- Digitalis
- Iron
- Antihypertensives (methyldopa, hydralazine, and others)
- Quinidine
- Antidepressants (e.g., Prozac, Wellbutrin)
- Valproic acid
- Antiretrovirals
- Protease inhibitors
- 5-Aminosalicylic acid products
- Metformin
- Interferon products
- Immunosuppressives (cyclosporine, tacrolimus)
- Potassium preparations
- Nonsteroidal anti-inflammatory drugs (NSAIDs)

- Lipid-lowering agents
- Alcohol
- Heavy metals (especially arsenic, cadmium, mercury)
- Mushrooms

Acute exacerbation of chronic diarrhea

Chronic Diarrhea

Osmotic diarrhea
- Carbohydrate malabsorption
  - Ingestion of poorly absorbable carbohydrates (sorbitol, mannitol, fructose, lactulose, fiber)
  - Congenital disaccharidase deficiencies
  - Lactase deficiency
  - Isomaltase-sucrase deficiency
  - Trehalase deficiency
  - Acquired disaccharidase deficiencies
    - Nontropical sprue
    - Tropical sprue
    - Viral gastroenteritis
- Maldigestion syndromes (see 4-G)
- Malabsorption syndromes (see 4-G)
- Osmotic solutes
  - Magnesium-containing laxatives, antacids, or nutritional supplements
  - Sodium citrate
  - Sodium phosphate
  - Sodium sulfate
  - Polyethylene-glycol lavage solution
  - Enteral feedings
- Reduced absorptive surface
  - Intestinal resection
  - Intestinal bypass
- Other osmotic causes
  - Congenital chloridorrhea
  - Postgastrectomy “dumping” syndrome

Secretory diarrhea
- Stimulant laxatives
  - Bisacodyl
  - Cascara
  - Senna
  - Ricinoleic acid
  - Phenolphthalein
  - Docusate sodium

- Aloe
- Danthron
- Infections
  - Enterotoxigenic bacteria (*E. coil*, cholera)
  - Enteroviruses (Norwalk agent, rotavirus)
  - Chronic infections (mycobacterial, fungal, parasitic)
  - Bacterial overgrowth (intestinal stasis)
  - AIDS (see previous Acute Diarrhea section)
- Inflammation
  - Crohn disease
  - Ulcerative colitis
  - Lymphocytic colitis
  - Collagenous colitis
  - Celiac disease
- Neoplasms
  - Zollinger-Ellison syndrome (gastrinoma)
  - Pancreatic cholera syndrome (VIPoma)
  - Carcinoid syndrome
  - Medullary carcinoma of the thyroid
  - Glucagonoma
  - Sympathetic tissue tumors (ganglioneuromas)
  - Villous adenoma
  - Carotid body tumor
  - Pheochromocytoma
  - Intestinal lymphoma (e.g., HIV-infected patients)
- Other
  - Fatty acid malabsorption
  - Pancreatic insufficiency
  - Bile acid malabsorption
  - Postcholecystectomy bile acid–induced diarrhea
  - Postvagotomy diarrhea
  - Congenital absorptive defects
  - Hyperthyroidism
  - Collagen vascular disease
  - Intestinal resection
  - Hypoparathyroidism
  - Addison disease
  - Food allergy

Exudative diarrhea

- Infectious causes
  - Bacteria/viral infections (see previous Acute Diarrhea section)
  - Amebic colitis

- Parasitic infestation
- Pseudomembranous colitis
- Diverticulitis

Idiopathic and other colitides
- Ulcerative colitis
- Crohn disease
- Radiation enterocolitis
- Ischemic colitis
- Chemotherapy-induced mucositis
- Graft-versus-host disease

Abnormal motility
- Idiopathic chronic diarrhea
- Irritable bowel syndrome
- Neoplasm (obstruction)
- Postvagotomy
- Postsurgical (e.g., gastrectomy, pyloroplasty)
- Gastroileal or gastrocolonic fistula
- Decreased rectal compliance
- Scleroderma
- Diabetic diarrhea
- Amyloidosis

Other causes/unknown/multifactorial
- Portal hypertension
- Drugs (see previous Acute Diarrhea section)
- Alcohol
- Partial bowel obstruction
- Heavy metal poisoning
- Fecal incontinence (masquerading as diarrhea)
- Uremia
- Cirrhosis
- Pernicious anemia
- Pellagra
- Immunoglobulin deficiencies
- Chronic opiate abuse
- Eosinophilic gastroenteritis
- Systemic mastocytosis
- Protein-losing enteropathy
- Long-distance running

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4. Schiller LR. Chronic diarrhea, pp. 476–490. See Bibliography, 4.

4-G. Maldigestion and Malabsorption Syndromes

Maldigestion Syndromes

Pancreatic disorders
- Chronic pancreatitis
- Pancreatic resection
- Pancreatic carcinoma
- Congenital pancreatic enzyme deficiency
- Cystic fibrosis
- Nonbeta islet cell tumors
- Severe protein malnutrition
- Effect of vagotomy on pancreatic secretion

Hepatobiliary disease
- Extrahepatic biliary obstruction
- Chronic intrahepatic cholestasis (e.g., primary biliary cirrhosis)
- Severe hepatocellular injury

Impaired enzyme or bile salt function due to
- Inadequate mixing (e.g., after gastric/small bowel surgery)
- Low pH in small bowel (e.g., Zollinger-Ellison syndrome)
- Ileal resection
- Severe diffuse ileal disease (e.g., Crohn disease)
- Fibrosis (i.e., dcleroderma)
- Dysmotility

Malabsorption Syndromes

Mucosal disease
- Celiac disease
- Collagenous sprue
- Tropical sprue
- Crohn disease

Disaccharidase diseases and carbohydrate malabsorption
- Congenital enterokinase deficiencies
- Congenital glucose-galactose malabsorption
- Congenital fructose malabsorption
- Lactase deficiency
- Sucrase-isomaltase deficiency
- Trehalase deficiency

- Short bowel syndrome
  - Massive resection
  - Enteroenteric fistulas
  - Jejunoileal bypass surgery
  - Gastroileal anastomosis (inadvertent)
- Neoplasms
  - Intestinal lymphoma
  - Extraintestinal lymphoma
  - Retroperitoneal malignancy
  - Carcinoid syndrome
  - Adenocarcinoma
  - Extraintestinal carcinoma
- Cardiovascular disorders
  - Congestive heart failure
  - Constrictive pericarditis
  - Chronic mesenteric vascular insufficiency
- Endocrine disorders
  - Diabetes mellitus
  - Hypoparathyroidism
  - Hyperthyroidism
  - Adrenal insufficiency
- Systemic disorders
  - Amyloidosis
  - Protein malnutrition
  - Collagen vascular disease
    - Systemic lupus erythematosus
    - Scleroderma
    - Rheumatoid arthritis
    - Vasculitis
    - Neutropenic enteritis/colitis
  - Polyarteritis nodosa
  - Dermatitis herpetiformis
  - Psoriasis
  - Kohler-Dager syndrome
    - Immunoproliferative small bowel diseases (alpha-chain disease, lymphoma)
  - Mastocytosis
  - Food allergy
- Genetic disorders
  - Congenital disaccharidase deficiencies and carbohydrate malabsorption (see "Disaccharidase diseases and carbohydrate malabsorption" entry above)

- Abetalipoproteinemia (fat malabsorption)
- Chloridorrhea, congenital or acquired
- Magnesium deficiency
- Vitamin D–deficient rickets
- Selective vitamin B_{12} malabsorption
- Hartnup disease
- Cystinuria (amino acid malabsorption)

Inflammation/infection

- Crohn disease
- Behçet disease
- Eosinophilic gastroenteritis
- Radiation enteritis
- Graft-versus-host disease
- Infectious enteritis
  - Bacterial
  - Bacterial overgrowth
    - Surgical blind loop
    - Stricture, fistula
    - Crohn disease
    - Small bowel diverticula
    - Hypomotility states
      - Intestinal diabetic neuropathy
      - Scleroderma
      - Intestinal pseudo-obstruction
  - Whipple disease
- Mycobacterial (*Mycobacterium tuberculosis*, *M. avium* complex)
- Parasitic (*Giardia*, *Cryptosporidium*, *I. belli*)
- Viral (CMV, HIV)

Drugs (partial list)

- Cholestyramine
- Colchicine
- Broad-spectrum antibiotics (e.g., neomycin)
- Cytotoxic drugs
- Phenindione
- Methotrexate
- Mefenamic acid
- Alcohol
- NSAIDs
- Iron salts
- Laxatives
- Biguanides
- Para-aminosalicylic acid

Other causes
- Intestinal lymphangiectasia
- Pernicious anemia
- Iron deficiency
- Protein-losing gastroenteropathy
- Idiopathic steatorrhea
- Paneth cell deficiency
- Congenital malrotation of the intestine
- Immunodeficiency
- Immunoproliferative small intestinal disease

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4-H. Gastrointestinal Bleeding

Upper Gastrointestinal Bleeding

Inflammation
- Esophageal ulcer
  - Infectious (CMV, HSV)
  - Idiopathic HIV–related esophageal ulcer
  - Medication induced
  - Barrett ulcer
- Gastric ulcer[1]
- Duodenal ulcer[1]
- Stomal ulceration
- Erosive esophagitis[1]
- Bile acid–induced esophagitis or gastritis
- Erosive gastritis[1]
- Erosive duodenitis[1]
- Stress ulceration
- Medication-induced esophagitis
- NSAID-induced gastrointestinal ulceration[1]
- Graft-versus-host disease
- Caustic ingestion
- Eosinophilic gastroenteritis
- Behçet disease
- Crohn disease
- Gastric sarcoidosis
- Hypertrophic gastropathy

- Infection
  - Esophageal moniliasis
  - Herpes esophagitis
  - CMV esophagitis or gastritis
  - *H. pylori*–associated gastritis
  - Bacterial, fungal, and viral enteritis
  - *M. avium* complex
- Neoplasms
  - Esophageal carcinoma
  - Gastric carcinoma
  - Small bowel carcinoma
  - Gastrointestinal stromal tumors (GISTs)
  - Ampullary carcinoma
  - Lymphoma
  - Kaposi sarcoma
  - Upper gastrointestinal polyps
  - Leiomyoma
  - Sarcoma
  - Neurofibroma
  - Carcinoid tumor
  - Hemangioma
  - Plasmacytoma
  - Metastatic neoplasms
    - Melanoma
    - Breast cancer
    - Renal cell cancer
  - Heterotopic pancreatic tissue
- Vascular lesions
  - Esophageal varices[1]
  - Gastric varices
  - Portal hypertensive gastropathy
  - Duodenal varices
  - Ischemic enteritis
  - Aortoenteric fistula
  - Hereditary hemorrhagic telangiectasia
  - Angiodysplasia
  - Arteriovenous malformations
  - Vasculitis (see vasculitides listed in Lower Gastrointestinal Bleeding section)
  - Dieulafoy lesion
  - Gastric antral vascular ectasia (watermelon stomach)
- Other causes
  - Mallory-Weiss tear[1]
  - Esophageal rupture (Boerhaave syndrome)

- Duodenal diverticulum
- Meckel diverticulum
- Other gastrointestinal diverticula
- Anticoagulant or antiplatelet therapy
- Blood diseases and coagulopathies (e.g., hemophilia, thrombotic thrombocytopenic purpura)
- Uremia
- Amyloidosis
- Hemobilia
- Blue rubber bleb nevus syndrome
- Epistaxis
- Hemoptysis
- Ehlers-Danlos syndrome
- Pseudoxanthoma elasticum
- Intramural hematomas
- Whipple disease
- Celiac disease
- Gastrointestinal foreign bodies
- Gastric prolapse into duodenum
- Volvulus
- Intussusception

Lower Gastrointestinal Bleeding

Inflammation
- Ulcerative colitis/proctitis
- Crohn disease
- Radiation colitis[1]
- Solitary rectal ulcer syndrome
- Stercoral ulcer
- Anal trauma
- Neutropenic enteritis or colitis
- Medication-induced ulceration (i.e., NSAIDs, chemotherapy)
- Eosinophilic colitis
- Diversion colitis
- Pouchitis
- Behçet disease
- Graft-versus-host disease

Infection
- Bacterial
  - Pseudomembranous colitis
  - *Salmonella*

- *Shigella*
- *Campylobacter*
- *Yersinia enterocolitica*
- *E. coli*
- *Vibrio*
- Gonorrhea (proctitis)
- Lymphogranuloma venereum
- Tuberculosis
- Actinomycosis
- Syphilis

Parasitic
- Ameba
- Schistosoma
- Whipworm

Viral
- Condyloma acuminata (anal warts)
- CMV
- HSV

Fungal
- Histoplasmosis

Neoplasms
- Colon polyps[1]
- Carcinoma of the colon and rectum
- Carcinoma of the anus
- Familial adenomatous polyposis
- Gardner syndrome
- Peutz-Jeghers syndrome
- Juvenile polyposis
- Cronkhite-Canada syndrome
- Hamartomas
- Leiomyomas
- Leiomyosarcomas
- Kaposi sarcoma
- Sarcomas
- Lymphomas
- Neurofibromas
- Hemangiomas
- Melanomas
- Carcinoid tumors
- Metastatic neoplasms

Vascular lesions
- Ischemic colitis[1]
  - Mesenteric arterial thrombus

- Mesenteric arterial embolus
- Nonocclusive small bowel ischemia
- Mesenteric venous thrombosis
- Internal hemorrhoids[1]
- External hemorrhoids[1]
- Portal colopathy
- Angiodysplasia[1]
- Dieulafoy lesion of the colon
- Colonic varices
- Vasculitis
  - Polyarteritis nodosa
  - Systemic lupus erythematosus
  - Rheumatoid vasculitis
  - Dermatomyositis
  - Stevens-Johnson syndrome
  - Henoch-Schönlein purpura
  - Hemolytic uremic syndrome
  - Churg-Strauss syndrome
  - Wegener granulomatosis
  - Essential mixed cryoglobulinemia
  - Giant cell arteritis
  - Köhlmeier-Degos disease
- Aortointestinal fistula
- Arteriovenous malformation
- Hereditary hemorrhagic telangiectasia

Other causes

- All upper gastrointestinal sources
- Anal fissure
- Foreign body
- Diverticulosis[1]
- Incarcerated hernia
- Volvulus
- Intussusception
- Prolapse of the rectum
- Uremia
- Amyloidosis
- Anticoagulation
- Blood diseases and coagulopathy
- Long-distance running
- Blue rubber bleb nevus syndrome
- Pseudoxanthoma elasticum
- Ehlers-Danlos syndrome
- Endometriosis

Colitis cystica profunda
Pneumatosis intestinalis

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[1]Common causes of acute bleeding.

4-I. Abdominal Distention

Mechanical Bowel Obstruction

Extraluminal compression
- Congenital abnormalities
  - Annular pancreas
  - Malrotation
- Neoplasms
  - Carcinomatosis
  - Sarcoma
  - Pseudomyxoma peritonei
- Inflammatory disorders
  - Postsurgical or inflammatory adhesions
  - Intra-abdominal abscess
- Other extraluminal causes
  - Hernias
  - Volvulus
  - Intussusception
  - Intra-abdominal hematoma
  - Pregnancy
  - Superior mesenteric artery syndrome

Intrinsic lesions
- Congenital abnormalities
  - Congenital adhesive bands
  - Meckel diverticulum
  - Congenital atresia/stenosis
  - Intestinal duplication
  - Mesenteric cysts

- Imperforate anus
- Hirschsprung disease
- Neoplasms
  - Adenomatous polyps
  - Polyposis syndromes (e.g., Peutz-Jeghers syndrome)
  - Malignant tumors
- Inflammatory disorders
  - Crohn disease
  - Ulcerative colitis
  - Diverticulitis
  - Diverticular stricture
  - Tuberculosis
  - Endometriosis
  - Actinomycosis
  - Ischemic injury
- Other intrinsic causes
  - Radiation stenosis
  - Chemical injury (potassium chloride, NSAIDs)
  - Bowel wall hematoma
  - Surgical anastomosis
  - Pneumatosis intestinalis
  - Trauma

Intraluminal contents
- Foreign body
- Gallstone (gallstone ileus)
- Parasites (*Ascaris*)
- Fecaliths
- Enteroliths
- Feces
- Bezoar
- Food impaction
- Meconium

Adynamic Ileus, Nonmechanical Obstruction

Intra-abdominal causes
- Peritoneal inflammation (see 4-J)
- Traumatic
  - Postoperative
  - Penetrating wounds
- Bacterial infections
  - Pneumonia/empyema
  - Urosepsis
  - Systemic infections

- Chemical irritants
  - Blood
  - Gastric contents (perforated ulcer)
  - Bile
  - Pancreatic enzymes (acute pancreatitis)
- Vascular insufficiency
  - Intramural strangulation (distention from mechanical ileus)
  - Extramural strangulation (compression of mesenteric vessels)
  - Mesenteric artery thrombosis or embolus
- Retroperitoneal irritation
  - Retroperitoneal hemorrhage
  - Psoas abscess
  - Pyelonephritis
  - Renal colic
  - Perinephric abscess
  - Pancreatitis
  - Pancreatic abscess
  - Cancer
  - Lymphoma

Extra-abdominal causes

- Toxic, metabolic
  - Pneumonia
  - Empyema
  - Uremia
  - Diabetic complications
  - Porphyria cutanea tarda
  - Severe systemic infection
  - Heavy metal poisoning (e.g., lead)
  - Severe electrolyte imbalance (e.g., hypokalemia)
- Traumatic
  - Thoracic trauma
  - Retroperitoneal trauma
  - Intracranial trauma
  - Spinal trauma
- Drugs
  - Narcotics
  - Anticholinergics
  - Phenothiazines
  - Antihistamines
  - Catecholamines

Other
- Connective tissue diseases
- Osteomyelitis of spine
- Mechanical ventilation

Vascular Obstruction
Mesenteric artery thrombosis or embolus
Mesenteric venous thrombosis

Pseudo-obstruction Syndromes
Excessive Intraluminal Gas
Functional bowel diseases (e.g., irritable bowel syndrome)
Aerophagia
Increased intestinal gas production

Ascites (see 4-Q)
References
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3. Summers RW. Approach to the patient with ileus and obstruction, pp.829–843. See Bibliography, 3.

4-J. Peritonitis

Infections
- Bacterial
  - Spontaneous bacterial peritonitis (usually in cirrhotics with ascites)
  - Secondary bacterial peritonitis (associated with perforation)
  - Mycobacterial (primarily *M. tuberculosis*)
  - HIV-associated peritonitis (from opportunistic organisms)
- Fungal
  - Candidiasis
  - Histoplasmosis
  - Cryptococcosis
  - Coccidioidomycosis
- Parasitic
  - Schistosomiasis
  - Ascariasis

- Enterobiasis
- Amebiasis
- Strongyloidiasis

Viscus perforation
- Boerhaave syndrome
- Peptic ulcer disease
- Appendicitis
- Cholecystitis
- Diverticulitis
- Necrotizing enterocolitis
- Strangulated bowel
  - Small bowel adhesion
  - Incarcerated hernia
  - Intussusception
  - Volvulus
- Gastrointestinal neoplasms
- Ulcerative colitis (especially with toxic megacolon)
- Crohn disease
- Ischemic bowel
- Ingested foreign body
- Meckel diverticulum

Ruptured visceral abscess or cyst
- Liver
- Kidney
- Spleen
- Tubo-ovarian

Trauma
- Blunt trauma
- Penetrating wounds
- Surgical injury, including laparoscopic surgery
- Instrumentation
  - Endoscopic perforation
  - Therapeutic abortion with perforation
  - Paracentesis
  - Bile leak

Neoplasms
- Primary mesothelioma
- Secondary carcinomatosis
- Pseudomyxoma peritonei

Vascular causes
- Mesenteric embolus
- Mesenteric nonocclusive ischemia
- Ischemic colitis

- Portal vein thrombosis
- Mesenteric vein thrombosis
- Vasculitis
  - Systemic lupus erythematosus
  - Allergic vasculitis (Henoch-Schönlein purpura)
  - Köhlmeier-Degos disease
  - Polyarteritis nodosa

Granulomatous peritonitis
- Parasitic infestations
- Sarcoidosis
- Tumors
- Crohn disease
- Starch granules

Gynecologic disorders
- Chlamydia peritonitis
- Salpingitis
- Endometriosis
- Teratoma
- Leiomyomatosis
- Dermoid cyst

Chemical irritants
- Bile
- Blood
- Gastric juice
- Barium
- Enema or douche contents

Others
- Chronic peritoneal dialysis
- Eosinophilic peritonitis
- Chylous peritonitis (see 4-Q)
- Whipple disease
- Sclerosing peritonitis
- Peritoneal lymphangiectasis
- Peritoneal encapsulation
- Peritoneal loose bodies and peritoneal cysts
- Mesothelial hyperplasia and metaplasia
- Splenosis
- Familial Mediterranean fever

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4-K. Pancreatitis

Obstruction
- Gallstone pancreatitis
- Choledocholithiasis/biliary sludge
- Ampullary or pancreatic tumors
- Metastatic carcinoma to pancreas
- Periampullary diverticulum
- Choledochocele
- Duodenal cyst
- Pancreatic calculi
- Pancreatic duct stricture[1]
- Pancreatic pseudocyst
- Pancreatic abscess
- Sphincter of Oddi dysfunction
- Papillary stenosis
- Duodenal stricture or obstruction

Congenital/inherited disorders
- Pancreas divisum[1]
- Hereditary pancreatitis[1]
- Cystic fibrosis[1]
- Annular pancreas
- Heterotopic pancreas
- Duodenal duplication
- α_1-Antitrypsin deficiency[1]

Toxins
- Alcohol[1]
- Methanol
- Organophosphate insecticides
- Scorpion venom
- Occupational chemicals

Drugs
- Antibiotics/antivirals/antiprotozoals
  - Tetracycline
  - Sulfonamides
  - Metronidazole
  - Erythromycin
  - Pentamidine

- Nitrofurantoin
- Didanosine
- Stibogluconate
- Antihypertensives
  - Thiazide diuretics
  - Furosemide
  - Ethacrynic acid
  - Methyldopa
  - Angiotensin-converting enzyme inhibitors
- Immunomodulators
  - Azathioprine
  - 6-Mercaptopurine
- Antineoplastic agents
  - L-Asparaginase

Analgesics
- Acetaminophen
- Salicylates (i.e., sulindac)

Others
- Sulfasalazine
- 5-Acetylsalicylic acid products
- Oral contraceptives/estrogens
- Corticosteroids
- Valproic acid
- Cimetidine
- Ranitidine
- Octreotide
- Calcium

Metabolic disorders
- Hypertriglyceridemia
- Hypercalcemia
- Hyperparathyroidism[1]

Trauma
- Blunt or penetrating trauma[1]
- Surgical trauma
- Endoscopic retrograde cholangiopancreatography
- Endoscopic sphincterotomy
- Sphincter of Oddi manometry

Vascular causes
- Postoperative pancreatitis
- Atherosclerotic emboli
- Cardiopulmonary bypass surgery
- Malignant hypertension

- Ergotamine overdose
- Vasculitis (i.e., systemic lupus erythematosus, polyarteritis nodosa)

Infections
- Bacterial
  - *Mycoplasma*
  - *Campylobacter jejuni*
  - *M. tuberculosis*
  - Leptospirosis
  - *M. avium* complex
- Viral
  - Mumps
  - Rubella
  - Hepatitis A, B, C
  - HIV
  - CMV
  - Coxsackievirus B
  - Epstein-Barr virus
  - Adenovirus
  - Varicella
  - Echo virus
- Fungal
  - *Candida albicans* infection
  - Aspergillosis
- Parasitic
  - Clonorchiasis
  - Ascariasis
  - Cryptosporidiosis
  - Toxoplasmosis

Miscellaneous
- Autoimmune pancreatitis
- Penetrating gastrointestinal ulcer
- Duodenal Crohn disease
- Protein-calorie malnutrition
- Tropical pancreatitis[1]
- Reye syndrome
- Hypothermia
- Idiopathic pancreatitis[1]
- Posttransplantation
- Food allergy
- Chronic renal insufficiency
- Severe burns
- Long-distance running

Bulimia
Eosinophilic pancreatitis
Pancreatitis of pregnancy

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[1]Indicates causes of pancreatitis that frequently lead to chronic pancreatitis.

4-L. Hyperamylasemia Not Associated with Pancreatitis

Intra-abdominal Disorders

Common bile duct obstruction, stones
Acute cholecystitis
Biliary endoscopy (endoscopic retrograde cannulation of pancreatic duct)
Sphincter of Oddi stenosis/spasm
Perforated ulcer
Intestinal ischemia or infarction
Intestinal obstruction
Intestinal perforation
Abdominal surgery (postoperative)
Intra-abdominal hemorrhage
Afferent loop syndrome
Pregnancy
Ruptured ectopic pregnancy
Salpingitis
Ovarian cysts
Dissecting aortic aneurysm
Peritonitis

Appendicitis
Tumors (e.g., lung, ovary)
Cintiosis
Splenic rupture

Salivary Gland Disorders

Parotitis (e.g., mumps)
Alcohol ingestion
Scorpion sting
Salivary calculi
Radiation sialoadenitis
Maxillofacial surgery

Drugs

Oxyphenbutazone
Phenylbutazone
Opiates

Miscellaneous

Chronic renal insufficiency
Salivary-type hyperamylasemia
Macroamylasemia
Cerebral trauma
Burns
Traumatic shock
Diabetic ketoacidosis
Renal transplantation
Pneumonia
Acquired bisalbuminemia
Prostatic disease
Anorexia nervosa
Acute myocardial infarction
Endoscopy
HIV

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4-M. Hepatomegaly

Palpable Liver without Hepatic Pathology

Normal variant
Thin or flaccid abdominal wall
Depressed right diaphragm (e.g., emphysema)
Subdiaphragmatic lesion (e.g., abscess)
Riedel lobe (prominent right lobe)

True Hepatic Enlargement

Inflammatory liver disease
- Hepatitis (see 4-O)
  - Infectious
    - Viral
    - Schistosomiasis
    - Other
  - Alcoholic
  - Other toxins
  - Drug induced
  - Autoimmune
  - Nonalcoholic fatty liver disease
    - Hepatic steatosis
    - Steatohepatitis
  - Steatosis
  - Other
- Abscess
  - Pyogenic
  - Amebic
- Cholangitis
  - Suppurative
  - Sclerosing
- Pericholangitis (especially related to ulcerative colitis)

Chronic liver disease, cirrhosis (see 4-P)
- Alcoholic
- Posthepatitic (viral B and C)
- Postnecrotic
- Cholestatic

Metabolic disorders
- Hemochromatosis
- α_1-Antitrypsin deficiency
- Wilson disease
- Cystic fibrosis

- Other causes
  - Extrahepatic biliary obstruction
    - Choledocholithiasis
    - Biliary stricture
    - Pancreatitis
    - Carcinoma
      - Bile ducts (cholangiocarcinoma)
      - Head of pancreas
      - Ampulla of Vater
    - External compression
  - Hepatic congestion
    - Congestive heart failure
    - Constrictive pericarditis
    - Budd-Chiari syndrome (hepatic outflow obstruction)
    - Thrombosis
    - Tumor
    - Web (inferior vena cave)
  - Veno-occlusive disease
    - Jamaican herbal tea
    - After bone marrow transplantation
  - Infiltrative disorders, storage diseases
    - Lipid accumulation (macrovesicular steatosis)
      - Fatty liver (hepatic steatosis)
        - Alcohol
        - Diabetes mellitus
        - Obesity
        - Severe protein malnutrition
        - Nonalcoholic steatohepatitis
        - Jejunoileal bypass
        - Parenteral hyperalimentation
        - Corticosteroids, Cushing syndrome
        - Macrovesicular steatosis
          - Fatty liver of pregnancy
          - Massive tetracycline therapy
          - Toxins (e.g., carbon tetrachloride, dichlorodiphenyltrichloroethane)
          - Reye syndrome
      - Lipid storage disease (especially Gaucher disease, Niemann-Pick disease)
    - Glycogen accumulation
      - Glycogen storage disease
      - Diabetic glycogenosis

- Granulomatous infiltration (especially sarcoidosis, miliary tuberculosis, disseminated fungal diseases, some drug reactions)
- Myelo- and lymphoproliferative disorders
  - Lymphoma
  - Myeloid metaplasia
  - Multiple myeloma
  - Leukemia
- Amyloidosis
- Congenital hepatic fibrosis
- Hemochromatosis
- Wilson disease
- α_1-Antitrypsin deficiency
- Hurler syndrome

Neoplasms
- Primary
  - Malignant
    - Hepatocellular carcinoma
    - Cholangiocarcinoma
    - Angiosarcoma
  - Benign
    - Hepatic adenoma
    - Hemangioma
    - Focal nodular hyperplasia
    - Nodular regenerative hyperplasia
- Metastatic
  - Pancreas
  - Colon
  - Lung
  - Breast
  - Stomach
  - Kidney
  - Esophagus
  - Carcinoid

Cysts
- Congenital
  - Solitary
  - Polycystic
- Acquired (especially echinococcal)

4-N. Jaundice

Primarily Unconjugated Hyperbilirubinemia

Increased production
- Hemolysis, intravascular or extravascular (see 7-B)
- Ineffective erythropoiesis
- Hematomas, pulmonary embolus

Decreased hepatic uptake
- Gilbert syndrome
- Drugs
  - Flavaspidic acid
  - Iodinated contrast agents
  - Rifampin

Decreased systolic binding proteins (e.g., newborn or premature infants)

Portacaval shunt

Prolonged fasting

Decreased glucuronidation
- Crigler-Najjar syndrome, types I and II
- Gilbert syndrome
- Physiologic jaundice of newborn
- Breast milk jaundice
- Hepatic parenchymal disease
- Noncirrhotic portal fibrosis

Primarily Conjugated Hyperbilirubinemia

Decreased liver excretion, intrahepatic
- Familial or hereditary disorders
  - Dubin-Johnson syndrome
  - Rotor syndrome
  - Benign recurrent intrahepatic cholestasis
  - Intrahepatic cholestasis of pregnancy
- Acquired disorders
  - Hepatitis (see 4-O)
  - Cirrhosis (see 4-P)
  - Alcoholic liver disease
  - Primary sclerosing cholangitis
  - Pericholangitis
  - Drugs and toxins, especially:
    - Chlorpromazine
    - Erythromycin estolate
    - Isoniazid

- Halothane
- Levofloxacin
- Amoxicillin clavulanate

- Others
  - Hepatic malignancy, primary or metastatic
  - Congestive heart failure
  - Shock
  - Sepsis
  - Toxemia of pregnancy
  - Hepatic trauma
  - Sarcoidosis
  - Amyloidosis
  - Sickle cell hepatopathy
  - Postoperative jaundice
  - Total parenteral nutrition
  - Idiopathic cholestasis associated with lymphoma
  - Intrahepatic biliary obstruction
    - Primary biliary cirrhosis
    - Primary sclerosing cholangitis
    - Liver allograft rejection
    - Graft-versus-host disease
    - Ductopenic syndromes (e.g., Alagille syndrome)
    - Neoplasms (primary, metastatic, lymphoma)

Extrahepatic biliary obstruction

- Congenital
  - Biliary atresia
  - Idiopathic dilatation of common bile duct
  - Cystic fibrosis
  - Choledochal cysts
- Acquired
  - Cholecystitis
  - Common bile duct obstruction
    - Choledocholithiasis
    - Tumors (benign, malignant)
      - Gallbladder
      - Bile ducts
      - Ampulla of Vater
      - Pancreas
      - Lymphoma
      - Metastatic tumors

External compression
Strictures
  Common bile duct
  Sphincter of Oddi
  Primary sclerosing cholangitis
  AIDS (*Cryptosporidium*)
Pancreatitis
Parasites (*Ascaris*)

4-O. Hepatitis, Abnormal "Liver Function Tests"

Causes of Acute Liver Injury with Alanine Aminotransferase or Aspartate Aminotransferase >1,000 IU/L

Acute viral hepatitis
Ischemic hepatopathy ("shock" liver)
Toxin, drug induced (e.g., acetaminophen hepatotoxicity)
Autoimmune hepatitis (occasional)
Choledocholithiasis (initial, rare)

Causes of Hepatitis

Chronic
  Viral (type B or C)
  Drug induced
  Wilson disease
  α_1-Antitrypsin deficiency
  Autoimmune hepatitis
  Alcoholic hepatitis
  Nonalcoholic steatohepatitis
Infection
  Viral
    Hepatitis A
    Hepatitis B
    Hepatitis C
    Hepatitis D (delta, only with hepatitis B)
    Hepatitis E (underdeveloped countries)
    Hepatitis G (does not lead to chronic liver disease)
    Infectious mononucleosis (Epstein-Barr virus)
    CMV
    Varicella-zoster
    Coxsackie
    Rubella

- Measles
- HSV
- Other

Bacterial (not necessarily hepatitis, per se)

- Pyogenic abscesses
  - Numerous aerobic and anaerobic organisms
- Hepatic dysfunction in bacterial sepsis
  - *E. coli*
  - *Klebsiella pneumoniae*
  - *Pseudomonas aeruginosa*
  - *Proteus* spp.
  - *Bacteroides* spp.
  - *S. aureus*
  - Aerobic and anaerobic streptococci
- Hepatic dysfunction in gram-positive infections
  - Pneumococcal
  - Streptococcal
  - Staphylococcal
  - Clostridia species
- Hepatic dysfunction in gram-negative infections
  - *E. coli*
  - Paracolon bacteria
  - *P. aeruginosa*
  - *Proteus*
  - *Bacteroides*
  - *Aerobacter*
  - *Klebsiella*
  - Enterobacteriaceae
  - *Salmonella*
  - Gonococcal
  - Legionnaires bacillus
  - Other
    - Brucellosis
    - Typhoid fever
    - Tularemia

Mycobacterial

- Tuberculosis
- Leprosy

Spirochetal

- Syphilis (congenital, secondary, or late)
- Leptospirosis
- Relapsing fever (*Borrelia* species)

- Mycotic
  - Histoplasmosis
  - Coccidioidomycosis
  - Blastomycosis
  - Nocardiosis
  - Cryptococcosis
  - Candidiasis
  - Actinomycosis
- Parasitic (e.g., malaria, toxoplasmosis, amebiasis, schistosomiasis, others)
- Rickettsial (e.g., Q fever)

Toxins

- Industrial toxins (e.g., carbon tetrachloride, yellow phosphorus, trichloroethylene, others)
- Plant toxins
  - Mushrooms (e.g., *Amanita phalloides*)
  - Aflatoxin

Drug-Induced Liver Disease, Including Hepatitis

- Drugs implicated in the etiology of chronic liver injury
  - Acetaminophen
  - Aspirin
  - Dantrolene
  - Ethanol
  - Isoniazid
  - Methyldopa
  - Nitrofurantoin
  - Oxyphenisatin
  - Perhexiline maleate
  - Propylthiouracil
  - Sulfonamides
- Specific classes of drugs associated with acute and/or chronic liver dysfunction
  - Anesthetics
    - Chloroform
    - Halothane
    - Enflurane
    - Methoxyflurane
    - Cyclopropane
  - Analgesics, anti-inflammatory agents
    - Acetaminophen
    - Salicylates

- Propoxyphene
- Phenylbutazone
- Indomethacin
- Ibuprofen
- Naproxen
- Sulindac

Antibacterial agents
- Erythromycin
  - Estolate
  - Ethylsuccinate
  - Lactobionate
- Tetracyclines
- Nitrofurantoins
- Sulfonamides
- Penicillin
- Oxacillin
- Cloxacillin
- Carbenicillin
- Chloramphenicol
- Clindamycin
- Levofloxacin
- Amoxicillin clavulanate

Antituberculous agents
- Isoniazid
- Rifampin
- Ethionamide
- Para-aminosalicylic acid
- Pyrazinamide

Antifungal, antiparasitic agents
- Antimony
- Arsenic
- Thiabendazole
- Hycanthone
- 5-Fluorocytosine
- Quinacrine
- Griseofulvin
- Ketoconazole
- Itraconazole

Anticonvulsants
- Phenytoin
- Valproic acid
- Trimethadione

- Antihypertensives, diuretics
  - Chlorothiazide
  - Furosemide
  - Chlorthalidone
  - Methyldopa
  - Hydralazine
  - Captopril
- Antiarrhythmic agents
  - Quinidine
  - Aprindine
  - Procainamide
  - Amiodarone
- Antimetabolites
  - 6-Mercaptopurine
  - Methotrexate
  - Azathioprine
  - 6-Thioguanine
  - Chlorambucil
  - 5-Fluorouracil
  - Nitrogen mustard
  - Cyclophosphamide
- Hormones
  - Androgens (e.g., methyltestosterone)
  - Corticosteroids
  - Estrogens
- Oral hypoglycemics
  - Chlorpropamide
  - Tolbutamide
  - Tolazamide
  - Acetohexamide
  - Glyburide
  - Troglitazone
- Antithyroid drugs
  - Methimazole
  - Carbimazole
  - Propylthiouracil
- Psychoactive agents
  - Phenothiazines (especially chlorpromazine)
  - Imipramine
  - Benzodiazepines
  - Meprobamate
  - MAO inhibitors

- Haloperidol
- Diazepam
- Chlordiazepoxide
- Desipramine
- Amitriptyline

Others

- Doxapram
- Cimetidine
- Ranitidine
- Perhexiline maleate
- Cinchophen
- Gold salts
- Allopurinol
- Pyridium
- Papaverine
- Oxyphenisatin
- Nicotinic acid
- Disulfiram

Others

Autoimmune hepatitis
Wilson disease
Granulomatous hepatitis of unknown etiology
Hepatitis associated with systemic disorders

- Hyperthermia
- Cardiac failure
- Shock
- Burns
- Hyperthyroidism
- Hypoxia

4-P. Cirrhosis, Chronic Liver Disease

Alcoholic
Infectious

- Viral hepatitis (especially B and C)
- Schistosomiasis
- Other infections (uncommon; e.g., congenital syphilis, brucellosis)

Biliary

- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Secondary biliary cirrhosis (chronic extrahepatic obstruction)

- Autoimmune cholangiopathy
- Autoimmune chronic active hepatitis
- "Cryptogenic" cirrhosis
  - Posthepatitic (non-B, non-C)
  - Postnecrotic
- Chemical
  - Toxins
    - Alcohol
    - Carbon tetrachloride
    - Dimethylnitrosamine
    - Phosphorus
    - Vinyl chloride
    - Arsenic
    - Beryllium
    - Pesticides
  - Drugs
    - Halothane
    - Isoniazid
    - Methotrexate
    - Methyldopa
    - MAO inhibitors
    - Nitrofurantoin
    - Oxyphenisatin
- Congestive
  - Severe chronic right heart failure
    - Tricuspid insufficiency
    - Constrictive pericarditis
    - Cor pulmonale
    - Mitral stenosis
  - Hepatic vein obstruction (Budd-Chiari syndrome)
  - Veno-occlusive disease
- Hereditary or familial disorders
  - Wilson disease
  - Cystic fibrosis
  - α_1-Antitrypsin deficiency
  - Hemochromatosis
  - Galactosemia
  - Glycogen storage diseases
  - Hereditary fructose intolerance
  - Tyrosinosis
  - Hypervitaminosis A
  - Thalassemia (secondary iron overload)
  - Sickle cell disease

- Osler-Rendu-Weber syndrome
- Abetalipoproteinemia

Others
- Sarcoidosis
- Granulomatous cirrhosis
- Congenital hepatic fibrosis
- Indian childhood cirrhosis
- Nutritional (e.g., jejunoileal bypass surgery)
- Nonalcoholic steatohepatitis

4-Q. Ascites

Without Peritoneal Disease

Portal hypertension
- Cirrhosis (see 4-P)
- Alcoholic hepatitis
- Hepatic congestion
  - Congestive heart failure
  - Tricuspid insufficiency
  - Constrictive pericarditis
  - Inferior vena cava obstruction
  - Hepatic vein obstruction (Budd-Chiari syndrome)
  - Cardiomyopathy
- Portal vein occlusion
  - Thrombosis
  - Tumor
- Idiopathic tropical splenomegaly
- Partial nodular transformation
- Hypervitaminosis A
- Fulminant hepatic failure
- Idiopathic

Hypoalbuminemia
- Cirrhosis (see 4-P)
- Nephrotic syndrome
- Protein-losing enteropathy
- Lymphangiectasia
- Severe malnutrition

Miscellaneous
- Myxedema
- Hepatocellular carcinoma (usually with cirrhosis)
- Ovarian disease
  - Tumor (Meigs syndrome)
  - Struma ovarii
  - Ovarian overstimulation syndrome

- Pancreatic ascites
  - Rupture of pseudocyst
  - Leak from pancreatic duct
- Bile ascites
  - Gallbladder rupture
  - Traumatic bile leak
- Chylous ascites
  - Rupture (traumatic, surgical) of abdominal lymphatics
  - Congenital lymphangiectasia
  - Obstructed lymphatics (especially secondary to malignancy, tuberculosis, filariasis)
  - Constrictive pericarditis
  - Cirrhosis
  - Sarcoidosis

With Peritoneal Disease

- Infection
  - Mycobacterial
  - Bacterial
    - Primary (spontaneous bacterial peritonitis in cirrhosis)
    - Secondary (ruptured viscus)
  - Fungal (rare, especially candidiasis, histoplasmosis, cryptococcosis)
  - Parasitic (rare, especially schistosomiasis, ascariasis, enterobiasis)
  - AIDS
- Neoplasm
  - Primary mesothelioma
  - Metastatic carcinomatosis
    - Ovarian
    - Pancreatic
    - Gastric
    - Colonic
    - Lymphoma
- Miscellaneous
  - Peritoneal vasculitides
    - Systemic lupus erythematosus
    - Henoch-Schönlein purpura
    - Köhlmeier-Degos disease
  - Eosinophilic peritonitis
  - Familial Mediterranean fever
  - Pseudomyxoma peritonei
  - Whipple disease

Granulomatous peritonitis
Foreign bodies (especially starch)
Sarcoidosis
Gynecologic lesions (especially endometriosis, ruptured dermoid cyst)
Peritoneal lymphangiectasis

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3. Yamada T, Alpers DH, Laine L, Owyang C, Powell DW, eds. *Textbook of Gastroenterology*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2003.
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5. Castell DO, Richter JE, eds. *The Esophagus*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2003.
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7. Bacon BR, O'Grady J, Di Bisceglie AM, Lake JR, eds. *Comprehensive Clinical Hepatology*. 2nd ed. London: Philadelphia: Elsevier; 2006.
8. Schiff ER, Sorrell MF, Maddrey WC, eds. *Schiff's Diseases of the Liver*. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2007.

5

GENITOURINARY SYSTEM

5-A. Hematuria

Pseudohematuria (Dyes and Pigments)

Beets
Food dyes
Phenytoin
Rifampin
Pyridium
Urates
Porphyrins
Myoglobin
Free hemoglobin (intravascular hemolysis)

Renal Parenchymal Causes

Primary glomerulopathy
- Postinfectious glomerulonephritis
- Thin basement membrane disease
- Immunoglobulin A (IgA) nephropathy (Berger disease)
- Membranoproliferative glomerulonephritis
- Focal glomerulosclerosis
- Crescentic glomerulonephritis

Multisystem and hereditary diseases
- Diabetes mellitus
- Lupus erythematosus
- Goodpasture syndrome

- Polyarteritis nodosa, other vasculitides
- Endocarditis, shunt nephritis
- Hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura
- Henoch-Schönlein purpura
- Malignant hypertension
- Polycystic kidney disease
- Hereditary nephritis (Alport syndrome)
- Fabry disease
- Nail-patella syndrome

Other

- Exercise
- Pyelonephritis, acute
- Nephrolithiasis
- Renal cyst
- Renal trauma
- Renal neoplasm
- Coagulopathy, thrombocytopenia
- Interstitial nephritis, acute
- Analgesic nephropathy
- Sickle cell trait or disease
- Medullary sponge kidney
- Lymphomatous or leukemic infiltration
- Hydronephrosis
- Oxaluria
- Vascular anomalies, intrarenal arteriovenous fistula
- Acute febrile illnesses (e.g., malaria)
- Papillary necrosis
- Renal infarction (acute renal artery occlusion, renal vein thrombosis)
- Hematuria loin pain syndrome
- Renal transplant rejection

Lower Urinary Tract Causes

Congenital anomalies (e.g., ureterocele)
Neoplasms (bladder, ureter, prostate, urethral), benign or malignant
Cystitis, prostatitis, urethritis
Calculi
Trauma
Foreign body
Coagulopathy
Varices (renal pelvis, ureter, bladder)

Radiation cystitis
Drugs (especially cyclophosphamide, anticoagulants)
Schistosomiasis
Genitourinary tuberculosis

Non–Urinary Tract Causes

Neoplasm of adjacent organs
Diverticulitis
Pelvic inflammatory disease
Appendicitis

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1. Cohen RA, Brown RS. Microscopic hematuria. *N Engl J Med*. 2003;348:2330–2338.
2. Koenig KG, Bolton WK. Clinical evaluation and management of hematuria and proteinuria, p. 815. See Bibliography, 6.

5-B. Polyuria

Central diabetes insipidus (see 3-U)
Renal disease
- Nephrogenic diabetes insipidus, congenital
- Chronic renal insufficiency (especially tubulointerstitial disease)
- Diuretic phase of acute renal failure
- Postobstructive diuresis, partial or intermittent obstruction
- Hypercalcemia
- Hypokalemia
- Sickle cell trait or disease
- Multiple myeloma
- Amyloidosis
- Sarcoidosis
- Sjögren syndrome
- Decreased protein intake

Osmotic diuresis
- Diabetes mellitus, poorly controlled
- Mannitol or urea administration
- Iodinated contrast dye
- Hyperalimentation
- Tube feedings

Drugs
- Alcohol
- Diuretics

- Lithium
- Demeclocycline
- Methicillin
- Gentamicin
- Amphotericin B
- Phenothiazines
- Sulfonylureas
- Phenytoin
- Propoxyphene
- Methoxyflurane
- Colchicine
- Vinblastine
- Foscarnet
- Clonidine
- Norepinephrine
- Narcotic antagonists

Water load

- Psychogenic polydipsia
- Intravenous fluid therapy
- Deliberate water consumption (e.g., marathon preparation)
- Drug-induced polydipsia (e.g., phenothiazines, anticholinergics)

Reference

1. Berl T, Schrier RW. Disorders of water metabolism, p. 1. See Bibliography, 1.

5-C. Proteinuria

Benign/Physiologic

Fever
Exercise
Orthostatic
Contrast dye

Usually Nonnephrotic (<3 g/day)

Chronic pyelonephritis
Arteriolar nephrosclerosis
Malignant hypertension
Interstitial nephritis, acute or chronic
Acute tubular necrosis
Urinary tract obstruction
Nephrolithiasis
Renal neoplasm

Renal trauma
Polycystic kidney disease
Hereditary nephritis (Alport syndrome)
Glomerular disease, especially:
- IgA nephropathy (Berger disease)
- Crescentic glomerulonephritis
- Hemolytic-uremic syndrome
- Systemic sclerosis

Genitourinary tuberculosis

Often Nephrotic

Primary renal disease, especially:
- Minimal change disease
- Membranous glomerulopathy
- Membranoproliferative glomerulonephritis
- Focal segmental glomerulosclerosis

Systemic disease, especially:
- Diabetes mellitus
- Lupus erythematosus
- Polyarteritis nodosa
- Wegener granulomatosis
- Henoch-Schönlein purpura
- Mixed cryoglobulinemia
- Amyloidosis (primary or secondary)
- Neoplasm
  - Solid tumors (especially lung, colon, stomach, breast)
  - Hodgkin disease, other lymphomas
  - Multiple myeloma
- Sarcoidosis
- Myxedema
- Graves disease
- Sickle cell disease

Toxins, drugs
- Gold
- Mercury
- Heroin
- Nonsteroidal anti-inflammatory drugs
- Penicillamine
- Captopril
- Trimethadione and other anticonvulsants

Allergens
- Pollens
- Poison ivy and oak

- Snake venom
- Bee or insect stings
- Antitoxin (e.g., tetanus toxoid)

Infection, especially:
- Bacterial (e.g., streptococcal, staphylococcal)
- Hepatitis B and C
- Cytomegalovirus (CMV)
- Epstein-Barr virus (infectious mononucleosis)
- Human immunodeficiency virus (HIV)
- Syphilis
- Malaria
- Helminthic (e.g., schistosomiasis)
- Leprosy

Miscellaneous
- Congestive heart failure
- Tricuspid insufficiency
- Constrictive pericarditis
- Pre-eclampsia
- Renal vein thrombosis, inferior vena cava obstruction
- Massive obesity
- Hereditary diseases, especially:
  - Congenital nephrotic syndrome
  - Fabry disease
  - Nail-patella syndrome

References

1. Glassock RJ. The glomerulopathies, p. 623. See Bibliography, 1.
2. See Bibliography, 2.

5-D. Glomerulopathy

Primary Renal Disease

Minimal change disease
Membranous glomerulopathy
Membranoproliferative glomerulonephritis
Focal segmental glomerulosclerosis
Crescentic glomerulonephritis
Mesangial proliferative glomerulonephritis (e.g., IgA nephropathy)

Infection

Bacterial, especially:
- Streptococcal
- Endocarditis
- Shunt infection

- Septicemia, especially pneumococcal or staphylococcal
- Meningitis

Viral, especially:

- Hepatitis B and C
- Mononucleosis
- Rubella
- Varicella
- Mumps
- CMV
- HIV
- Syphilis

Parasitic infestation (especially malaria)
Tuberculosis

Systemic Disease

Diabetes mellitus
Lupus erythematosus
Scleroderma
Rheumatoid arthritis
Mixed connective tissue disease
Polyarteritis nodosa
Wegener granulomatosis
Hemolytic-uremic syndrome
Thrombotic thrombocytopenic purpura
Henoch-Schönlein purpura
Mixed cryoglobulinemia
Goodpasture syndrome
Waldenström macroglobulinemia
Amyloidosis
Fibrillary/immunotactoid glomerulopathies
Neoplasm

- Solid tumors (especially lung, stomach, colon, breast)
- Hodgkin disease, other lymphoma
- Multiple myeloma, light-chain nephropathy

Sarcoidosis
Pre-eclampsia
Postpartum renal failure
Sickle cell disease
Hepatic cirrhosis

Drugs, Toxins

Mercury
Gold

Penicillamine
Probenecid
Heroin
Amphetamines
Trimethadione

Other

Radiation
Hereditary nephritis (Alport syndrome)
Fabry disease
Nail-patella syndrome
Congenital nephrotic syndrome
Renal transplant rejection

References

1. Glassock RJ. The glomerulopathies, p. 623. See Bibliography, 1.
2. See Bibliography, 2.

5-E. Interstitial Nephropathy

Infection, especially:
- Bacterial (pyelonephritis, acute or chronic)
- Mycoplasmal
- Toxoplasmosis
- Leptospirosis
- Hantavirus
- Brucellosis
- Mononucleosis
- Legionnaires disease

Urinary tract obstruction, vesicoureteral reflux
Papillary necrosis
Drugs
- Analgesics (especially aspirin, phenacetin)
- Methicillin and penicillin analogs
- Sulfonamides
- Cephalosporins
- Tetracycline
- Rifampin
- Amphotericin B
- Acyclovir
- Furosemide
- Thiazides

- Nonsteroidal anti-inflammatory drugs
- Allopurinol
- Phenytoin
- Azathioprine
- Lithium
- Cimetidine
- Warfarin
- Polymyxins
- Chinese herbs (aristolochic acid)

Heavy metals
- Lead
- Cadmium
- Uranium
- Copper
- Beryllium

Oxalate deposition
- Hereditary
- Small bowel disease or resection
- Ethylene glycol intoxication
- Methoxyflurane anesthesia

Uric acid deposition
- Gout
- Tumor lysis syndrome

Hypercalcemia
- Hyperparathyroidism
- Neoplasm, multiple myeloma
- Milk-alkali syndrome
- Sarcoidosis

Hypokalemia

Radiation

Neoplastic disease
- Multiple myeloma
- Light-chain nephropathy
- Leukemic or lymphomatous infiltration
- Waldenström macroglobulinemia

Vascular causes
- Arteriolar nephrosclerosis
- Renal artery stenosis
- Atheroembolic disease
- Sickle cell trait or disease

Hereditary causes
- Hereditary nephritis
- Medullary sponge kidney

- Medullary cystic disease
- Polycystic kidney disease
- Cystinosis
- Fabry disease

Systemic lupus erythematosus
Mixed cryoglobulinemia
Sarcoidosis
Sjögren syndrome
Amyloidosis
Balkan nephropathy
Transplant rejection

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1. Eknoyan G. Acute tubulointerstitial nephritis, p. 1160. See Bibliography, 2.
2. Eknoyan G. Chronic tubulointerstitial nephropathies, p. 1860. See Bibliography, 2.

5-F. Renal Tubular Acidosis

Distal (Type I)

Pyelonephritis, chronic
Obstructive uropathy
Drugs, toxins
- Amphotericin B
- Analgesics
- Toluene
- Lithium
- Cyclamate

Nephrocalcinosis, especially:
- Primary hyperparathyroidism
- Vitamin D intoxication
- Primary hypercalciuria
- Medullary sponge kidney
- Hyperthyroidism

Autoimmune diseases
- Hypergammaglobulinemic states, especially:
  - Hyperglobulinemic purpura
  - Cryoglobulinemia
  - Familial hypergammaglobulinemia
- Systemic lupus erythematosus
- Sjögren syndrome
- Thyroiditis

- Chronic active hepatitis
- Primary biliary cirrhosis
- Diffuse interstitial pulmonary fibrosis

Genetically transmitted diseases
- Sickle cell disease
- Ehlers-Danlos syndrome
- Hereditary elliptocytosis
- Fabry disease
- Wilson disease
- Medullary cystic disease
- Hereditary fructose intolerance

Hepatic cirrhosis
Balkan nephropathy
Oxalate nephropathy
Multiple myeloma
Renal transplantation
Idiopathic (sporadic or hereditary)

Proximal (Type II)

Primary (sporadic or hereditary)
Carbonic anhydrase deficiency (e.g., genetic or acetazolamide induced)
Fanconi syndrome (multiple proximal tubular defects)
- Drugs and toxins
  - Outdated tetracycline
  - Toluene
  - Gentamicin
  - Streptozotocin
  - Lead
  - Cadmium
  - Mercury
- Multiple myeloma
- Amyloidosis
- Sjögren syndrome
- Vitamin D–deficient, –dependent, and –resistant states
- Cystinosis
- Tyrosinemia
- Lowe syndrome
- Wilson disease
- Hereditary fructose intolerance
- Pyruvate carboxylase deficiency
- Medullary cystic disease
- Paroxysmal nocturnal hemoglobinuria

Osteopetrosis
Renal transplantation

Type IV

Aldosterone deficiency
- Adrenal insufficiency
- Adrenal enzyme deficiency, congenital adrenal hyperplasia, especially 21-hydroxylase deficiency
- Selective aldosterone deficiency
  - Hyporeninemic hypoaldosteronism
  - Diabetes
  - Tubulointerstitial disease
  - Nonsteroidal anti-inflammatory drugs
  - Cyclosporine
  - HIV infection
  - Sickle cell disease
  - Obstructive uropathy
- Heparin
- Angiotensin-converting enzyme (ACE) inhibitors

Mineralocorticoid resistance
- Pseudohypoaldosteronism
- Obstructive uropathy
- Sickle cell disease
- Drugs (spironolactone, triamterene, amiloride)

References

1. Shapiro JI, Kaehny WD. Pathogenesis and management of metabolic acidosis and alkalosis, p. 115. See Bibliography, 1.
2. Rose BD, p. 578. See Bibliography, 4.

5-G. Urinary Tract Obstruction

Urethral

Congenital urethral stenosis, web, atresia
Posterior urethral valves
Inflammation or stricture
Trauma

Bladder Neck

Prostatic hypertrophy, prostatitis
Carcinoma (prostate, bladder)
Bladder infection

Trauma
Functional
- Neuropathy (peripheral neuropathy, spinal cord injury or trauma)
- Drugs (parasympatholytics, ganglionic blockers)

Ureteral

Ureteral-pelvic junction stricture
Intraureteral
- Clots
- Stones
- Crystals (e.g., sulfa, uric acid, indinavir)
- Papillae (necrosed)
- Trauma (edema, stricture)
- Tumor
- Foreign bodies

Extraureteral
- Endometriosis
- Retroperitoneal tumor or metastases, especially:
  - Cervical
  - Endometrial
  - Ovarian
  - Prostatic
  - Lymphoma
  - Sarcoma
- Fibrosis
  - Idiopathic
  - Associated with inflammation, drugs (e.g., methysergide), surgery, radiation, inflammatory bowel disease
- Pregnancy
- Aortic or iliac aneurysm
- Aberrant vessels
- Surgical ligation
- Retroperitoneal hemorrhage
- Lymphocele

References

1. Seifter JL, Brenner BM. Urinary tract obstruction, p. 1722. See Bibliography, 3.
2. Klahr S. Obstructive nephropathy: pathophysiology and management, p. 498. See Bibliography, 1.

5-H. Nephrolithiasis

Calcium-Containing Stones

Idiopathic
Primary hypercalciuria (absorptive, renal leak), with or without hyperuricosuria
Hypercalcemic states (see 1-L)
- Primary hyperparathyroidism
- Malignancy
- Immobilization
- Milk-alkali syndrome
- Vitamin D excess
- Sarcoidosis
- Hyperthyroidism

Renal tubular acidosis, distal
Medullary sponge kidney
Carbonic anhydrase inhibitors (e.g., acetazolamide)
Cushing disease or syndrome
Hypoparathyroidism
Hyperoxaluria
- Primary (congenital)
- Increased metabolic production (e.g., ethylene glycol or methoxyflurane excess)
- Increased gastrointestinal absorption
  - Increased dietary intake
  - Small bowel disease or resection (e.g., jejunoileal bypass, celiac sprue, Crohn disease)

Calcium-Magnesium-Ammonium Phosphate Stones (Struvite)

Chronic infection (usually with urea-splitting organisms, for example, *Proteus*, *Klebsiella*, *Pseudomonas*), especially associated with:
- Chronic Foley catheter use
- Ileal loop

Uric Acid and/or Xanthine Stones

Gout
Leukemia, lymphoma (especially after chemotherapy)
Purine pathway enzyme deficiency states
- Lesch-Nyhan syndrome
- Glycogen storage disease
- Xanthinuria

Drugs (e.g., aspirin, probenecid)
Gastrointestinal disorders associated with chronic diarrhea (especially with ileostomy)

Cystine Stones

Cystinuria

Other

Acyclovir (intratubular)
Indinavir

Reference

1. Hruska KA, Beck AM. Nephrolithiasis, p. 717. See Bibliography, 2.

5-I. Acute Renal Failure

Prerenal azotemia
Hypovolemia
- Hemorrhage
- Gastrointestinal losses
- Sweating
- Diuretic use
- Third spacing (e.g., intestinal ileus)
- Burns

Decreased effective circulating volume
- Cirrhosis/ascites, hepatorenal syndrome
- Nephrotic syndrome
- Cardiac causes (e.g., congestive heart failure, acute myocardial infarction, pericardial tamponade)

Catabolic states, for example:
- Starvation with stress
- Sepsis, serious infection
- Postsurgical state
- Steroids
- Tetracycline

Breakdown of blood in gastrointestinal tract or resorption of hematoma

Drugs, Toxins

Heavy metals
- Mercury
- Arsenic

- Lead
- Cadmium
- Uranium
- Bismuth
- Copper
- Platinum

Carbon tetrachloride, other organic solvents
Ethylene glycol
Pesticides
Fungicides
X-ray contrast media (iodinated)
Gadolinium
Antibiotics
- Penicillin
- Tetracycline
- Aminoglycosides
- Cephalosporins
- Amphotericin B
- Sulfonamides
- Acyclovir
- Antiretroviral agents (especially indinavir, tenofovir, cidofovir)
- Rifampin
- Polymyxin

Other drugs
- Nonsteroidal anti-inflammatory drugs
- ACE inhibitors
- Furosemide
- Phenytoin
- Phenindione
- Methoxyflurane
- Cyclosporine
- Ethylenediaminetetraacetic acid (EDTA)

Ischemic Disorders

Major trauma, surgery
Massive hemorrhage, severe volume depletion
Pancreatitis
Septic shock
Crush injury
Hemolysis, transfusion reaction
Rhabdomyolysis

Glomerular/Vascular Diseases

Poststreptococcal glomerulonephritis
Systemic lupus erythematosus
Scleroderma
Polyarteritis nodosa, hypersensitivity angiitis
Henoch-Schönlein purpura
Bacterial endocarditis
Serum sickness
Goodpasture syndrome
Crescentic glomerulonephritis, idiopathic
Wegener granulomatosis
Drug-induced vasculitis
Malignant hypertension
Hemolytic-uremic syndrome
Thrombotic thrombocytopenic purpura
Abruptio placentae
Postpartum renal failure
Transplant rejection

Interstitial/Intratubular Diseases

Interstitial nephritis (see 5-E), especially:
- Infection
- Drugs
- Oxalate deposition
- Hypercalcemia
- Multiple myeloma

Pyelonephritis, papillary necrosis
Hyperuricemia
Radiation

Major Vessel Diseases

Renal artery thrombi, emboli, stenosis
Renal vein or inferior vena cava thrombosis
Dissecting aneurysm (aorta with or without renal arteries)

Postrenal Causes[1]

Urethral obstruction
Bladder neck obstruction
Ureteral obstruction

References

1. Lee VWS, Harris D, Anderson RJ, Schrier RW. Acute renal failure, p. 986. See Bibliography, 2.
2. Edelstein CL, Schrier RW. Acute renal failure: pathogenesis, diagnosis, and management, p. 401. See Bibliography, 1.

[1]See 5-G.

5-J. Renal Failure, Reversible Factors

Infection, upper or lower urinary tract
Obstruction
Volume depletion
Drugs, toxins
Congestive heart failure
Hypertension
Pericardial tamponade
Hypercalcemia
Hyperuricemia (>15–20 mg/dL)
Hypokalemia

Reference

1. Wang W, Chan L. Chronic renal failure: manifestations and pathogenesis, p. 456. See Bibliography, 1.

5-K. Urinary Diagnostic Indices[a]

TABLE 5-1.

	Prerenal Azotemia	Oliguric Acute Renal Failure
Urine osmolality (mOsm/kg H_2O)	>500	<400
Urine Na^+ (mEq/L)	<20	>40
Urine/plasma creatinine	>40	<20
Fractional excretion of Na^+ (%)[b]	<1	>2

[a]These indices are useful only in oliguric states.
[b]Fractional excretion of Na^+ =

$$\frac{(\text{urine } Na^+ \text{concentration})\,(\text{plasma creatinine concentration})}{(\text{plasma } Na^+ \text{concentration})(\text{urine creatinine concentration})} \times 100\%$$

Reference

1. Edelstein CL, Schrier RW. Acute renal failure: pathogenesis, diagnosis, and management, p 401. See Bibliography, 4.

5-L. Chronic Kidney Disease

Glomerulopathy, primary renal[1]
Glomerulopathy associated with systemic disease[1]
Interstitial disease[2]
Urinary tract obstruction[3]
Vascular diseases
- Nephrosclerosis
- Malignant hypertension
- Cortical necrosis
- Renal artery stenosis, thrombosis, emboli
- Renal vein thrombosis, inferior vena cava thrombosis

Genetically transmitted disease
- Polycystic kidney disease
- Hereditary nephritis
- Fabry disease
- Oxalosis
- Cystinosis
- Medullary cystic disease
- Medullary sponge kidney
- Nail-patella syndrome
- Congenital nephrotic syndrome

References

1. See Bibliography, 1.
2. See Bibliography, 2.

[1]See 5-D.
[2]See 5-E.
[3]See 5-G.

5-M. Stages of Chronic Kidney Disease

Stage 1: glomerular filtration rate (GFR) >90 mL/min/1.73 m^2, but with signs of kidney disease based on abnormal imaging studies and/or proteinuria
Stage 2: GFR 60–90 mL/min/1.73 m^2
Stage 3: GFR 30–60 mL/min/1.73 m^2
Stage 4: GFR 15–30 mL/min/1.73 m^2
Stage 5: GFR <15 mL/min/1.73 m^2

Reference

National Kidney Foundation K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Available at: www.kidney.org/professionals/kdoqi/guidelines_ckd/toc.htm.

5-N. Indications for Dialysis

Biochemical Criteria

Volume overload
Serum K^+ >6 mEq/L (despite medical management)
Serum HCO_3 <10 mEq/L, pH <7.20
Blood urea nitrogen >80–100 mg/dL
Serum creatinine >8–10 mg/dL
Creatinine clearance or GFR <10–15 mL/min

Symptomatic Criteria

Central nervous system symptoms (e.g., lethargy, confusion, seizures, asterixis)
Gastrointestinal symptoms (e.g., nausea, vomiting)
Pericarditis
Bleeding diathesis

Miscellaneous Indications (Conditions Not Necessarily Associated with Renal Failure)

Hypercalcemia
Hypermagnesemia
Hyperuricemia
Hypernatremia
Hypothermia
Drug overdose, toxin ingestion

Reference

1. Zawada ET. Indications for dialysis, p. 3. See Bibliography, 5.

5-O. Erectile Dysfunction

Aging
Psychogenic causes
Testicular causes (primary or secondary)
Congenital hypogonadism (especially Froehlich syndrome, Klinefelter syndrome, hypogonadotropic eunuchoidism)

- Acquired hypogonadism
  - Viral orchitis
  - Trauma
  - Radiation
  - Hepatic insufficiency
  - Chronic pulmonary disease
  - Chronic renal failure
  - Granulomatous disease (especially leprosy)
- Testicular carcinoma
- Pituitary tumor, especially when associated with hyperprolactinemia
- Pituitary insufficiency

Neurologic disease
- Anterior temporal lobe lesion
- Spinal cord disease (e.g., multiple sclerosis)
- Autonomic and peripheral polyneuropathies (e.g., diabetic)
- Loss of sensory input
  - Tabes dorsalis
  - Dorsal root ganglia disease
- Lesions of nervi erigentes
  - Aortic bypass surgery
  - Prostatectomy
  - Rectosigmoid surgery

Drugs, especially:
- Cardiovascular agents
  - Thiazides
  - Beta-blockers
  - Calcium channel blockers
  - Clonidine
  - Methyldopa
  - Guanethidine
  - Digoxin
  - Gemfibrozil
- Antidepressants (e.g., tricyclics, monoamine oxidase inhibitors, serotonin reuptake inhibitors)
- Antipsychotic agents (e.g., phenothiazines, haloperidol, thioridazine)
- Central nervous system depressants (e.g., diazepam, chlordiazepoxide, barbiturates, butyrophenones)
- Addictive drugs (e.g., ethanol, heroin, methadone, cocaine)
- Anticholinergic agents
- Antiandrogens (e.g., finasteride, leuprolide, spironolactone)

- Estrogens
- H_2 antagonists

Alcoholism
Vascular disease (e.g., Leriche syndrome)
Priapism, previous
Penile disease
- Trauma
- Peyronie disease

Reference

1. McVary KT. Sexual dysfunction, p. 271. See Bibliography, 3.

5-P. Menorrhagia and Nonmenstrual Vaginal Bleeding

Midcycle ovulatory bleeding (normal variant)
Inadequate corpus luteum (luteal phase defect)
Uterine or endometrial disease
- Endometritis
- Endometriosis
- Uterine adenomyosis
- Endometrial polyps
- Uterine leiomyomas
- Carcinoma
- Intrauterine synechiae
- Intrauterine device

Vaginal or cervical disease
- Vaginitis, cervicitis
- Cervical scarring
- Carcinoma

Abortion
Ectopic pregnancy
Ovarian destructive lesions (e.g., tumor, chronic salpingo-oophoritis)
Hypothalamic or pituitary lesion (e.g., tumor, sarcoidosis)
Adrenal disease (hyper- or hypofunction)
Thyroid disease (hyper- or hypofunction)

Anovulatory Bleeding

Estrogen withdrawal bleeding
Estrogen breakthrough bleeding
- Chronic, continuous estrogen therapy

Polycystic ovarian disease
Estrogen-secreting ovarian tumor
Progesterone breakthrough bleeding (e.g., continuous low-dose oral contraceptives)
Stress, psychogenic factors

Reference

1. Carr BR, Bradshaw KD. Disorders of the ovary and female reproductive tract, p. 2198. See Bibliography, 3.

Bibliography

1. Schrier RW, ed. *Renal and Electrolyte Disorders*. 6th ed. Philadelphia: Lippincott-Raven; 2003.
2. Schrier RW, ed. *Diseases of the Kidney and Urinary Tract*. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.
3. Kasper DS, et al., eds. *Harrison's Principles of Internal Medicine*. 16th ed. New York: McGraw-Hill; 2005.
4. Rose BD. *Clinical Physiology of Acid-Base and Electrolyte Disorders*. 5th ed. New York: McGraw-Hill; 2001.
5. Daugirdas JT, Ing TS, eds. *Handbook of Dialysis*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.
6. Neilson EG, Couser WG, eds. *Immunologic Renal Diseases*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.

6

HEMATOLOGIC SYSTEM

6-A. Anemia: Hypoproliferative (Low Reticulocyte Count)

Nutrient Deficiency

- Iron deficiency
  - Chronic blood loss
  - Pregnancy
  - Dietary deficiency
  - Malabsorption
    - Subtotal gastrectomy
    - Malabsorption syndromes
  - Hemoglobinuria or hemosiderinuria
    - Intravascular hemolysis
  - Hemodialysis
- Vitamin B_{12} deficiency
  - Dietary deficiency (rare)
  - Impaired absorption
    - Insufficient intrinsic factor
      - Pernicious anemia
      - Gastrectomy (total or partial)
      - Gastric mucosal injury (e.g., lye ingestion)
      - Congenital
  - Malabsorption syndromes
    - Sprue, tropical or nontropical
    - Ileal resection

- Regional ileitis
- Infiltrative intestinal disease (e.g., lymphoma)
- Chronic pancreatitis
- Familial selective malabsorption
- Drug-induced malabsorption

Competitive absorption
- *Diphyllobothrium latum* (fish tapeworm)
- Blind-loop syndromes

Increased requirements
- Pregnancy
- Neoplasia

Folate deficiency

Dietary deficiency (especially in alcoholics, infants)

Impaired absorption
- Malabsorption syndromes
  - Sprue, tropical or nontropical
  - Whipple disease
  - Small intestinal resection
  - Infiltrative intestinal disease (e.g., lymphoma)
  - Scleroderma
  - Amyloidosis
- Drug-induced malabsorption (anticonvulsants)

Increased requirements
- Pregnancy
- Infancy
- Hemolytic anemia
- Chronic exfoliative dermatitis
- Neoplasia
- Uremia

Impaired metabolism
- Trimethoprim
- Methotrexate
- Pyrimethamine
- Alcohol

Other nutritional deficiencies
- Vitamin A
- Pyridoxine (rare)
- Vitamin C
- Starvation
- Protein deficiency (kwashiorkor)

Anemia of Chronic Disease

- Chronic infection
  - Subacute bacterial endocarditis
  - Osteomyelitis
  - Chronic pyelonephritis
  - Chronic pulmonary infection (e.g., bronchiectasis)
  - Tuberculosis
  - Chronic fungal infection
  - Pelvic inflammatory disease
- Chronic inflammatory diseases
  - Rheumatoid arthritis
  - Rheumatic fever
  - Systemic lupus erythematosus
  - Vasculitis
  - Inflammatory bowel disease
  - Acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV) infection
- Malignancy
- Chronic renal disease
- Chronic liver disease
- Chronic lung disease
- Endocrine dysfunction
  - Hypothyroidism
  - Hyperthyroidism
  - Hypogonadism
  - Adrenal insufficiency
  - Panhypopituitarism
  - Hyperparathyroidism
- Pregnancy

Bone Marrow Disorders

- Congenital
  - Red cell aplasia (Diamond-Blackfan anemia)
  - Congenital dyserythropoietic anemias
  - Hereditary sideroblastic anemias
- Aplastic
  - Pancytopenia (see 6-L)
  - Pure red cell aplasia
    - Congenital (Diamond-Blackfan anemia)
    - Acquired
      - Associated with thymoma, chronic lymphocytic leukemia, and so forth
      - Drug induced

- Toxic
  - Megaloblastic
    - Antimetabolites (e.g., 5-fluorouracil, 6-thioguanine, 6-mercaptopurine, azathioprine)
  - Sideroblastic (e.g., alcohol, lead, isoniazid, chloramphenicol)
  - Aplastic (see 6-L)
- Infiltrative, with or without fibrosis
  - Infection
    - Tuberculosis
    - Fungal disease
  - Gaucher and other lipid storage diseases
  - Malignancy
    - Hematologic (leukemia, lymphoma, myeloma)
    - Marrow metastases
- Neoplastic
  - Leukemia, acute and chronic
  - Lymphoproliferative disorders
    - Lymphoma, with marrow involvement
      - Hodgkin disease
      - Non-Hodgkin lymphoma (NHL)
    - Plasma cell myeloma
    - Hairy cell leukemia
  - Myeloproliferative disorders
    - Agnogenic myeloid metaplasia with fibrosis
    - Essential thrombocythemia
    - Chronic myelogenous leukemia
  - Myelodysplastic syndromes
    - Refractory anemia (RA)
    - RA with ringed sideroblasts
    - RA with excess of blasts (RAEB)
    - RAEB in transformation
    - Chronic myelomonocytic leukemia

Other

Marathon runner's anemia (physiologic)

References

1. Aboulafia DM, Mitsuyasu RT. Hematologic abnormalities in AIDS. *Hematol Oncol Clin N Am.* 1991;5:195–214.
2. Caro J. Anemia of chronic renal failure, p. 449. See Bibliography, 2.
3. Gregg, XT, Prchal, JT. Anemia of endocrine disorders, p. 454. See Bibliography, 2.

4. Means RT Jr. Anemias secondary to chronic disease and systemic disorders, p. 1445. See Bibliography, 2.
5. Beutler E. Iron deficiency, p. 551. See Bibliography, 2.
6. Herbert V. Hematologic complications of alcoholism I, II. *Semin Hematol.* 1980;17:164–176.
7. Dressendorfer RH, Wade CE, Amsterdam EA. Development of pseudoanemia in marathon runners during a 20-day road race. *JAMA.* 1981;246:1215–1218.
8. See Bibliography, 3.
9. Beutler E. Anemia resulting from other nutritional deficiencies, p. 555. See Bibliography, 2.

6-B. Anemia: Hyperproliferative (Increased Reticulocyte Count)

Blood Loss
Hypersplenism
Hemolytic Anemia

- Hereditary
  - Membrane abnormalities
    - Hereditary spherocytosis
    - Hereditary elliptocytosis
    - Hereditary stomatocytosis
    - Acanthocytosis (abetalipoproteinemia)
    - Others
  - Enzyme deficiencies
    - Glucose-6-phosphate dehydrogenase
    - Pyruvate kinase
    - Others
  - Hemoglobinopathies
    - Qualitative
      - Sickle cell anemia
      - Hemoglobin C disease
      - Unstable hemoglobin disease
      - Others
    - Unbalanced chain synthesis
      - Thalassemias
- Acquired
  - Nonimmune
    - Traumatic
      - Prosthetic valves and other cardiac abnormalities
      - March hemoglobinuria
      - Burns
      - Ionizing irradiation

- Microangiopathic hemolytic anemia
  - Disseminated intravascular coagulation (DIC)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Hemolytic uremic syndrome
  - Antiphospholipid antibody syndrome
  - Vasculitis
  - Malignant hypertension
- Infectious agents
  - Malaria
  - *Clostridium perfringens*
  - *Bartonella*
  - Babesiosis
  - Others
- Chemical agents
  - Naphthalene
  - Arsine
  - Copper
  - Chlorates
  - Venoms
  - Distilled water (intravenous)
  - Others
- Paroxysmal nocturnal hemoglobinuria
- Hypophosphatemia
- Spur cell anemia (liver disease)

Immune

- Warm antibody mediated
  - Incompatible blood transfusion
  - Hemolytic disease of newborn
  - Idiopathic
  - Secondary
    - Infectious
      - Viral [e.g., Epstein-Barr virus, cytomegalovirus (CMV)]
    - Collagen-vascular disorders
      - Systemic lupus erythematosus
      - Rheumatoid arthritis
    - Malignancy
      - Lymphoproliferative disorders
      - Solid tumors
    - Other
      - Sarcoidosis
      - Inflammatory bowel disease

Drugs (many)
Cold antibody mediated
Idiopathic
Secondary
Infectious
Viral (e.g., Epstein-Barr virus)
Mycoplasma pneumoniae
Malignancy
Paroxysmal cold hemoglobinuria

References

1. Baker KR, Moake J. Hemolytic anemia resulting from physical injury, p. 709. See Bibliography, 2.
2. Beutler E. Disorders of red cells resulting from enzyme abnormalities, infection with microorganisms, pp. 603, 723. See Bibliography, 2.
3. Packman CH. Hemolytic anemia resulting from immune injury, p. 729. See Bibliography, 2.

6-C. Polycythemia

Spurious
Decreased plasma volume (e.g., dehydration, burns)
"Stress" erythrocytosis (Gaisböck's syndrome)
Secondary
Appropriate (associated with tissue hypoxia)
Decreased arterial partial pressure of oxygen (PO_2)
Altitude
Chronic pulmonary disease
Alveolar hypoventilation
Cyanotic congenital heart disease
Normal arterial PO_2
Carboxyhemoglobinemia (e.g., cigarette smoking)
Hemoglobinopathies (with an increased affinity for oxygen)
Cobalt ingestion
Red cell enzyme deficiencies
Inappropriate
Renal disorders
Hydronephrosis
Renal cysts
Post–renal transplant erythrocytosis
Renal cell carcinoma

- Endocrine disorders
  - Cushing syndrome
  - Primary hyperaldosteronism
  - Pheochromocytoma
  - Androgen therapy
- Hepatoma
- Cerebellar hemangioblastoma
- Uterine leiomyoma
- Familial erythrocytosis (e.g., Chuvash polycythemia)
- Ovarian dermoid cyst

Primary

- Polycythemia rubra vera
- Primary familial and congenital polycythemia

References

1. Means RT Jr. See Bibliography, 1.
2. Prchal JT, Beutler E. Primary and secondary polycythemias (erythrocytosis), p. 779. See Bibliography, 2.

6-D. Granulocytopenia

Infections

- Viral
  - Influenza
  - Infectious mononucleosis
  - Infectious hepatitis
  - Rubella
  - Chickenpox
  - Smallpox
  - Poliomyelitis
  - Others
- Bacterial
  - Overwhelming bacteremia
  - Typhoid fever
  - Tularemia
  - Brucellosis
- Mycobacterial
  - Miliary tuberculosis
- Rickettsial
- Protozoan
  - Malaria

Chemical agents, drugs, physical agents

- Predictable
  - Antineoplastic agents

- Benzene
- Ionizing radiation
- Idiosyncratic
  - Aminopyrine
  - Anticonvulsants
  - Antibiotics (e.g., chloramphenicol)
  - Antithyroid drugs
  - Clozapine
  - Ethanol
  - Phenothiazines
  - Sulfonamides
  - Others (immune suppression of production, e.g., ibuprofen)
- Systemic illness
  - Systemic lupus erythematosus
  - Felty syndrome
  - AIDS or HIV infection
- Hypersplenism
- Nutritional
  - Vitamin B_{12} or folate deficiency
  - Cachexia
  - Copper deficiency
  - Alcoholism
- Bone marrow dysfunction or accelerated destruction
  - Acute leukemias (aleukemic)
  - Lymphoproliferative disorders
  - Myelofibrosis
    - Primary: myeloproliferative disorders
    - Secondary
      - Tumor infiltration
      - Infection
  - Aplastic anemia
  - Myelodysplastic syndromes
- Immune neutropenia
  - Drug induced
  - Collagen vascular disease
    - Systemic lupus erythematosus
    - Rheumatoid arthritis
    - Sjögren syndrome
  - Neoplasia
  - Autoimmune neutropenia
    - Idiopathic
    - Drugs
    - Collagen vascular disease

Other
- Neutropenia associated with splenomegaly (e.g., sarcoidosis)
- Benign neutropenia of blacks
- Chronic idiopathic neutropenia
- Congenital neutropenia (e.g., Kostmann syndrome)
- Cyclic neutropenia
- Benign familial neutropenia

References

1. Dale DC. Neutropenia and neutrophilia, p. 907. See Bibliography, 2.
2. Budman DR, Steinberg AD. Hematologic aspects of systemic lupus erythematosus. *Ann Intern Med.* 1977;86:220–229.
3. Aboulafia DM, Mitsuyasu RT. Hematologic abnormalities in AIDS. *Hematol Oncol Clin N Am.* 1991;5:195–214.

6-E. Granulocytosis

Reactive

Infection
- Bacterial (primarily)
- Mycobacterial
- Fungal
- Rickettsial
- Viral
- Spirochetal
- Parasitic

Physical stimuli
- Exercise
- Trauma
- Seizures

Inflammation, acute and chronic
- Collagen vascular disorders
- Hypersensitivity reactions
- Gout
- Vasculitis
- Nephritis
- Inflammatory bowel disease
- Hepatitis
- Pancreatitis
- Dermatitis

Neoplasm
Tissue necrosis
  Myocardial infarction
  Gangrene
  Burns
Drugs, toxins, especially:
  Corticosteroids
  Epinephrine
  Lithium
  Endotoxin
  Histamine
  Lead
  Growth factors [granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF)]
Hematologic disorders
  Hemorrhage
  Postsplenectomy, functional asplenia
  Recovery from agranulocytosis
  Hemolytic anemia
  Bone marrow infiltration (e.g., solid tumor, tuberculosis)
Metabolic disorders
  Diabetic ketoacidosis
  Cushing syndrome
  Eclampsia
  Uremia
  Thyroid storm
Pregnancy

Autonomous

Myeloproliferative disorders
  Chronic myelogenous leukemia
  Polycythemia rubra vera
  Agnogenic myeloid metaplasia
  Essential thrombocythemia
Acute leukemia

Congenital Causes

Down syndrome

Reference

1. Dale DC. Neutropenia and neutrophilia, p. 907. See Bibliography, 2.

6-F. Lymphocytosis

Infections
- Viral
  - Infectious mononucleosis
  - Infectious lymphocytosis
  - CMV infection
  - Mumps
  - Measles
  - Chickenpox
  - Viral hepatitis
  - Others
- Bacterial
  - Pertussis
  - Brucellosis
  - Tuberculosis
- Spirochetal
  - Syphilis, secondary and congenital
- Protozoan
  - Toxoplasmosis

Hematologic disorders
- Lymphocytic leukemia, acute and chronic
- NHL with marrow involvement

Drug hypersensitivity
- Phenytoin
- *p*-Aminosalicylic acid

Miscellaneous
- Thyrotoxicosis
- Postcardiopulmonary bypass syndrome
- Serum sickness
- Immune thrombocytopenic purpura
- Immune hemolytic anemia

Reference

1. Kipps TJ. Lymphocytosis and lymphocytopenia, p. 1087. See Bibliography, 2.

6-G. Lymphocytopenia

Immunodeficiency syndromes
- AIDS or HIV infection
- Congenital immunodeficiency syndromes
  - Wiskott-Aldrich syndrome
  - Ataxia-telangiectasia
  - DiGeorge syndrome

Common variable immunodeficiency
Increased lymphocyte destruction
Radiation therapy
Antineoplastic chemotherapy
Antilymphocyte/antithymocyte globulin
Corticosteroid or adrenocorticotropic hormone administration or excess
Increased lymphocyte loss
Thoracic duct drainage
Intestinal lymphectasia
Intestinal lymphatic obstruction (e.g., lymphoma)
Whipple disease
Severe right-sided heart failure
Tricuspid insufficiency
Constrictive pericarditis
Other
Sarcoidosis
Advanced malignancy
Miliary tuberculosis
Renal failure
Aplastic anemia
Collagen-vascular disorders
Systemic lupus erythematosus
Idiopathic
Idiopathic $CD4^+$ T-lymphocytopenia

References

1. Kipps TJ. Lymphocytosis and lymphocytopenia, p.1087. See Bibliography, 2.
2. Spivak JL, Bender BS, Quinn TC. Hematologic abnormalities in the acquired immune deficiency syndrome. *Am J Med.* 1984;77:224–228.

6-H. Monocytosis

Infections
Tuberculosis
Subacute bacterial endocarditis
Syphilis
Hematologic disorders
Myelodysplastic syndromes
Acute nonlymphocytic leukemia (especially acute monocytic leukemia)

- Myeloproliferative disorders
- Lymphoproliferative disorders
  - Hodgkin disease
  - NHL
  - Myeloma
- Malignant histiocytosis
- Postsplenectomy
- Recovery from neutropenia
  - Infectious
  - Drug induced
  - Postchemotherapy
  - Growth factor use (GM-CSF)
- Benign familial neutropenia

Collagen-vascular disorders
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Temporal arteritis
- Polyarteritis nodosa
- Polymyositis

Malignancy
- Any solid tumor

Gastrointestinal disorders
- Sprue
- Ulcerative colitis
- Regional enteritis
- Alcoholic liver disease

Miscellaneous
- Sarcoidosis

Reference

1. Lichtman MA. Monocytosis and monocytopenia, p. 987. See Bibliography, 2.

6-I. Eosinophilia

Infections
- Bacterial
  - Scarlet fever
  - Tuberculosis
  - Leprosy
  - Others
- Viral (especially hanta and herpes viruses)
- Fungal (e.g., coccidiomycosis)

- Mycobacterial (usually drug reaction)
- Parasitic
  - Protozoans (e.g., toxoplasmosis, amebiasis, malaria)
  - Metazoans (e.g., trichinosis, filariasis, schistosomiasis)
  - Arthropods (e.g., scabies)

Allergic disorders
- Allergic rhinitis
- Asthma
- Bronchopulmonary aspergillosis
- Urticaria
- Angioneurotic edema
- Serum sickness
- Food allergy

Skin disorders
- Psoriasis
- Atopic dermatitis or eczema
- Erythema multiforme
- Dermatitis herpetiformis
- Exfoliative dermatitis
- Pityriasis rosea
- Ichthyosis
- Pemphigus vulgaris
- Facial granuloma

Drug reactions [e.g., interleukin-2 (IL-2) therapy]

Hematologic disorders
- Myeloproliferative disorders
- Lymphoproliferative disorders
- Acute nonlymphocytic leukemia
- Chronic myelogenous leukemia
- Acute eosinophilic leukemia
- Langerhans cell histiocytosis
- Myelodysplastic syndromes
- Postsplenectomy
- Hypereosinophilic syndrome

Malignancy
- Advanced solid tumors

Collagen-vascular disorders
- Rheumatoid arthritis
- Polyarteritis nodosa
- Vasculitis (e.g., Churg-Strauss syndrome)
- Dermatomyositis
- Systemic lupus erythematosus
- Eosinophilic fasciitis

Gastrointestinal disorders
- Eosinophilic gastroenteritis
- Ulcerative colitis
- Regional enteritis
- Celiac disease

Others
- Adrenal insufficiency
- Löffler syndrome
- Chronic eosinophilic pneumonia
- Sarcoidosis
- Radiation therapy
- Chronic renal disease
- Familial eosinophilia
- Cystic fibrosis
- Endomyocardial fibrosis
- Hyper–immunoglobulin E syndrome
- Eosinophilia-myalgia and toxic oil syndrome

References

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2. Chusid MJ, Dale DC, West BC, Wolff SM. The hypereosinophilic syndrome. *Medicine.* 1975;54:1–27.
3. Pearson DJ, Rosenow EC. Chronic eosinophilic pneumonia (Carrington's): a follow-up study. *Mayo Clin Proc.* 1978;53:73–78.

6-J. Thrombocytopenia

Pseudothrombocytopenia

Decreased Production

Primary hematologic disorders
- Aplastic anemia
- Acute leukemia
- Lymphoproliferative disorders
  - Lymphoma
  - Myeloma
  - Chronic lymphocytic leukemia
- Myeloproliferative disorders
  - Agnogenic myeloid metaplasia with myelofibrosis
  - Chronic myelogenous leukemia (accelerated phase)

- Myelodysplastic syndromes
- Selective megakaryocytic aplasia

Bone marrow infiltration
- Solid tumor
- Infection
  - Tuberculosis
  - Other
- Gaucher disease
- Osteopetrosis

Drugs, especially:
- Selective megakaryocytic suppression
  - Alcohol
  - Estrogens
  - Interferon
  - Thiazides
- Nonselective myelosuppression
  - Predictable (e.g., antineoplastic chemotherapy)
  - Idiosyncratic (e.g., phenylbutazone)

Cyclic thrombocytopenia

Irradiation

Nutritional deficiency
- Folate
- Vitamin B_{12}
- Iron (rare)

Viral infections
- Influenza, CMV, parvovirus
- Rubella
- HIV
- Infectious mononucleosis
- Thai hemorrhagic fever
- Dengue fever
- Others

Paroxysmal nocturnal hemoglobinuria

Hereditary disorders
- Wiskott-Aldrich syndrome
- May-Hegglin anomaly

Congenital causes, especially:
- Fanconi anemia
- Amegakaryocytic thrombocytopenia with congenital malformations
- Congenital rubella or CMV infection
- Maternal thiazide ingestion

Increased Destruction

- Congenital: nonimmune
  - Erythroblastosis fetalis
  - Maternal pre-eclampsia
  - Congenital viral infection
  - Giant cavernous hemangioma
- Congenital: immune
  - Maternal drug ingestion
  - Isoimmune neonatal thrombocytopenia
  - Maternal autoimmune thrombocytopenic purpura
- Acquired: nonimmune
  - Infections
    - Bacterial
      - Sepsis
      - Typhoid fever
    - Viral
      - Infectious mononucleosis
      - CMV
      - Herpes
    - Malaria
    - Rickettsial
      - Rocky Mountain spotted fever
  - Toxic shock syndrome
  - Microangiopathic hemolytic anemia
    - DIC
    - TTP
    - Hemolytic-uremic syndrome
    - Vasculitis
    - HELLP (hemolysis, elevated liver enzyme levels, and a low platelet count) syndrome
  - Drugs
  - Extracorporeal circulation and other artificial surfaces
  - Anaphylaxis
- Acquired: immune
  - Drug induced, especially:
    - Alpha-methyldopa
    - Gold salts
    - Heparin
    - Indomethacin
    - Procainamide
    - Quinine/quinidine
    - Sulfonamides

- Thiazides
- Others

Neoplasia associated
- Lymphoproliferative disorders (e.g., chronic lymphocytic leukemia, Hodgkin disease, large granular lymphocytic leukemia)
- Solid tumors

Collagen-vascular disorders
- Antiphospholipid syndrome
- Systemic lupus erythematosus
- Rheumatoid arthritis

AIDS or HIV infection
Hepatitis C
Helicobacter pylori
Posttransfusion purpura
Idiopathic autoimmune thrombocytopenic purpura
- Acute
- Chronic

Sarcoidosis
Hashimoto thyroiditis
Hyperthyroidism
Autoimmune hepatitis
Agammaglobulinemia
Hypogammaglobulinemia
Immunoglobulin A deficiency

Sequestration/Dilution

Hypersplenism
Hypothermia
Extracorporeal circulation
Massive blood transfusion
Kasabach-Merritt syndrome
Gestational

References

1. Schafer A. Essential thrombocytopenia and thrombocytosis, p. 1785. See Bibliography, 2.
2. Coller BS, Beau Mitchel W, French DL. Hereditary qualitative platelet disorders, p. 1795. See Bibliography, 2.
3. Abrams CS, Shattil SJ, Bennet JS. Acquired qualitative platelet disorders, p. 1833. See Bibliography, 2.
4. Aboulafia DM, Mitsuyasu RT. Hematologic abnormalities in AIDS. *Hematol Oncol Clin N Am*. 1991;5:195–214.

6-K. Thrombocytosis

Primary

Myeloproliferative disorders
- Essential thrombocythemia
- Polycythemia vera
- Chronic myelogenous leukemia
- Agnogenic myeloid metaplasia with myelofibrosis

Secondary

Chronic inflammatory disorders
- Collagen-vascular disorders
  - Rheumatoid arthritis
  - Polyarteritis nodosa
  - Wegener granulomatosis
  - Other vasculitis
- Chronic infections
  - Tuberculosis
  - Osteomyelitis
  - Others
- Acute infections
- Inflammatory bowel disease
  - Ulcerative colitis
  - Regional ileitis
- Sarcoidosis
- Hepatic cirrhosis

Malignancy
Acute hemorrhage
Iron deficiency
Hemolytic anemia
Splenectomy
Postexercise
Recovery from thrombocytopenia (rebound)
- Myelosuppressive drug induced
- Vitamin B_{12} or folate deficiency
- Alcohol induced

Drug induced
- All-*trans*-retinoic acid
- Cytokines and growth factor
- Epinephrine
- Vincristine

Reference

1. Shafer AI. Essential thrombocythemia and thrombocytosis, p. 1785. See Bibliography, 2.

6-L. Pancytopenia

- Aplastic anemias
  - Congenital
    - Fanconi anemia
  - Drug or chemical induced, or both
    - Alcohol
    - Benzene
    - Chloramphenicol
    - Cytotoxic chemotherapy
    - Gold salts
    - Phenylbutazone
    - Others
  - Radiation exposure
  - Idiopathic
  - Infection
    - Viral, especially hepatitis
  - Immunologic
- Hematologic neoplasia
  - Leukemia (aleukemic)
  - Lymphoproliferative disorders
    - Lymphoma with marrow involvement
    - Plasma cell myeloma
    - Hairy cell leukemia
  - Myeloproliferative disorders
    - Agnogenic myeloid metaplasia with myelofibrosis
  - Myelodysplastic syndromes
- Marrow infiltration/replacement
  - Infection
    - Tuberculosis
    - Fungal
  - Gaucher and other lipid storage diseases
  - Solid tumor
  - Osteopetrosis
- Nutritional deficiencies
  - Vitamin B_{12}
  - Folate
- Other
  - Collagen vascular diseases
    - Systemic lupus erythematosus
  - Paroxysmal nocturnal hemoglobinuria
  - Hypersplenism

Bacterial sepsis
Viral infection
AIDS or HIV infection
Sarcoidosis

References

1. Guinan EC, Shimamura A. Acquired and inherited aplastic anemia syndromes, p. 1397. See Bibliography, 1.
2. Dessypris EN, Lipton JM. Red cell aplasia, p. 1421. See Bibliography, 1.
3. Segal GB, Lichtman MA. Aplastic anemia, p. 419. See Bibliography, 2.

6-M. Lymphadenopathy

Benign

Infection
- Bacterial (any)
  - Mycobacterial
  - *Bartonella* (cat scratch disease)
- Fungal (e.g., histoplasmosis)
- Viral (e.g., infectious mononucleosis)
- Protozoal (e.g., toxoplasmosis)
- Rickettsial (e.g., scrub typhus)
- Chlamydial (e.g., lymphogranuloma venereum)

Local inflammation
- Trauma
- Dermatitis

Hypersensitivity reaction
- Serum sickness
- Drug reaction, especially:
  - Allopurinol
  - Carbamazepine
  - Gold salts
  - Hydralazine
  - Phenytoin
  - Primidone

Collagen-vascular disorders
- Systemic lupus erythematosus
- Mixed connective tissue disease
- Rheumatoid arthritis

- Sjögren syndrome
- Dermatomyositis

Endocrine disorders
- Hyperthyroidism
- Severe hypertriglyceridemia

AIDS or HIV infection
Lipid storage diseases
Sarcoidosis
Amyloidosis
Other
- Primary biliary cirrhosis
- Mucocutaneous lymph node syndrome
- Angioimmunoblastic lymphadenopathy
- Autoimmune hemolytic anemia
- Graft-versus-host disease
- Silicone related
- Castleman disease
- Familial Mediterranean fever
- Kawasaki disease
- Dermatopathic lymphadenitis
- Kikuchi disease
- Rosai-Dorfman disease
- Vascular transformation of sinuses
- Inflammatory pseudotumor of lymph node

Malignant

Acute leukemia
Lymphoproliferative disorders
- Malignant histiocytosis
- Lymphoma
- Plasma cell myeloma
- Chronic lymphocytic leukemia
- Hairy cell leukemia
- Lymphomatoid granulomatosis

Myeloproliferative disorders
- Chronic myelogenous leukemia
- Agnogenic myeloid metaplasia

Solid tumors, metastatic

Reference

1. Cousar JB. Hematopoietic-lymphoid neoplasms: principles of diagnosis, p. 71. See Bibliography, 1.

6-N. Splenomegaly

- Infection, especially:
  - Bacterial (e.g., subacute bacterial endocarditis or septicemia)
  - Viral
    - HIV
    - Infectious mononucleosis
    - CMV
  - Rickettsial
  - Fungal (e.g., histoplasmosis)
  - Protozoal (e.g., malaria)
- Hematologic neoplasms
  - Acute leukemia
  - Lymphoproliferative disorders
    - Lymphoma
    - Chronic lymphocytic leukemia
    - Hairy cell leukemia
  - Myeloproliferative diseases
  - Myelodysplastic syndromes
- Nonhematologic neoplasm
  - Primary (e.g., angiosarcoma)
  - Secondary (especially melanoma)
- Disordered immunoregulation
  - Rheumatoid arthritis (Felty syndrome)
  - Systemic lupus erythematosus
  - Serum sickness
  - Drug reactions
  - Thyrotoxicosis
  - IL-2 therapy
- Nonmalignant hematologic disorders
  - Autoimmune hemolytic anemia, thrombocytopenia, and neutropenia
  - Congenital hemolytic anemias
    - Hemoglobinopathies
    - Hereditary spherocytosis and ovalocytosis
  - Megaloblastic anemias
  - Myelofibrosis and extramedullary hematopoiesis
  - Iron deficiency anemia
  - Angioimmunoblastic lymphadenopathy
  - Paroxysmal nocturnal hemoglobinuria
- Congestive splenomegaly
  - Portal hypertension of any cause
  - Splenic or portal vein compression, thrombosis, or aneurysm

- Congestive heart failure
- Budd-Chiari syndrome
- Cirrhosis
- Hepatic *Echinococcus*

Infiltrative disorders
- Gaucher and other lipid storage diseases
- Histiocytic disorders
- Amyloidosis

Other
- AIDS or HIV infection
- Sarcoidosis
- Splenic trauma/hemorrhage
- Splenic cysts
- Splenic abscess

Reference

1. Jandl JH. The spleen and hypersplenism, p. 407. See Bibliography, 3.

6-O. Disorders of Hemostasis

Platelet Disorders

Quantitative platelet disorders (see 6-J)

Qualitative platelet disorders
- Congenital
  - Bernard-Soulier syndrome
  - Glanzmann thrombasthenia
  - Storage pool deficiencies
  - von Willebrand disease
- Acquired
  - Uremia
  - Myeloproliferative disorders
  - Myelodysplastic syndromes
  - Dysproteinemias
  - Drug induced
    - Aspirin, clopidogrel
    - Dextran
    - Dipyridamole
    - Hydroxyethyl starch
    - Nonsteroidal anti-inflammatory drugs
    - Sulfinpyrazone
    - Others
  - Extracorporeal circulation

Coagulation Disorders

- Congenital
  - Factor deficiencies
    - VIII (hemophilia A)
    - IX (hemophilia B)
    - XI
    - V
    - VII
    - X
    - II
    - Combined deficiency of vitamin K–dependent factors
  - Fibrinogen disorders
    - Afibrinogenemia
    - Hypofibrinogenemia
    - Dysfibrinogenemia
  - von Willebrand disease
- Acquired
  - Vitamin K deficiency
    - Malabsorption syndromes
    - Broad-spectrum antibiotic therapy
    - Cholestatic jaundice
    - Dietary deficiency
    - Hemorrhagic disease of the newborn
    - Oral anticoagulant use/abuse (warfarin)
  - Factor X deficiency and amyloidosis
  - Circulating anticoagulants
    - Factor VIII
      - Associated with hemophilia A
      - Autoimmune disorders
      - Lymphoproliferative disorders/dysproteinemias
      - Pregnancy
      - Drug therapy
        - Penicillin
    - Factor IX and others
    - Lupus anticoagulant
      - With factor II deficiency
  - Consumptive coagulopathies
    - DIC
  - Liver disease
  - Liver transplantation
  - Acquired dysfibrinogenemia

Fibrinolytic states
Heparin administration
Massive blood transfusion

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2. Abram CS, Shattil SJ, Bennett JS. Acquired qualitative platelet disorders, p. 1833. See Bibliography, 2.
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7. See Bibliography, 4.

6-P. Hypercoagulable States

Congenital

Antithrombin III deficiency
Protein C deficiency
Protein S deficiency
Homocystinuria
Dysfibrinogenemias
Hyperlipidemia
Prothrombin mutation 20010
Antiphospholipid antibody syndrome

Acquired

Oral contraceptive and other estrogen use
Lupus anticoagulant
Venous stasis of any cause
Trauma
Stroke
Obesity

- Postsurgical, especially:
  - Orthopaedic
  - Urologic
  - Abdominal gynecologic cancer
- Myeloproliferative disorders
  - Essential thrombocythemia
  - Polycythemia vera
- Paroxysmal nocturnal hemoglobinuria
- Heparin-associated thrombocytopenia
- Prothrombin complex concentrate infusion
- Nephrotic syndrome
- Antiphospholipid antibody syndrome
- Pregnancy
- DIC
- TTP
- Malignancy (with DIC) (Trousseau syndrome)
- Sickle cell anemia
- Hyperviscosity syndromes
- Previous venous thrombosis or insufficiency
- Venous trauma, including intravascular devices

References

1. Griffin JH. Control of coagulation reactions, p. 1695. See Bibliography, 2.
2. Schafer AI. The hypercoagulable states. *Ann Intern Med.* 1985;102:814–828.

6-Q. Disorders of Immunoglobulin Synthesis

Hypogammaglobulinemia

- Congenital
  - X-linked agammaglobulinemia
  - Selective immunoglobulin A deficiency
  - Severe combined immunodeficiency
- Acquired
  - Common variable immunodeficiency
  - Lymphoproliferative disorders
    - Plasma cell myeloma
    - Lymphoma
    - Chronic lymphocytic leukemia
  - Radiation therapy
  - Antineoplastic chemotherapy
  - Associated with thymoma

Hypergammaglobulinemia

Polyclonal
- Chronic inflammatory disease
  - Chronic infections
  - Collagen-vascular disorders
  - Malignancy
  - Hepatic cirrhosis
  - Chronic active hepatitis
  - AIDS or HIV infection
  - Inflammatory bowel disease
  - Sarcoidosis
  - Others
- Angioimmunoblastic lymphadenopathy

Monoclonal
- Lymphoproliferative malignancies
  - Plasma cell myeloma
  - NHL
  - Chronic lymphocytic leukemia
  - Macroglobulinemia
  - Heavy-chain diseases
- Amyloidosis
- Monoclonal gammopathy of undetermined significance

References

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2. Lichtman MA, et al., eds. *Williams Hematology*. 7th ed. New York: McGraw-Hill; 2006.
3. Jandl JH, ed. *Blood: Textbook of Hematology*. Boston: Little, Brown and Company; 1987.
4. Hoffman R, et al., eds. *Hematology. Basic Principles and Practice*. 4th ed. Philadelphia: Elsevier; 2005.

7

INFECTIOUS DISEASE

7-A. Fever of Unknown Origin in the United States[1]

Infection

Bacterial

- Bacterial endocarditis
- Sinusitis
- Osteomyelitis
- Intravascular catheter infections
- Bronchiectasis
- Relapsing mastoiditis
- Dental abscess
- *Bartonella* (cat scratch disease)
- Upper abdominal sources
  - Cholangitis
  - Cholecystitis
  - Empyema of the gallbladder
  - Subphrenic, pancreatic, hepatic, and splenic abscesses
- Lower abdominal sources
  - Appendicitis
  - Appendiceal abscess
  - Diverticulitis
  - Pelvic inflammatory disease or abscess
  - Perirectal abscess
  - Peritonitis

- Mesenteric lymphadenitis
- Septic pelvic thrombophlebitis

Genitourinary sources
- Perinephric, intrarenal abscess
- Prostatic abscess
- Pyelonephritis
- Tubo-ovarian abscess
- Suppurative thrombophlebitis
- Ureteral obstruction
- Renal tuberculosis

Acute rheumatic fever

Bacteremia without primary focus, especially:
- Meningococcemia
- Gonococcemia
- Salmonellosis
- Listeriosis
- Brucellosis
- Ehrlichiosis
- Borreliosis
- Yersiniosis
- Tularemia
- Leptospirosis
- Nocardiosis
- Actinomycosis

Tuberculosis (TB), especially *Mycobacterium tuberculosis* (extrapulmonary, miliary, renal, TB meningitis), *Mycobacterium avium* complex, *Mycobacterium kansasii*

Viral, especially Epstein-Barr virus (EBV) (infectious mononucleosis), hepatitis, Coxsackie B, cytomegalovirus (CMV), human immunodeficiency virus (HIV), parvovirus B19, dengue, human herpes virus 6 (HHV6)

Chlamydial, *Rickettsia* (especially Q fever, psittacosis), *Anaplasma*, *Ehrlichia*, Rocky Mountain spotted fever

Parasitic, protozoan, especially:
- Amebiasis
- Malaria
- Trichinosis
- Toxoplasmosis
- *Pneumocystis carinii* (*jiroveci*)

- Babesiosis
- Chagas disease
- *Strongyloides*

Fungal, especially:

- Candidiasis
- Aspergillus
- Histoplasmosis
- Blastomycosis
- Cryptococcosis
- Coccidiomycosis
- Sporotrichosis
- Mucormycosis

Malignancy

Leukemia, lymphoma, especially Hodgkin disease

Solid tumor, especially carcinoma of:

- Kidney (especially hypernephroma)
- Lung
- Pancreas
- Liver (especially hepatoma)
- Colon

Metastatic carcinoma (especially to liver, central nervous system)

Carcinomatosis

Myelodysplastic syndrome

Atrial myxoma

Collagen-Vascular Disease

Systemic lupus erythematosus (SLE)

Rheumatoid arthritis

Rheumatic fever

Adult Still disease

Polyarteritis nodosa, hypersensitivity vasculitis

Wegener granulomatosis

Temporal arteritis

Cryoglobulinemia

Churg-Strauss vasculitis

Takayasu arteritis

Familial Mediterranean fever

Pseudogout

Behçet disease

Drugs

Antibiotics, especially:
- Penicillins
- Cephalosporins
- Sulfonamides
- Amphotericin B
- Quinolones
- TB therapy, especially isoniazid (INH)

Allopurinol
Phenytoin
Barbiturates
Procainamide
Quinidine
Nonsteroidal anti-inflammatory therapy
Antineoplastic therapy
Interferon
H_2 blockers
Methyldopa

Other

Pulmonary emboli, multiple
Thrombophlebitis
Sarcoidosis
Hepatitis (alcoholic or granulomatous)
Inflammatory bowel disease
Whipple disease
Thyroiditis
Pheochromocytoma
Thyrotoxicosis
Myelofibrosis
Serum sickness
Hemolytic states
Trauma with hematoma in closed spaces (especially perisplenic, perihepatic, perivesicular)
Dissecting aneurysm
Periodic fever (especially familial Mediterranean fever)
Sarcoidosis
Gout
Addison disease
Adrenal insufficiency
Weber-Christian disease
Cyclic neutropenia
Cat scratch fever

Kikuchi disease
Postpericardiotomy syndrome
Factitious fever
Habitual hyperthermia

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[1]Defined as temperature of >38.3°C daily for 2 to 3 weeks, with cause undiagnosed despite 1 week of intensive studies in hospital.

7-B. Most Common Organisms Causing Specific Infections

Infection	Organisms
Skin and soft tissue	
Cellulitis	
Orbital	*Streptococcus pneumoniae* [including penicillin-resistant *S. pneumoniae* (PRSP)], *Haemophilus influenzae*, group A streptococci (macrolide/erythromycin resistance reported), *Moraxella catarrhalis*, *Staphylococcus aureus* [including methicillin-resistant *S. aureus* (MRSA)]
Nondiabetic—extremities	Group A > B, C, G streptococci, *S. aureus* (including MRSA)
Diabetic—extremities	Streptococci (groups A, C, G), *S. aureus*, *Escherichia coli*, *Proteus* spp., *Klebsiella* spp., *Enterobacter* spp., *Pseudomonas aeruginosa*, *Enterococcus* spp., *Clostridia* spp.
Necrotizing fasciitis	Streptococci (groups A, C, G), *Clostridia* spp. + Enterobacteriaceae, MRSA
Burns	*S. aureus* (including MRSA), streptococci, *Enterobacter* spp., *Staphylococcus epidermidis*, *P. aeruginosa*, fungi, herpes simplex virus (HSV)
Wounds	
Traumatic	Polymicrobial: *S. aureus* (including MRSA), group A and anaerobic streptococci, Enterobacteriaceae, *Clostridium perfringens*, *Clostridium tetani*
Water exposure	*P. aeruginosa*, *Aeromonas* spp.
Salt water exposure	*Vibrio vulnificus*, *Vibrio damsela*

Postoperative	
Nongenitourinary, nongynecologic, nongastrointestinal	*S. aureus* (including MRSA), *S. epidermidis*, group A streptococci, Enterobacteriaceae
Genitourinary, gynecologic, gastrointestinal	*S. aureus* (including MRSA), *S. epidermidis*, group A, B, C streptococci, Enterobacteriaceae, *Enterococcus* spp. [including vancomycin-resistant *Enterococcus* (VRE)], *Bacteroides* spp., *Clostridium* spp.
Decubiti	
Polymicrobial	Streptococci (anaerobic and groups A, C, G), *Enterococcus* spp. (including VRE), *S. aureus* (including MRSA), Enterobacteriaceae, *Pseudomonas* spp., *Bacteroides* spp.
Bites—dog	*Streptococcus viridans*, *Pasteurella multocida*, *S. aureus* (including MRSA), *Eikenella corrodens*, *Bacteroides* spp., *Fusobacterium* spp., eugonic fermenter-4 (EF-4), *S. epidermidis*, *Capnocytophagia* spp., dysgonic fermenter-2 (DF-2)
Bites—cat	*P. multocida*, *S. aureus*, *Bartonella henselae* (cat scratch disease), *B. henselae* and *Bartonella quintana* both (bacillary angiomatosis, peliosis hepatitis), *B. quintana* only (trench fever)
Bites—human	*S. viridans*, *S. epidermidis*, *S. aureus*, *E. corrodens*, *Peptostreptococcus* spp., *Bacteroides* spp., *Haemophilus parainfluenzae*, *Peptococcus* spp., *Fusobacterium* spp., *Corynebacterium* spp.

(continued)

7-B. Most Common Organisms Causing Specific Infections (continued)

Infection	Organisms
Bites—tick	*Borrelia burgdorferi* (Lyme disease), *Ehrlichia chaffeensis* (human monocytic ehrlichiosis), *Anaplasma* (*Ehrlichia*) phagocytophilia (human granulocytic ehrlichiosis), *Rickettsia rickettsii* (Rocky Mountain spotted fever), *Babesia microti* (babesiosis), *Borrelia recurrentis* (relapsing fever), *Rickettsia conorii* (spotted fever, especially boutonneuse fever), *Francisella* tularemia (rare)
Respiratory Infections	
Sinusitis	
Acute	*S. pneumoniae* (including PRSP), *H. influenzae*, *M. catarrhalis*, group A streptococci, *S. aureus* (including MRSA), mixed anaerobes, viruses
Chronic	Acute plus *Bacteroides* spp., *Prevotella*, *Peptostreptococcus*, *Fusobacterium*, *P. aeruginosa*
Diabetic	Acute plus *P. aeruginosa*, *Rhizopus* spp. (Mucoraceae), *Aspergillus* sp.
Neutropenic	Acute plus *Aspergillus* spp. (especially *fumigatus*)
Pharyngitis	
Acute	Streptococci (groups A, C, G), viruses (especially Coxsackievirus, EBV, enterocytophatogenic human orphan virus, enterovirus, HSV I–II, HIV, HHV6), *Corynebacterium diphtheriae*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Candida albicans*, *Chlamydia pneumoniae*
Neutropenic	Acute pharyngitis, especially *C. albicans*, HSV I–II, CMV

Bronchitis	
Acute	Viral, *M. pneumoniae*, *C. pneumoniae*, *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, *Bordetella pertussis*
Lung abscess	*Bacteroides* spp., *Fusobacterium* spp., *Peptostreptococcus* spp., *Prevotella* spp., microaerophilic streptococci, *S. viridans*
Aspiration pneumonia	*Streptococcus* spp., *Bacteroides* spp., *Fusobacterium* spp., *Peptostreptococcus* spp., *M. catarrhalis*, *E. corrodens*, *Nocardia* spp.
Health care–acquired aspiration pneumonia	Aspiration pneumonia, plus *S. aureus* (including MRSA), Enterobacteriaceae, *Candida* spp., *Legionella* spp., *Stenotrophomonas* spp.
Pneumonia	
Community-acquired pneumonia (CAP) without coexistent disease, <60 years	*S. pneumoniae* (including PRSP), *M. pneumoniae*, respiratory viruses, especially influenzae, parainfluenzae, adenovirus, respiratory syncytial virus (RSV), *H. influenzae*, *Legionella* spp., *C. pneumoniae*, *Chlamydia psittaci*
Postinfluenza pneumonia	*S. pneumoniae*, *H. influenzae*, *S. aureus* (including MRSA) (rare)
CAP with coexistent disease, >60 years[a]	*S. pneumoniae*, *M. pneumoniae*, respiratory viruses, especially influenzae, *H. influenzae*, *C. pneumoniae*, *Legionella* spp., *Klebsiella pneumoniae*, *M. catarrhalis*, anaerobic bacteria if aspiration (see Aspiration pneumonia), *M. tuberculosis*, fungi
Important exposure history for CAP	*Actinomyces israelii* (especially in aspiration of poor dentition) *S. pneumoniae* (including PRSP), *H. influenzae*, *M. catarrhalis*: chronic obstructive pulmonary disease

(continued)

7-B. Most Common Organisms Causing Specific Infections (continued)

Infection	Organisms
	S. pneumoniae (including PRSP), anaerobes, *K. pneumoniae*: alcohol use/abuse
	S. aureus (including MRSA) 2/2 hematogenous spread: intravenous drug users
	P. aeruginosa, *H. influenzae*, *S. pneumoniae* (including PRSP), *Aspergillus*, *M. avium* complex: bronchiectasis
	Coxiella burnetii: Q fever (livestock exposure or unpasteurized milk exposure)
	Brucella spp.: cattle, swine, goat exposure
	Francisella tularensis: rabbit, tick, and deerfly exposure
	Pseudomonas pseudomallei: melioidosis (Southeast Asia travel, exposure)
	Salmonella spp.: raw, undercooked eggs, poultry, raw cookie batter, melon, tomatoes
	Coccidioides immitis: inhalation of spores in Southwest United States
	Histoplasma capsulatum: inhalation of organisms from bird droppings (bats, chickens, starlings)
	Blastomyces dermatitidis: inhalation of organisms from contaminated soil
	Yersinia pestis: rat flea, infected close human contact exposure
	Legionella spp.: inhalation of organisms from contaminated water supply systems, contaminated soil
	M. pneumoniae: high incidence in closed populations (i.e., boarding schools, college dormitories, military recruit camps)

Health care–acquired pneumonia (with or without mechanical ventilation)	Aerobic gram-negative bacilli [*Enterobacter aerogenes*, cloacae, *P. aeruginosa*, *Burkholderia cepacia*, *S. pneumoniae* (including PRSP), *K. pneumoniae*, *Klebsiella oxytoca*, *Acinetobacter calcoaceticus* var. anitratum or lwoffi, *S. aureus* (including MRSA), *Legionella* spp.]
Neutropenia and health care–acquired pneumonia (with or without mechanical ventilation)	See Health care–acquired pneumonia, plus fungi [*C. albicans*, *Aspergillus* spp. (especially *fumigatus*, *flavus*)]
Pneumonia	
Immunocompromised host	*S. pneumoniae*, *S. aureus* (including MRSA), aerobic gram-negative bacilli, *Legionella* spp., *Nocardia* spp. (especially with steroid use, malignancy, lymphoma, HIV), *Cryptococcus neoformans* (inhalation of organisms from pigeon droppings in soil, HIV, malignancy, diabetes mellitus, steroid use, chemotherapy), *Aspergillus* spp. (inhalation of organisms from soil or air, malignancy, especially neutropenia, steroid use, posttransplant, chemotherapy), phycomycetes: leukemia and lymphoma, *Toxoplasma gondii* [ingestion of raw or rare meat, cat feces containing cysts of *T. gondii* (e.g., litter or sandbox exposure)] Viruses [especially influenza, HSV, CMV, varicella-zoster virus (VZV), adenovirus, *M. tuberculosis*] Fungi (especially *Candida* spp., *Aspergillus* spp.)

(continued)

7-B. Most Common Organisms Causing Specific Infections (continued)

Infection	Organisms
Pneumonia with associated bioterrorism exposure Potential organisms/manifestations	*Bacillus anthracis* (anthrax) *F. tularensis* (tularemia) *Clostridium botulinum* (botulism) *Y. pestis* (plague) Hemorrhagic fever viruses (Ebola/Marburg) Variola major virus (smallpox) Hantavirus Pandemic influenza Severe acute respiratory syndrome (SARS): *Coronavirus*
HIV infection	See HIV, Pulmonary section (7-F)
Meningitis	*S. pneumoniae* (including PRSP), *Neisseria meningitidis*, enterovirus, *H. influenzae* (rare), EBV, HIV, HSV II, VZV, CMV, mumps, West Nile virus, Eastern equine, Western equine, St. Louis virus, California virus, rabies virus, lymphocytic choriomeningitis, *B. burgdorferi*, *Ehrlichia* spp.
Young, elderly, and immunocompromised	*S. pneumoniae* (including PRSP), *Listeria monocytogenes*, gram-negative bacilli, *C. neoformans*, *H. influenzae* (rare since *H. influenzae* type b vaccine), leptospirosis, cerebral malaria, trichinosis, rickettsiae, mycobacteria, amebiasis, *Mycoplasma*, *Treponema pallidum* (syphilis)

Brain abscess	*S. pneumoniae* (including PRSP), streptococci, *Bacteroides* spp., Enterobacteriaceae, *Propionibacterium acnes*, *S. aureus* (including MRSA), *Nocardia* spp., *L. monocytogenes*
Otitis media	*S. pneumoniae* (including PRSP), *H. influenzae*, *M. catarrhalis*, group A streptococci, *S. aureus*, viruses, gram-negative bacilli
Mastoiditis	*S. pneumoniae* (including PRSP), group A streptococci, *S. aureus* (including MRSA), *H. influenzae*, *P. aeruginosa*, anaerobes
Conjunctivitis	Viral (adenovirus 8 and 19), *S. aureus* (including MRSA), *S. pneumoniae*, *H. influenzae*, *N. gonorrhoeae*, *Chlamydia trachomatis*
Keratitis	*S. aureus* (including MRSA), *S. epidermidis*, *S. pneumoniae*, group A streptococci, gram-negative bacilli, *P. aeruginosa*, *Acanthamoeba* (contact lens users), *L. monocytogenes* (especially in diabetic patients), *Hartmannella* (soft contact lens users)
Vaginitis	*Candida* spp. (*C. albicans* >> *Candida glabrata*, *Candida tropicalis*), *Trichomonas vaginalis*, polymicrobial (especially *Gardnerella vaginalis*, *Prevotella* spp.), *Mobiluncus*, *Mycoplasma hominis*
Cervicitis, nonspecific urethritis	*N. gonorrhoeae*,[b] *C. trachomatis*, *M. hominis*, *Ureaplasma*, HSV, *Mycoplasma genitalium*
Pelvic inflammatory disease	*N. gonorrhoeae*,[b] *C. trachomatis*, *Bacteroides* spp., gram-negative bacilli, streptococci
Other urogenital sexually transmitted diseases	*T. pallidum* (syphilis), human papillomavirus (HPV) 6, 11, 16, 18 (anogenital warts), *Haemophilus ducreyi* (chancroid), *C. trachomatis* (lymphogranuloma venereum), *Calymmatobacterium granulomatis* (granuloma inguinale), HSV type II (genital herpes), *Candida* spp., group B streptococci, *Gardnerella* (balanitis), *N. gonorrhoeae*, *C. trachomatis* (proctitis)

(continued)

7-B. Most Common Organisms Causing Specific Infections (continued)

Infection	Organisms
Prostatitis	*N. gonorrhoeae*, *C. trachomatis*, gram-negative bacilli, *P. aeruginosa* (usually chronic in males >35 years of age), *Enterococcus* (including VRE), *M. Tuberculosis*, mycoplasmas, ureaplasmas
Urinary tract infection	
Cystitis	Enterobacteriaceae [especially *E. coli*, *Enterococcus* (including VRE), *Staphylococcus saprophyticus*, *C. trachomatis*]
Pyelonephritis	Enterobacteriaceae [especially *E. coli*, *Klebsiella* spp., *Enterococcus* spp. (including VRE), *P. aeruginosa*, *Proteus mirabilis*]
Perinephric abscess	Enterobacteriaceae [especially *E. coli*, *Klebsiella* spp., *Enterococcus* spp. (including VRE), *P. aeruginosa*, *P. mirabilis*, *S. aureus* (including MRSA), 2/2 hematogenous spread]
Sepsis, septic shock	
Nonimmunocompromised host	*S. viridans*, *S. pneumoniae* (including PRSP), group B streptococci, *S. aureus* (including MRSA), *S. epidermidis*, *E. coli*, *Enterococcus* spp. (including VRE), *Klebsiella* spp., *Proteus* spp., *P. aeruginosa*, anaerobes, *H. influenzae*, *N. meningitidis*
Health care acquired	Enterobacteriaceae, *Enterococcus* spp. (including VRE), *S. aureus* (including MRSA), *S. epidermidis*, *Candida* spp., anaerobes

Immunocompromised host, neutropenia	Enterobacteriaceae (especially *P. aeruginosa*, *E. coli*, *Klebsiella* spp.), *S. pneumoniae* (including PRSP), *S. viridans*, coagulase-negative *Staphylococcus*, *S. aureus* (including MRSA), *C. albicans*, *Aspergillus* spp., VRE, *L. monocytogenes*, anaerobes, *Fusobacterium* spp. (see 7-C)
Postsplenectomy	*S. pneumoniae* (including PRSP), *H. influenzae*, *N. meningitidis*, *B. microti*, *Capnocytophaga* (DF-2)
Intravenous line infections, sepsis	Coagulase-negative *Staphylococcus*, *S. aureus* (including MRSA), *Candida* spp., *Pseudomonas* spp., *Acinetobacter* spp., *Enterobacter* spp.
In immunocompromised hosts	Coagulase-negative *Staphylococcus*, *S. aureus* (including MRSA), *Candida* spp., *Pseudomonas* spp., *Acinetobacter* spp., *Corynebacterium jeikeium* (JK), *Aspergillus* spp., *Enterococcus* spp. (including VRE)
HIV	See 12-A
Toxic shock syndrome	*S. aureus* (toxin mediated), beta streptococci groups A, B, C, G, *Clostridium sordelli*
Gastroenteritis	Enteric viruses (especially rotaviruses, Norwalk virus), *Shigella* spp., *Salmonella* spp., *C. jejuni*, *E. coli* 0157:H7, *Clostridium difficile*, *Entamoeba histolytica*, *Vibrio cholerae*, *Yersinia enterocolitica*, *L. monocytogenes*, *Vibrio parahaemolyticus*, *Giardia lamblia*, *Cyclospora* spp., *S. aureus*, *Bacillus cereus*
HIV associated	See 12-G
Peritonitis	
Secondary to bowel perforation	*E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Enterococcus* spp. (including VRE), *S. viridans*, *Bacteroides fragilis*, *P. aeruginosa*, *Clostridium* spp., *Peptostreptococcus* spp.

(continued)

7-B. Most Common Organisms Causing Specific Infections (continued)

Infection	Organisms
Spontaneous bacterial peritonitis	*S. pneumoniae* (including PRSP), Enterobacteriaceae (especially *E. coli*), *K. pneumoniae* [extended spectrum beta-lactamase producers (ESBL)], *Enterococcus* spp. (including VRE), group A streptococci, anaerobes
Intra-abdominal abscess	*E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Enterococcus* spp. (including VRE), streptococci, *Bacteroides* spp., *S. aureus* (including MRSA), *Clostridium* spp., *Peptostreptococcus* spp., *Peptococcus* spp.
Diverticulitis	Enterobacteriaceae (especially *E. coli*, *Klebsiella* spp., *Proteus* spp.), enterococci, *B. fragilis*, *Peptostreptococcus* spp., *Clostridium* spp.
Complicated appendicitis	*E. coli*, *P. aeruginosa*, *Bacteroides* spp., *Peptostreptococcus* spp., *Peptococcus* spp., alpha-hemolytic streptococci, *Enterococcus* spp. (including VRE)
Acute cholecystitis	*E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Enterococcus* spp. (including VRE), *Bacteroides* spp., *Fusobacterium* spp., *Clostridium* spp.
Cholangitis	*E. coli*, *Klebsiella* spp., *Enterococcus* spp. (including VRE), *Bacteroides* spp., *Clostridium* spp.
Arthritis	
Acute monoarticular	*N. gonorrhoeae*,[b] *S. aureus* (including MRSA), *S. pneumoniae* (including PRSP), *B. burgdorferi*
Acute polyarticular	*N. gonorrhoeae*,[b] *S. aureus* (including MRSA), *B. burgdorferi*, *N. meningitidis*, arthritis secondary to syphilis, parvovirus B19, rubella virus, EBV, HIV, hepatitis B
Chronic	*Mycobacteria* spp., fungi, *Nocardia* spp., *Brucella* spp.

Endocarditis	
Native valve	*S. viridans*, *S. aureus* (including MRSA), *Enterococcus* spp. (including VRE), *Streptococcus bovis*, *S. epidermidis*, HACEK (*H. parainfluenzae*, *Haemophilus aphrophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, *Kingella*), fungi, *C. psittaci*, *C. burnetii*, *Brucella* spp., *Bartonella* spp. (*henselae/quintana*)
Early prosthetic valve (<2 months postoperative)	*S. epidermidis*, *S. aureus* (including MRSA), streptococci, Enterobacteriaceae, diphtheroids, fungi
Late prosthetic valve (>2 months postoperative)	*S. epidermidis*, *S. viridans*, *S. aureus* (including MRSA), *S. bovis*, Enterobacteriaceae, *Enterococcus* spp. (including VRE), diphtheroids, fungi (*Candida* spp., *Aspergillus* spp.), *P. acnes*
Osteomyelitis	
Acute	*S. aureus* (including MRSA), *S. epidermidis*, group A and B streptococci, *E. coli*, *Salmonella* spp. (usually with history of sickle cell disease, thalassemia, after iron chelation therapy), *Klebsiella* spp., *Pseudomonas* spp., *S. Pneumoniae* (including PRSP), *M. tuberculosis*
Chronic	*S. aureus* (including MRSA), *Klebsiella* spp., *P. aeruginosa*, *Enterobacter* spp.

[b]Coexisting disease: diabetes mellitus, ethanol use, chronic obstructive pulmonary disease, congenital hepatic fibrosis, cigarette use, malnutrition, chronic renal failure, liver disease, postsplenectomy.
[b]Note increased resistance of *N. gonorrhoeae* to fluoroquinolones.

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7-C. Infections in the Immunocompromised Host

Immune System Abnormalities	Infections, Organisms
Neutropenia	*E. coli*, *P. aeruginosa*, *S. aureus* (including MRSA), *S. epidermis*, *K. pneumoniae*, *Enterococcus faecalis*, *Enterococcus faecium* (including VRE), *Enterobacter cloacae*, *E. aerogenes*, *Proteus* spp., *Serratia marcescens*, *C. jeikeium* (JK), *Bacillus* spp., *Bacteroides* spp., *Capnocytophaga* spp., *Clostridium* spp., *Aeromonas* spp., *Streptococcus* spp., *Legionella* spp., *Leuconostoc* spp., *Rhodococcus equi*, *Candida* spp., *Aspergillus* spp., *Fusarium*, zygomycetes (*Mucor*, *Rhizopus*), *Pseudallescheria boydii*, *B. henselae*, HSV, CMV, influenzae, RSV, *Trichosporon* spp., *Leptotrichia buccalis*, *Stomatococcus mucilaginosus*
Cell-mediated deficiency (see 12-A)	
HIV, AIDS, lymphoma, SLE, congenital immunodeficiencies, drugs (corticosteroids, acyclosporine, zathioprine, cyclophosphamide)	*Salmonella* spp., *L. monocytogenes*, *Legionella* spp., *Nocardia* spp. *(asteroides/brasiliensis)*, *Bacillus* spp., *Candida* spp., *C. neoformans*, *T. gondii*, *Cryptosporidium*, HSV, VZV, CMV, EBV, *M. tuberculosis*, *M. avium* complex, *Pneumocystis jiroveci (carinii)*, *Pseudomonas* spp., *Aspergillus* spp., *Strongyloides stercoralis*, *G. lamblia*, *E. histolytica*, *H. capsulatum*

(continued)

7-C. Infections in the Immunocompromised Host (continued)

Immune System Abnormalities	Infections, Organisms
Defective chemotaxis	
Diabetes mellitus, Hodgkin disease, alcoholism, corticosteroid use, renal failure, SLE, Job syndrome, trauma, lazy leukocyte syndrome	Especially *Staphylococcus* spp. (including MRSA), *Streptococcus* spp., *Candida* spp. (*albicans/parapsilosis*)
Defective neutrophil killing	
Chronic granulomatous disease, myeloperoxidase deficiency, Chédiak-Higashi syndrome	Especially *S. aureus* (including MRSA), *E. coli*, *C. albicans*
B-lymphocyte defects	
Multiple myeloma, chronic lymphatic leukemia, burns, enteropathies, acquired and congenital agammaglobulinemia	*S. pneumoniae* (including PRSP), *H. influenzae*, *N. meningitidis*, *N. gonorrhoeae*, *Salmonella* spp., *Campylobacter* spp.
Posttransplant infections	
Bone marrow transplant	Coagulase-negative *Staphylococcus*, *S. viridans*, *S. aureus* (including MRSA), *Corynebacterium* spp., *E. coli*, *Klebsiella* spp. (including ESBL organisms), *Enterobacter* spp., *P. aeruginosa*, *S. pneumoniae*, *H. influenzae*, *Candida* spp., *Aspergillus* spp., *Trichosporon*, *Fusarium*, *Rhizopus*, HSV, CMV, EBV, VZV, *P. carinii*, *T. gondii*

Renal transplant	*S. aureus* (including MRSA), *E. coli*, *P. aeruginosa*, *Candida* spp., *C. neoformans*, *L. monocytogenes*, *Salmonella* spp., *Legionella* spp., *Nocardia* spp., HSV, VZV, CMV, *M. tuberculosis*, hepatitis B and C, *R. equi*, human parvovirus B19
Liver transplant	*S. aureus* (including MRSA), *E. faecalis*, *E. faecium* (including VRE), *Candida* spp., CMV, *Aspergillus* spp., *E. coli*, *Enterobacter* spp., *Klebsiella* spp. (including ESBL organisms), *C. neoformans*, hepatitis B and C, polymicrobial cholangitis and peritonitis
Heart, heart-lung transplant	*S. aureus* (including MRSA), *S. epidermidis*, *E. coli*, *Klebsiella* spp. (including ESBL organisms), *P. aeruginosa*, *N. asteroides*, *Aspergillus* spp., CMV, HSV, *P. carinii*, *C. neoformans*, *T. gondii*
Central nervous system	Especially *N. asteroides*, *L. monocytogenes*, *T. gondii*, *C. neoformans*, *Candida* spp., infections posttransplant zygomycetes (*Mucor*), *A. fumigatus*, VZV, John Cunningham virus (JCV)-progressive multifocal leukoencephalopathy (see Meningitis, Brain abscess, 7-B)

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7-D. Antimicrobial Drugs of Choice

Organism	Drugs
Gram-Positive Cocci	
Staphylococcus aureus (methicillin sensitive)	Oxacillin, nafcillin, cefazolin, clindamycin, vancomycin, trimethoprim and sulfamethoxazole (TMP/SMX), daptomycin, linezolid, dalfopristin/quinupristin (Synercid)
S. aureus (methicillin resistant)	Vancomycin, TMP/SMX, doxycycline, minocycline, rifampin, linezolid, daptomycin, tigecycline, dalfopristin/quinupristin (Synercid) (depends on sensitivities), clindamycin (if D test negative)
Staphylococcus epidermidis (methicillin sensitive)	Cefazolin, oxacillin, ampicillin/sulbactam or clavulanate, nafcillin, TMP/SMX
Staphylococcus epidermidis (methicillin resistant)	Vancomycin, TMP/SMX, daptomycin
Staphylococcus saprophyticus	TMP/SMX, ampicillin/clavulanate, fluoroquinolones (FQs)
Streptococcus viridans, *Streptococcus bovis* [penicillin (PCN) sensitive]	Penicillin G (PCN G), cefazolin and aminoglycoside, ceftriaxone, vancomycin (PCN allergy)
S. viridans, *S. bovis* (intermediate PCN sensitive)	PCN G and gentamicin

(continued)

7-D. Antimicrobial Drugs of Choice (continued)

Organism	Drugs
Nutritionally variant *Streptococcus*, tolerant *Streptococcus*	Ampicillin and gentamicin, vancomycin and gentamicin, cefazolin
S. viridans, *S. bovis* (PCN resistant)	PCN G and gentamicin
Enterococcus spp. (PCN or ampicillin sensitive, or both)	Ampicillin and gentamicin
Enterococcus spp. (PCN resistant)	Vancomycin and gentamicin
Enterococcus spp. (VRE)	
Usually *Enterococcus faecium*	High-dose PCN G or ampicillin, linezolid, dalfopristin/quinupristin (Synercid), doxycycline (depends on sensitivities)
Streptococcus pneumoniae (PCN sensitive)	PCN G, ampicillin, cefazolin, cefuroxime, cefotaxime, ceftriaxone, erythromycin, clarithromycin, azithromycin, vancomycin
S. pneumoniae (intermediate PCN sensitive)	Ceftriaxone, cefotaxime, high-dose PCN G, ampicillin, imipenem, vancomycin
S. pneumoniae (PCN resistant; PRSP)	Vancomycin and rifampin, high-dose cefotaxime, ceftriaxone (if not meningeal infection), imipenem, meropenem, ertapenem, FQ (moxifloxacin/gatifloxacin/levofloxacin)
Streptococcus pyogenes (groups A, B, C, F, G)	PCN G, ampicillin, cefazolin [vancomycin or dalfopristin/quinupristin (Synercid) if + PCN allergy]

Gram-Positive Bacilli	
Corynebacterium diphtheriae	Erythromycin, clindamycin, PCN G
Corynebacterium (JK strain)	Vancomycin, PCN G and gentamicin, FQ, erythromycin
Nocardia spp.	TMP/SMX, sulfonamides, amikacin and ceftriaxone
Bacillus anthracis	PCN G, FQ, erythromycin, doxycycline
Bacillus spp.	Vancomycin, clindamycin, imipenem, FQ
Lactobacillus spp.	PCN G or ampicillin and gentamicin, clindamycin, erythromycin
Leuconostoc spp.	PCN G, ampicillin, clindamycin, erythromycin, minocycline
Listeria monocytogenes	Ampicillin or PCN G and gentamicin (TMP/SMX if + PCN allergy)
Gram-Negative Cocci	
Neisseria gonorrhoeae	Ceftriaxone, Cefixime, Cefpodoxime, FQ, TMP/SMX, azithromycin (note increased FQ resistance)
Neisseria meningitides	PCN G, ceftriaxone, cefotaxime, chloramphenicol, TMP/SMX
Moraxella (*Branhamella*) *catarrhalis*	Ampicillin (β-lactamase–negative only), TMP/SMX, cefuroxime, ampicillin-clavulanate, ampicillin-sulbactam, ceftriaxone, cefotaxime, clarithromycin, azithromycin
Gram-Negative Bacilli	
Campylobacter jejuni	FQ, azithromycin, doxycycline, erythromycin, clarithromycin (note increased resistance to FQs)

(continued)

7-D. Antimicrobial Drugs of Choice (continued)

Organism	Drugs
Haemophilus influenzae	Amoxicillin-clavulanate, ampicillin-sulbactam, cefuroxime, TMP/SMX, cefotaxime, ceftriaxone, azithromycin, clarithromycin, chloramphenicol
Haemophilus ducreyi	Ceftriaxone, azithromycin, FQ, erythromycin, amoxicillin-clavulanate
Escherichia coli	Ampicillin, TMP/SMX, cefazolin, cefotetan, cefoxitin, ampicillin-clavulanate, ampicillin-sulbactam, FQ, ceftriaxone, cefotaxime, mezlocillin, ticarcillin-clavulanate, piperacillin-tazobactam, gentamicin, tobramycin, imipenem, meropenem, aztreonam
Klebsiella pneumoniae	Cefazolin, cefuroxime, cefotetan, cefoxitin, cefepime, aztreonam, tigecycline (esp. ESBL-producing organisms)
Klebsiella oxytoca	TMP/SMX, FQ, cefotaxime, ceftriaxone, aztreonam, amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, mezlocillin, imipenem
Enterobacter aerogenes	TMP/SMX, FQ, cefotaxime, cefepime, meropenem, ertapenem
Enterobacter cloacae	Ceftriaxone, ticarcillin-clavulanate, mezlocillin, piperacillin-tazobactam, aztreonam, meropenem, ertapenem, imipenem, gentamicin, tobramycin, amikacin
Pseudomonas aeruginosa	Ceftazidime and aminoglycosides [gentamicin or tobramycin (AG)], cefepime and AG, ticarcillin-clavulanate and AG, FQ and AG, or imipenem, meropenem and AG, or aztreonam

Burkholderia cepacia (*Pseudomonas cepacia*)	TMP/SMX, ceftazidime, ticarcillin-clavulanate, chloramphenicol (imipenem, meropenem—depends on sensitivities)
Stenotrophomonas maltophilia (*Xanthomonas maltophilia*)	TMP/SMX, ticarcillin-clavulanate, chloramphenicol
Acinetobacter calcoaceticus-baumanni complex	FQ, ceftazidime, ticarcillin-clavulanate, mezlocillin, piperacillin-tazobactam, imipenem, TMP/SMX
Proteus mirabilis	Ampicillin, cefazolin, cefotaxime, ceftriaxone, cefotetan, cefoxitin, aztreonam, TMP/SMX, FQ, AG, meropenem
Proteus vulgaris	Cefotaxime, ceftriaxone, ceftazidime, FQ, imipenem, ticarcillin-clavulanate, ampicillin-sulbactam, aztreonam, mezlocillin, piperacillin-tazobactam, AG, TMP/SMX
Serratia marcescens	Cefotaxime, ceftazidime, ceftriaxone, FQ, ticarcillin-clavulanate, imipenem, aztreonam, mezlocillin, meropenem, AG, piperacillin-tazobactam
Citrobacter diversus	FQ, imipenem, TMP/SMX, cefotaxime, ceftazidime, aztreonam, meropenem
Citrobacter freundii	FQ, imipenem, TMP/SMX, AG
Providencia rettgeri, *Providencia stuartii*	Mezlocillin, ticarcillin, cefotaxime, ceftriaxone, FQ, aztreonam, TMP/SMX, imipenem, meropenem
Morganella morganii	FQ, mezlocillin, ticarcillin, piperacillin, cefotaxime, cefotetan, cefoxitin, TMP/SMX, ceftriaxone, aztreonam, imipenem, meropenem, ceftazidime

(continued)

7-D. Antimicrobial Drugs of Choice (continued)

Organism	Drugs
Bartonella henselae, *Bartonella quintana*	Erythromycin, doxycycline, clarithromycin, azithromycin, ciprofloxacin
Salmonella typhi	FQ, ceftriaxone, chloramphenicol, TMP/SMX, ampicillin (if ampicillin sensitive)
Shigella spp.	FQ, TMP/SMX, ampicillin
Capnocytophagia canimorsus (DF-2), *Capnocytophagia ochraceum* (DF-1)	Clindamycin, PCN G, amoxicillin clavulanate, ceftriaxone, cefotaxime, FQ, imipenem, cefoxitin
Pasteurella multocida	PCN, amoxicillin-clavulanate, tetracycline, ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam, ceftriaxone, cefotaxime, ceftazidime, chloramphenicol
Eikenella corrodens	Ampicillin, PCN, tetracycline, amoxicillin-clavulanate, ampicillin-sulbactam, TMP/SMX, FQ, doxycycline
Anaerobes	
Anaerobic streptococci, *Peptostreptococcus* spp.	PCN G, ampicillin, metronidazole, clindamycin, cefoxitin, cefotetan, mezlocillin, ticarcillin-clavulanate, imipenem
Bacteroides fragilis group	Metronidazole, clindamycin, ampicillin-sulbactam, cefoxitin, cefotetan, ticarcillin-clavulanate, mezlocillin, piperacillin-tazobactam, imipenem, chloramphenicol

Bacteroides melaninogenicus group	Metronidazole, clindamycin, PCN G, ampicillin, cefoxitin, cefotetan, ampicillin-sulbactam, mezlocillin, imipenem, chloramphenicol, meropenem
Bacteroides bivius	Metronidazole, clindamycin, cefoxitin, cefotetan, ampicillin-sulbactam, mezlocillin, ticarcillin-clavulanate, imipenem, chloramphenicol
Clostridium perfringens	PCN G, clindamycin, chloramphenicol, imipenem, doxycycline
Clostridium tetani	Metronidazole, PCN G, doxycycline, imipenem
Clostridium difficile	Oral metronidazole (mild-mod infections)/oral vancomycin (mod-severe infections): inital or relapse Nothing by mouth (NPO): intravenous metronidazole and oral vancomycin Oral nitazoxanide Multiple relapses/prolonged infection: intermittent/pulse dose or tapering dose of oral vancomycin +/– probiotics Multiple relapses: oral vancomycin followed by rifaximin If NPO can use IV metrodinazole, rectal vancomycin enemas (can be useful in severe infection w/ oral rx)
Other Organisms	
Legionella spp.	Erythromycin and rifampin, azithromycin +/– rifampin, FQ +/– rifampin, clarithromycin +/– rifampin, TMP/SMX +/– rifampin, doxycycline
M. pneumoniae	Erythromycin, clarithromycin, azithromycin, doxycycline, FQ

(continued)

7-D. Antimicrobial Drugs of Choice (continued)

Organism	Drugs
Chlamydia pneumoniae	Doxycycline, erythromycin, FQ, azithromycin, clarithromycin
Chlamydia trachomatis	Doxycycline, azithromycin, erythromycin, FQ, chloramphenicol
Borrelia burgdorferi	Doxycycline, amoxicillin +/– probenecid, cefuroxime-axetil, clarithromycin, ceftriaxone sodium (Rocephin), PCN G, cefotaxime (therapy depends on stage)
Babesia microti	Azithromycin and atovaquone, clindamycin and quinine
Ehrlichia chaffeensis, *Ehrlichia equi*, *Ehrlichia/Anaplasma phagocytophilia*	Doxycycline, tetracycline, chloramphenicol
Rickettsia spp.	Doxycycline, tetracycline, FQ
Leptospira	PCN, ampicillin, doxycycline
Brucella spp.	Doxycycline and rifampin, doxycycline and gentamicin or streptomycin, TMP/SMX or gentamicin, or both, ciprofloxacin
Helicobacter pylori	Omeprazole or rabeprazole or esomeprazole or lansoprazole and amoxicillin and clarithromycin OR bismuth and metronidazole and tetracycline and omeprazole OR rabeprazole and amoxicillin followed by rabeprazole and clarithromycin and tinidazole and omeprazole and clarithromycin or amoxicillin and omeprazole and clarithromycin
Actinomyces israelii	PCN G, ampicillin, clindamycin, doxycycline, ceftriaxone

Yersinia pestis (see 7-H)	
Bacillus anthracis (see 7-H)	
Clostridium botulinum (see 7-H)	
Poxvirus variolae (see 7-H)	
Fransicella tuarensis (see 7-H)	
Viruses (see 7-D and Chapter 12)	
Influenza A/B	Oseltamivir or zanamivir (Note: increased resistance to amantadine/rimantadine—not recommended for treatment)
RSV	Ribavirin aerosol, intravenous immunoglobulin, palivizumab
HSV	Acyclovir, valacyclovir, famciclovir
VZV	Acyclovir (valacyclovir, famciclovir efficacy data pending)
CMV (immunocompromised host),	Ganciclovir /valganciclovir, foscarnet, cidofovir–for retinitis only
West Nile virus	Interferon-α trials ongoing
Coronavirus (SARS)	Interferon-α +/– steroids ? efficacy
Hemorrhagic Fever Viruses	
Hantavirus pulmonary syndrome	Ribavirin effective only with renal involvement
Congo-Crimean hemorrhagic fever	Ribavirin
Lassa fever	Ribavirin

(continued)

7-D. Antimicrobial Drugs of Choice (continued)

Organism	Drugs
Fungi (see Chapter 12 and 7-D)	
Candida albicans	
Oral	Nystatin, clotrimazole troches, fluconazole, itraconazole
Urinary tract	Fluconazole, amphotericin B, caspofungin
Esophageal	Fluconazole, itraconazole, caspofungin, amphotericin B, voriconazole
Vaginal	Topical miconazole, clotrimazole, terconazole, nystatin, or oral fluconazole
Sepsis	Fluconazole, caspofungin, amphotericin B, amphotericin B lipid complex, voriconazole
Peritoneal (chronic ambulatory peritoneal dialysis)	Amphotericin B intraperitoneal, fluconazole, caspofungin
Aspergillus spp.	
Invasive (pulmonary and extrapulmonary)	Voriconazole, liposomal amphotericin B, amphotericin B cholesteryl sulfate complex, and caspofungin
Coccidioides immitis	Fluconazole, itraconazole, amphotericin B
Cryptococcus neoformans	Amphotericin B, fluconazole
Blastomyces dermatitidis	Itraconazole, amphotericin B, fluconazole
Histoplasma capsulatum	Liposomal amphotericin B, itraconazole

Sporothrix spp.	
Lymphocutaneous	Itraconazole, saturated solution of potassium iodide, fluconazole, ketoconazole
Extracutaneous and disseminated	Amphotericin B, itraconazole
Penicillium marneffei	
Pulmonary	Amphotericin B +/– flucytosine, followed by itraconazole, fluconazole
Phycomycetes *Mucor*, phycomycetes *Absidia*	Amphotericin B
Rhizopus	Amphotericin B, liposomal amphotericin B
Pseudallescheria boydii	Voriconazole, itraconazole, miconazole
Onychomycosis	
Tines versicolor	Ketoconazole, fluconazole, itraconazole, selenium sulfide lotion
Tinea capitis	Terbinafine, ketoconazole, itraconazole, fluconazole, griseofulvin
Tinea unguium	
Tinea corporis, *Tinea cruris*, *Tinea pedis*	Clotrimazole, econazole, ketoconazole cream, terbinafine, ketoconazole, fluconazole, itraconazole
Mycobacteria (see Chapter 12 and 7-D)	
M. tuberculosis	Isoniazid, rifampin, pyrazinamide and ethambutol or streptomycin (and pyridoxine, vitamin B_6), cycloserine, ethionamide, kanamycin, ciprofloxacin, ofloxacin, levofloxacin
M. avium intracellular complex, pulmonary and disseminated disease	Clarithromycin + ethambutol + rifabutin +/– either amikacin or streptomycin, azithromycin + ethambutol + rifabutin +/– amikacin or streptomycin

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7-E. Antimicrobial Prophylaxis in Surgery

Surgical Procedure[a]	Recommended Regimen	Alternative Regimen for Documented Allergy
Cardiac	Preoperative (preop) dose within 60 min of incision	Preop dose within 120 min of incision
Pacemaker	Cefazolin, 2 g IV × 1	Vancomycin, 1 g IV × 1
Gastrointestinal	Preop dose within 60 min of incision	
Esophageal, gastroduodenal	High risk[b] only: cefazolin, 1 g IV × 1	Clindamycin, 900 mg IV × 1 and gentamicin, 2 mg/kg × 1 (to maximum of 250 mg)
Biliary tract	High risk[c] only: cefotetan, 1 g IV × 1	Clindamycin, 900 mg IV × 1 and gentamicin, 2 mg/kg × 1 (to maximum of 250 mg)
Colorectal	Cefotetan, 1 g IV × 1 or cefoxitin, 2 g IV × 1 or cefazolin, 2 g IV and metronidazole, 500 mg IV × 1	Clindamycin, 900 mg IV × 1 and gentamicin, 2 mg/kg × 1 (to maximum of 250 mg)
Appendectomy, nonperforated	Cefotetan, 1 g IV × 1 or cefoxitin, 2 g IV × 1 or cefazolin, 2 g IV and metronidazole, 500 mg IV × 1	Clindamycin, 900 mg × 1 and gentamicin, 2 mg/kg × 1 (to maximum of 250 mg)
Genitourinary		
Genitourinary	High risk[d] only: ciprofloxacin, 500 mg PO × 1 or ciprofloxacin, 400 mg IV × 1	Bactrim (SMX/TMP), 10 mg/kg × 1 (10 mg/kg TMP based on lean body weight)

(continued)

7-E. Antimicrobial Prophylaxis in Surgery (continued)

Surgical Procedure[a]	Recommended Regimen	Alternative Regimen for Documented Allergy
Gynecologic obstetric		
Vaginal hysterectomy	Cefotetan, 1 g IV × 1 or cefoxitin, 2 g IV × 1	Clindamycin, 900 mg IV × 1 and gentamicin, 2 mg/kg × 1 (to maximum of 250 mg)
Abdominal hysterectomy	Cefotetan, 1 g IV × 1 or cefoxitin, 2 g IV × 1	Clindamycin, 900 mg IV × 1 and gentamicin, 2 mg/kg × 1 (to maximum of 250 kg)
Cesarean section	High risk[e] only: cefazolin, 2 g IV × 1 or ampicillin, 2 g + gentamicin, 2 mg/kg × 1; administer immediately after umbilical cord is clamped	Clindamycin, 900 mg IV × 1, and gentamicin, 2 mg/kg × 1 (to maximum of 250 mg)
Head and neck	Preop dose within 60 min of incision	
Entering oral cavity or pharynx	Cefazolin, 2 g IV × 1	Clindamycin, 900 mg IV × 1
Neurosurgery		Preop dose within 120 min of incision
Craniotomy	Cefazolin, 2 g IV × 1	Vancomycin, 1.0–1.5 g IV × 1
Orthopaedic		Preop dose within 120 min of incision
Total joint replacement, internal fixation of fractures	Cefazolin, 2 g IV × 1	Vancomycin, 1.0–1.5 g IV × 1
Thoracic	Preop dose within 60 min of incision	Preop dose within 120 min of incision

Noncardiac	Cefazolin, 2 g IV × 1	Vancomycin, 1.0–1.5 g IV × 1 and gentamicin, 2 mg/kg × 1 (to maximum of 250 mg)
Vascular		
Arterial surgery involving the abdominal aorta, prosthesis, or groin incision	Cefazolin, 2 g IV × 1	Vancomycin, 1.0–1.5 g IV × 1 and gentamicin, 2 mg/kg × 1 (to maximum of 250 mg)
Lower extremity amputation for ischemia	Cefazolin, 2 g IV × 1	Vancomycin, 1.0–1.5 g IV × 1 and gentamicin, 2 mg/kg × 1 (to maximum of 250 mg)

IV, intravenous; PO, oral.

[a]Refer to guidelines for patients with heart valve abnormalities.

Clarification of Recommended Regimens:

[b]Esophageal or gastroduodenal procedures: High risk includes patients with morbid obesity, esophageal obstruction, decreased gastric acidity, or decreased gastrointestinal motility.

[c]Biliary tract procedures: High risk includes patients with acute cholecystitis, nonfunctioning gallbladder, obstructive jaundice, common duct stones, or patients older than age 70 years.

[d]Genitourinary procedures: High risk includes patients with positive urine cultures or preoperative catheter.

[e]Cesarean section: High risk includes patients with active labor or premature rupture of membranes (not preterm).

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7-F. Noninfectious Causes of Pulmonary Infiltrates (Pseudopneumonia)

Congestive heart failure
Pulmonary emboli
Aspiration
Chemical pneumonitis
Wegener granulomatosis
Goodpasture syndrome
Lung carcinoma (especially alveolar cell carcinoma)
Metastatic disease
Connective tissue diseases
Vasculitis (especially SLE lung, rheumatoid lung)
Fat emboli
Adult respiratory distress syndrome
Eosinophilic lung disease
Allergic bronchopulmonary aspergillosis
Bronchoalveolar cell carcinoma
Hypersensitivity pneumonitis
Drug-induced pneumonitis
Pulmonary hemorrhage
Radiation pneumonitis
Acute interstitial pneumonitis
Sarcoidosis
Leukostasis (acute leukemia)
Alveolar hemorrhage
Idiopathic interstitial fibrosis [including bronchiolitis obliterans with organizing pneumonia (BOOP)]
Reperfusion lung injury (early post–lung transplant)
Acute lung rejection (late post–lung transplant)
Antineoplastic drug–induced pneumonitis (especially bleomycin, busulfan, methotrexate, mitomycin, nitrosoureas, cyclophosphamide, taxanes)

7-G. Differential Diagnosis of Noninfectious Causes of Cerebrospinal Fluid Pleocytosis

Vasculitis, SLE, Mollaret syndrome, subarachnoid hemorrhage, chemical irritation	Intrathecal chemotherapy, spinal anesthesia, status, post myelography, status, post seizures, Behçet syndrome, sarcoidosis, Sjögren syndrome, malignancy (especially leukemia, lymphoma), lead encephalopathy, rheumatoid arthritis, familial Mediterranean fever
Drugs	Nonsteroidal anti-inflammatory drugs, intravenous gamma globulin, carbamazepine, penicillins, isoniazid, ciprofloxacin, metronidazole, thymidine monophosphate, sulfamethoxazole, sulfonamides, ornithine-ketoacid transaminase-3, azathioprine

7-H. Potential Biologic Warfare Agents/ Presentation/Differential Diagnosis

Anthrax: organism = *B. anthracis*
- Route of infection: cutaneous/inhalation/gastrointestinal infection
- Cutaneous anthrax: most common form of disease
  - Incubation period: 1–14 days after inoculation of skin/mucous membrane to *B. anthracis*
  - Signs and symptoms (Sxs): pruritic painless papule(s) at inoculation site that enlarges, vesiculates, and develops surrounding edema and serosanguinous drainage, then develops eschar and lymphangitis
  - Differential diagnosis (DDx): tularemia, plague, rat bit fever, rickettsial spotted fever lesions, scrub typhus, spider bite, vasculitis, *Bartonella*
  - Diagnosis (Dx): aspirate/biopsy skin lesion: *B. anthracis* = large gram-positive (GP) rods (encapsulated), BC + GP rods, enzyme immunoassay-antigen (EIA-Ag)

detection, polymerase chain reaction (PCR) rapid diagnostic tests available, acute and convalescent serum helpful (for epidemiologic purposes, not outbreaks); not usually fatal

- Inhalation anthrax: life-threatening infection with *B. anthracis* (infection caused by aerosolization of anthrax endospores/particles and subsequent inhalation)
  - Incubation period: 1–7 days
  - Sxs: biphasic illness = prodrome of dry cough, fever, headache, myalgias; short period of improvement; then fulminant respiratory failure, hemodynamic failure, shock leading to death
  - DDx: CAP, *Legionella*, influenza/viral pneumonia
  - Clues that may help predict inhalation anthrax: chest x-ray (CXR) with mediastinal widening +/− pleural effusions, heart rate (HR) > 110, temperature (T) >100.4°F, change in MS, cyanosis, hemoconcentration
  - Sputum gram stain/lavage positive for GP rods
- Gastrointestinal anthrax: ingestion of *B. anthracis* spores in contaminated meat or water
  - Incubation period: 2–5 days
  - Sxs: nausea, vomiting, abdominal pain, bloody diarrhea
  - DDx: enterohemorrhagic *E. coli* (*E. coli* O157:H7)/hemolytic uremic syndrome (HUS), *Salmonella*, *Shigella*, *Campylobacter*, *C. difficile*, inflammatory bowel disease, *V. cholerae*
  - Treatment: anthrax
  - Cutaneous anthrax: Ciprofloxacin or Doxycycline
  - Pregnancy = no change in rx
  - If systemic sxs with cutaneous lesions, rx as systemic infection
  - Systemic infection (Bioterrorism inhalation, GI, oropharyngeal): Ciprofloxacin or Doxycycline + 1 or 2 of the following drugs (Vancomycin, Rifampin, PCN Ampicillin, Chloramphenicol, Imipenem, Clarithromycin, Clindamycin

Plague: organism = *Y. pestis*

- Route of infection: bubonic or septicemic
- Bubonic plague: most common form
  - Incubation period: 2–6 days after direct exposure of mucous membrane to infected material or flea bite of skin

- Sxs: skin lesion at inoculation site (pustule, vesicle, ulcer, or eschar) followed by abrupt onset of fever, chills, headache, malaise with associated pain/swelling/tenderness in regional lymph nodes = buboes (femoral > inguinal > cervical > axillary > epitrochlear > popliteal); if skin lesion is not treated, can develop secondary meningitis, pneumonia, and sepsis
- Primary pneumonic plague: uncommon, fulminant, fatal within 24 hours
  - Incubation period: 1–3 days after inhalation of droplets containing *Y. pestis*
  - Sxs: fever, headache, chills, myalgias, chest pain, productive cough, dyspnea, hemoptysis, and hypoxia
  - CXR: lobar pneumonia/cavitary pneumonia/acute respiratory distress syndrome (ARDS)
  - Dx: sputum with gram-negative rods (GNR) (coccobacilli), bipolar on gram stain, positive direct fluorescent antibody (DFA) *Y. pestis* F1Ag in tissues/body fluids
- Septicemic plague: primary or secondary
  - Primary occurs with *Y. pestis* sepsis after cutaneous exposure without lymphadenopathy (usually in elderly)
  - Secondary occurs with *Y. pestis* sepsis after bubonic or pneumonic plague
  - Sxs: fever, hypotension, disseminated intravascular coagulopathy, multiorgan system failure, ARDS
  - DDx: septic shock (bacterial, fungal)
  - Treatment: plague
  - Mild-moderate infection (skin): Ciprofloxacin, Doxycycline or Chloramphenicl
  - Pregnancy = Gentamicin or Streptomycin
  - Severe infection (septicemia, shock, pneumonia): Streptomycin > Gentamicin

- Botulism: organism = *C. botulinum*
  - Routes of infection: food-borne, inhalation
  - Food-borne botulism
    - Incubation period: 24–72 hours
    - Sxs: diarrhea, vomiting, dry mouth, fatigue, weakness, dysphagia, cranial nerve abnormalities, descending paralysis without fever

- Inhalation botulism
  - Incubation period: 2–4 days
  - Sxs: diarrhea, vomiting, dry mouth, fatigue, weakness, dysphagia, cranial nerve abnormalities, descending motor paralysis (without sensory loss), probable pulmonary hemorrhage
  - Treatment: botulism
  - Antitoxin administration
  - Supportive care
- Smallpox: organism = *Poxvirus variolae*
  - Route of infection: inhalation
  - Incubation period: 10–12 days
  - Sxs: initial prodrome (lasts 48–72 hours): fever, chills, headache, fatigue, backache, delirium; followed by centrifugal rash (erythematous-vesicular-pustular) that involves palms/soles
  - The more confluent/petechial the rash, the higher the mortality rate
  - Hemorrhagic skin lesions/rash associated with high fever, diffuse petechiae, bleeding from mucous membranes: almost 100% mortality
  - DDx: varicella with or without superinfection, drug reaction, secondary syphilis, viral exanthem, monkeypox, vaccine reaction, viral hemorrhagic fever
  - Treatment: smallpox
    - Cidofovir (experimental)
    - Supportive care
- Tularemia: organism = *F. tularensis*
  - Routes of infection: direct contact/inhalation/vectors/gastrointestinal
  - Food-borne tularemia: ingestion of water, juice contaminated with *F. tularensis*
    - Incubation period: 3–6 days
    - Sxs: unilateral tonsillitis/pharyngitis with lymphadenopathy
  - Ulceroglandular/glandular: direct contact of skin with *F. tularensis*
    - Sxs: development of papule (slow healing), associated with tender regional lymphadenopathy, may suppurate
  - Respiratory/inhalation: inhalation of *F. tularensis* or hematogenous seeding of lungs
    - Sxs: pulmonary infiltrates, hilar adenopathy, pleural effusions, necrotizing pneumonia, pneumonitis, ARDS

DDx: *Y. pestis* pneumonia, *B. anthracis* pneumonia, ARDS, shock lung
Treatment: tularemia
Mild-moderate infection: Ciprofloxacin
Bioterrorism-inhalation/septic shock-severe infection: Gentamicin + Ciprofloxacin

Viral hemorrhagic fever: organisms = Ebola, Marburg, Lassa fever, yellow fever, hantaviruses
- Routes of infection: contact with infected animals, arthropod vectors, inhalation
- Incubation period: 2–21 days for hantavirus/Lassa fever
- Incubation period: 3–10 days for Ebola/Marburg/yellow fever)
- Sxs of Lassa fever: gradual onset of fever, myalgias, cough, abdominal pain, bloody diarrhea; more severe Sxs include facial/laryngeal edema, pleural/pericardial effusions/bleeding/shock
- Sxs of hantavirus: febrile/flulike syndrome with back pain, conjunctival/pharyngeal injection; to hypotension with or without shock and hemorrhage; to oliguria, renal failure, hypertension, pulmonary edema (most deaths occur at this time); to recovery stage with diuretic phase if survive
- Hantavirus pulmonary syndrome (HPS): abrupt-onset fever, headache, myalgias; to nausea, diarrhea, abdominal pain; to productive or dry cough, fever, tachypnea, hypoxia, pulmonary edema, respiratory failure (ARDS); to death
- Ebola hemorrhagic fever: organism = Ebola virus
  - Sxs: acute-onset fever, headache, bloody diarrhea, abdominal pain, myalgias, severe conjunctival injection/gingival bleeding, oozing from venipuncture sites, petechiae; to seizures, coma, metabolic acidosis, severe coagulopathy associated with shock; to death
- Marburg hemorrhagic fever: organism = Marburg virus
  - Sxs: acute-onset fever, headache, chills, myalgias; to erythematous rash; to vomiting, diarrhea, jaundice, hepatic failure, coagulopathy, shock; to death
- Yellow fever: organism = yellow fever virus
  - Sxs: acute-onset mild to high fever, headache, diffuse pain, abdominal pain, jaundice, coagulopathy, hypotension, cardiac failure, pneumonia, renal failure, death

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8 INTEGUMENT

8-A. Alopecia

Nonscarring

Aging (pattern baldness)
Androgenic alopecia (e.g., secondary to ovarian or adrenal dysfunction)
Traction or other trauma (trichotillomania, heat exposure)
Drugs
- Cytotoxic agents, interferon
- Oral contraceptives (withdrawal)
- Amphetamines
- Anticoagulants (heparin, Coumadin)
- Beta-blockers, captopril
- Lithium, anticonvulsants
- Vitamin A, retinoids
- Immunoglobulin
- Cholesterol-lowering agents
- Cimetidine
- Isoniazid
- Propylthiouracil

Serious systemic illness, childbirth, weight loss, other stresses (telogen effluvium)
Cutaneous disease
- Seborrheic dermatitis
- Eczema

- Tinea capitis
- Psoriasis
- Cosmetics, other local irritants

Lupus erythematosus
Hypothyroidism, hyperthyroidism
Hypopituitarism
Syphilis, secondary
Nutritional deficiency states (kwashiorkor, marasmus, or iron, zinc, or biotin deficiency)
Human immunodeficiency virus (HIV) infection
Alopecia areata
Hereditary or congenital

Scarring

Physical and chemical agents
- Burns (hot combs or curlers)
- Freezing
- Mechanical trauma
- Acid, alkali
- Radiation
- Body art: tattooing, scarification

Infection
- Bacterial (including pyogenic infection, tertiary syphilis, leprosy, or lupus vulgaris)
- Fungal (e.g., ringworm)
- Viral (especially varicella-zoster, variola)
- Protozoal (leishmaniasis)

Systemic disease
- Lupus erythematosus, systemic or discoid
- Scleroderma or morphea
- Sarcoidosis
- Dermatomyositis
- Amyloidosis
- Neoplasm
  - Metastatic carcinoma
  - Lymphoma

Cutaneous disease
- Basal cell carcinoma
- Lichen planus
- Cicatricial pemphigoid
- Necrobiosis lipoidica diabeticorum

Congenital or idiopathic (pseudopelade of Brocq)

References

1. Habif T. Hair diseases. See Bibliography, 1.
2. Tosti A, Pazzaglia M. See Bibliography, 2.
3. Braverman P. Body art: piercing, tattooing, and scarification. *Adolesc Med*. 2006;17;505–519.

8-B. Erythema Multiforme

Infections
- Viral [especially herpes simplex virus (HSV), Epstein-Barr, Coxsackie virus, echovirus, and influenza]
- Bacterial (e.g., *Yersinia*, *Francisella tularensis*)
- *Mycoplasma pneumoniae*
- Chlamydial (lymphogranuloma venereum)
- Fungal (especially histoplasmosis, coccidioidomycosis)
- Parasitic (*Trichomonas*, malaria)

Vaccines [e.g., smallpox, polio, bacilli Calmette-Guérin (BCG)]

Drugs and toxins
- Antibiotics (especially penicillin, sulfonamides, tetracyclines)
- Metals (mercury, arsenic, gold)
- Antihistamines
- Barbiturates, codeine
- Phenytoin, carbamazepine
- Quinine
- Salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs)
- Hydralazine
- Thiazides

Neoplastic and hematologic disorders
- Lymphoma
- Leukemia
- Multiple myeloma
- Polycythemia vera

Physical factors and contact reactions
- Radiation and sunlight
- Cold
- Poison oak, fire sponge (*Tedania ignis*)

Collagen vascular disease
- Lupus erythematosus, systemic or discoid
- Rheumatoid arthritis
- Polyarteritis nodosa

- Wegener granulomatosis
- Dermatomyositis
- Reiter syndrome

Sarcoidosis
Menstruation, pregnancy
Löffler syndrome
Beer ingestion

References

1. Chung V. See Bibliography, 3.
2. Habif T. See Bibliography, 1, p. 626.
3. Lamoreux M, Sternbach MR, Hsu WT. Erythema multiforme. *Am Fam Physician*. 2006;74:1883–1888.

8-C. Erythema Nodosum

Infection
- Bacterial
  - Streptococci
  - *Yersinia*
  - Cat scratch fever (*Bartonella henselae*)
  - *Salmonella*
  - *Campylobacter*
  - *Mycoplasma pneumoniae*
  - Tularemia
  - Tuberculosis
  - Leprosy
  - Chlamydial (lymphogranuloma venereum, psittacosis)
- Fungal
  - Histoplasmosis
  - Coccidioidomycosis
  - Blastomycosis
- Viral
  - Hepatitis B and C, HSV, HIV

Drugs
- Antibiotics (penicillin, sulfonamides)
- Salicylates
- Iodides, bromides
- Oral contraceptives

Sarcoidosis
Behçet syndrome
Radiation therapy
Inflammatory bowel disease

Pregnancy
Leukemia, lymphoma, other malignancies
Idiopathic

References

1. Mandell G, et al. Chapter 49. See Bibliography, 4.
2. Goldman L. Chapter 475. See Bibliography, 5.
3. Schwartz R, Nervi S. Erythema nodosum: a sign of systemic disease. *Am Fam Physician*. 2007;75:695–700.

8-D. Hirsutism and Generalized Hypertrichosis

Anorexia, malnutrition
Drugs
- Minoxidil
- Androgenic steroids and corticosteroids
- Progestins
- Phenytoin
- Cyclosporin, penicillamine

Endocrine disorders
- Androgenital syndrome
- Adrenal hyperplasia, adenoma, carcinoma
- Pituitary tumor (especially Cushing disease, acromegaly, prolactin-secreting tumors)
- Polycystic ovary syndrome
- Ovarian tumor
- Hyperandrogenism, insulin resistance, acanthosis nigrans (HAIR-AN) syndrome
- Hypothyroidism

Central nervous system disease
- Encephalitis
- Multiple sclerosis
- Head trauma

Dermatomyositis
Hereditary or congenital conditions
- Cutaneous porphyria
- Hurler syndrome
- Morquio syndrome
- Insulin receptor gene mutation
- de Lange syndrome

Hamartomas
Idiopathic

References

1. Tosti A, Pazzaglia M. See Bibliography, 2.
2. Habif T. See Bibliography, 1, p. 846.
3. Essah PA. Dermatology of androgen related disorders. *Clin Dermatol*. 2006;24:289–298.

8-E. Maculopapular Eruption, Generalized

- Drugs (especially antibiotics)
- Infections
  - Viral
    - Rubeola (paramyxovirus)
    - Rubella
    - Roseola (herpesvirus-6)
    - Erythema infectiosum (human parvovirus)
    - Infectious mononucleosis (Epstein-Barr virus)
    - Cytomegalovirus
    - Other viruses (including adeno-, entero-, reo-, arbo-, rhabdovirus)
    - HIV (retrovirus)
    - Live virus vaccine (e.g., measles)
  - Bacterial
    - Streptococcal, staphylococcal
    - *Salmonella*
    - Meningococcemia, chronic
  - Mycoplasmal
  - Syphilis, secondary
  - Leptospirosis
  - Rat-bite fever (*Spirillum minus*)
  - Rickettsial (e.g., Rocky Mountain spotted fever, murine, typhus)
  - Psittacosis
  - Toxoplasmosis
  - Leprosy
  - Trichinosis
- Systemic lupus erythematosus
- Dermatomyositis
- Sarcoidosis
- Pityriasis rosea
- Graft-versus-host disease
- Kawasaki disease

References

1. Habif T. Chapter 14. See Bibliography, 1.
2. Gershon A, et al. *Krugman's Infectious Diseases of Children*. 11th ed. Philadelphia: Mosby; 2004.

8-F. Petechiae and Purpura

Platelet Disorders

Thrombocytopenia (see 6-J)
- Drugs
  - Cytotoxic agents
  - Aspirin, NSAIDs, heparin
  - Quinidine, quinine
  - Gold
  - Phenytoin, ethanol, thiazides
  - Estrogens

Insecticides
Disseminated intravascular coagulation
- Overwhelming infection
  - Bacterial (especially meningococcal, gonococcal, staphylococcal, gram-negative)
  - Viral (especially entero-, arbo-, adenovirus; HIV infection)
  - Rickettsial (Rocky Mountain spotted fever, louse-borne typhus)
  - Miliary tuberculosis
  - Malaria
- Anaphylaxis
- Neoplasm (especially leukemia, lymphoma, and carcinoma of the lung, prostate, or pancreas)
- Thrombotic thrombocytopenic purpura

Immune thrombocytopenic purpura
Posttransfusion purpura
Marrow failure
Splenic sequestration of platelets
Functional platelet disorders (e.g., von Willebrand disease)
Thrombocytosis

Vascular/Extravascular Causes

Vasculitis (palpable purpura)
- Henoch-Schönlein purpura
- Polyarteritis purpura

- Churg-Strauss syndrome
- Wegener granulomatosis
- Lupus erythematosus
- Rheumatoid arthritis
- Subacute bacterial endocarditis
- Hepatitis B
- Serum sickness
- Cryoglobulinemia
- Sjögren syndrome
- Waldenstrom macroglobulinemia
- Lymphoproliferative disorders (especially Hodgkin disease, lymphosarcoma)

Drugs
- Antibiotics (penicillin, sulfonamides, tetracycline)
- NSAIDs
- Thiazides
- Allopurinol
- Cimetidine
- Phenytoin
- Quinidine
- Propylthiouracil
- Ketoconazole
- Gold

Aging

Prolonged elevated venous pressure (coughing, Valsalva maneuver) or other trauma

Steroids (endogenous or exogenous)

Amyloidosis

Cholesterol or fat embolization, or both

Ehlers-Danlos syndrome

Pseudoxanthoma elasticum

Hereditary hemorrhagic telangiectasia

Scurvy

References

1. Visentin GP. Drug induced thrombocytopenia. *Hematol Oncol Clin North Am*. 2007;21:685–696.
2. Kaplan RN. Differential diagnosis and management of thrombocytopenia in childhood. *Pediatr Clin North Am* 2004;51:1109–1140.
3. Psaila B. Immune thrombocytopenic purpura. *Hematol Oncol Clin North Am*. 2007;21:743–759.

8-G. Pruritus

Pruritus with Diagnostic Skin Lesions

Infestation (especially scabies, lice, fleas)
Xerosis (dry skin; e.g., due to low humidity, excess bathing)
Infection, especially bacterial, fungal, varicella
Eczematous dermatitis (atopic or contact)
Urticaria (see 8-J)
Psoriasis
Dermatitis herpetiformis
Bullous pemphigoid
Lichen planus
Miliaria
Mastocytosis
Mycosis fungoides

Pruritus without Diagnostic Skin Lesions

Infestation (hookworm, onchocerciasis, ascariasis, trichinosis)
Drugs
- Opiates
- Aspirin
- Estrogens, progestins, androgens
- Erythromycin, sulfonylureas
- Phenothiazines
- Quinidine
- Vitamin B complex
- Psoralen/ultraviolet A radiation (PUVA)

Obstructive liver disease
- Bile duct obstruction (extrahepatic or intrahepatic)
  - Biliary cirrhosis
  - Drug-induced cholestasis (oral contraceptives, phenothiazines, chlorpropamide)
  - Intrahepatic cholestasis of pregnancy

Neoplasm
- Lymphoma, leukemia
- Abdominal malignancy
- Central nervous system malignancy
- Paraproteinemia
- Carcinoid tumor

Polycythemia vera
Iron deficiency
Diabetes mellitus
Hyperthyroidism

Chronic renal failure (with or without secondary hyperparathyroidism)
Neurodermatitis

References

1. Heymann W. Itch. *J Am Acad Dermatol*. 2006;54:705–706.
2. Waxler B. Primer of postoperative pruritis for anesthesiologists. *Anesthesiology*. 2005;103:168–178.

8-H. Pustules, Generalized

Acne vulgaris
Acne rosacea
Pyogenic infection (disseminated gonococcal, *Pseudomonas*, meningococcal)
Viral infection (vaccinia, variola)
Eosinophilic folliculitis in HIV infection
Disseminated cryptococcosis
Syphilis, secondary
Drugs
- Antibiotics
- Corticosteroids, androgenic steroids
- Oral contraceptives
- Lithium, halogens (iodide, bromide)
- Isoniazid

Pustular psoriasis
Sweet syndrome (acute febrile neutrophilic dermatosis)
Behçet syndrome
Polycystic ovary syndrome
Cushing disease, 21-hydroxylase deficiency

References

1. Mandell G, et al. Chapter 86. See Bibliography, 4.
2. Habif T. See Bibliography, 1, pp. 486, 490.

8-I. Telangiectasia

Normal variant (wind or sun exposure)
Endocrine disease
- Chronic liver disease (alcoholic cirrhosis)
- Pregnancy, estrogen or progesterone therapy
- Long-term topical steroid use
- Hyperthyroidism

Collagen vascular disease
- Lupus erythematosus, systemic or discoid
- Dermatomyositis
- Rheumatoid arthritis
- Systemic sclerosis, telangiectasia syndrome

Genetically transmitted disease
- Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia)
- Ataxia-telangiectasia
- Fabry disease
- Xeroderma pigmentosum

States associated with prolonged vasodilatation (varicose veins, rosacea, polycythemia vera)

Peripheral vascular disease (e.g., livedo reticularis, erythema ab igne)

Neoplastic disease
- Breast cancer
- Bile duct carcinoma
- Carcinoid tumor
- Cutaneous T-cell lymphoma

Radiation dermatitis

Mastocytosis

References

1. Hoffman R. *Hematology: Basic Principles and Practice*. 4th ed. Philadelphia: Elsevier, Churchill Livingston; 2005.
2. Habif T. Vascular tumors and malformations. See Bibliography, 1.

8-J. Urticaria

Specific antigen sensitivity (e.g., foods, food additives, Hymenoptera venom)

Physical agents
- Pressure, mechanical irritation, vibratory, water
- Cold, heat, sunlight
- Cholinergic urticaria

Atopic conditions, animal dander, mold

Drugs
- Opiates, codeine (histamine release)
- Antibiotics (penicillin, sulfonamides)
- X-ray contrast material, dyes
- NSAIDs, aspirin

- Thiazides
- Angiotensin-converting enzyme inhibitors

Transfusion of blood or blood components
Infections
- Bacterial (*Campylobacter* enteritis)
- Fungal (candidiasis)
- Viral (hepatitis B, infectious mononucleosis, Coxsackie)
- Protozoal, helminthes

Vasculitis
- Lupus erythematosus
- Rheumatoid arthritis
- Sjögren syndrome
- Serum sickness, hyperthyroidism
- Hepatitis B, acute
- Cryoglobulinemia

Mastocytosis (urticaria pigmentosa)
Occult malignancy (especially lymphoma)
Contact urticaria
- Plants (nettles) or animals (jellyfish)
- Ammonium persulfate (hair bleaches)

Pregnancy, premenstrual
Angioedema (hereditary and acquired)
Emotional stress

References

1. Dibbern D Jr. Urticaria: selected highlights and recent advances *Med Clin North Am*. 2006;90:187–209.
2. Adkinson N Jr. See Bibliography, 6.
3. Baxi S, Dinakar C. Urticaria and angioedema. *Immunol Allergy Clin North Am*. 2005;25:353–367.

8-K. Vesicles and Bullae, Generalized[1]

Physical agents
- Radiation, burns, chemicals, cosmetics
- Mechanical irritation, trauma
- Metals (nickel, chromate)

Plants (poison ivy and oak, primrose)
Resins
Drugs
- Barbiturates
- Penicillins, sulfonamides, nitrofurantoin
- Bacitracin, neomycin

- NSAIDs
- Thiazides, furosemide
- Phenytoin

Infections
- Bacterial
  - Disseminated gonococcus, *Pseudomonas*
  - Impetigo, erysipelas
  - Toxic epidermal necrolysis
  - Staphylococcal scalded skin syndrome
- Viral
  - HSV, herpes zoster
  - Varicella, variola (smallpox), vaccinia
  - Enterovirus (e.g., hand-foot-mouth disease)
  - Syphilis, congenital
  - Rickettsialpox

Erythema multiforme bullosum, Stevens-Johnson syndrome (see 8-B)
Pemphigoid (bullous, cicatricial)
Acute eczematous dermatitis, especially contact dermatitis
Porphyria
Diabetes mellitus
Bullous insect bite eruption
Linear immunoglobulin A disease

References

1. Sami N. Blistering diseases in the elderly: diagnosis and treatment. *Dermatol Clin North Am*. 2004;22: 73–86.
2. Habif T. Vesicles and bullous diseases. See Bibliography, 1.
3. McKenna J, Leiferman K. Dermatologic Drug Reactions. *Immunol Allergy Clin North Am*. 2004;24:399–423.

[1]Vesicles are <0.5 cm, and bullae are >0.5 cm.

8-L. Hypopigmentation

Vitiligo
- Diabetes
- Thyroid disease (thyroiditis)
- Pernicious anemia
- Collagen vascular diseases

Chemicals (monobenzyl ether of hydroquinone, mercury)

Congenital
- Albinism (partial or total)
- Nevus depigmentosus
- Tuberous sclerosis

Postinflammatory hypomelanosis
Tinea versicolor
Scleroderma
Vogt-Koyanagi-Harada syndrome
Melanoma
Sarcoidosis
Psoriasis
Secondary syphilis

References

1. Habif T. See Bibliography, 1, pp. 684–690.
2. Mollet I, Ongenae K, Naeyaert JM. Origin, clinical presentation and diagnosis of hypomelanotic skin disorders. *Dermatol Clin*. 2007;25:363–371.
3. The National Vitiligo Foundation. Homepage. http://www.nvfi.org/

8-M. Nail Pigmentation

Drug induced
- Anticoagulants, aspirin
- Anticonvulsants
- Antimalarials (blue-brown)
- Antiretrovirals
- Chemotherapy
- Retinoids
- Tetracyclines (blue-grey)

Heavy metals
- Arsenic, thallium (white Mees lines)
- Silver salts, Wilson disease (blue nails)
- Mercury (grey-brown nails)
- Lithium (yellow nails)

Melanoma, nevi, lentigo
Hematoma (trauma)
Radiation induced
Ethnic (racial) pigmentation
Yellow nail syndrome
Pseudomonas aeruginosa (green-black)
Fungal infections

Splinter hemorrhages
- Amyloidosis
- Bacterial endocarditis
- Periarteritis nodosa
- Scurvy

Addison disease, hyperthyroidism
Acromegaly
Pregnancy
Scleroderma
Acquired immunodeficiency syndrome
Malnutrition

References

1. Tosti A, Iorizzo M, Piraccini BM, Starace M. The nail in systemic diseases. *Dermatol Clin*. 2006;24:341–347.
2. Andre J, Lateur N. Pigmented nail disorders. *Dermatol Clin*. 2006;24:329–339.
3. Piraccini B. Drug induced nail disorders. *Dermatol Clin*. 2006;24:387–391.
4. Braun R, Baran R, Le Gal FA, et al. Diagnosis and management of nail pigmentation. *J Am Acad Dermatol*. 2007;56:835–847.

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1. Habif T. *Clinical Dermatology: A Color Guide to Diagnosis and Therapy*. 4th ed. Philadelphia: Mosby; 2004.
2. Tosti A, Pazzaglia M. Drug reactions affecting hair: diagnosis. *Dermatol Clin*. 2007;25:223–231.
3. Chung V et al. Clinical and pathologic findings of paraneoplastic dermatoses. *J Am Acad Dermatol*. 2005;54:745–762.
4. Mandell G et al. *Principles and Practice of Infectious Diseases*. 6th ed. Philadelphia: Churchill Livingstone; 2005.
5. Goldman L, Ausiello D. *Cecil Textbook of Medicine*. 22nd ed. Philadelphia: WB Saunders; 2004.
6. Adkinson N Jr. *Middleton's Allergy: Principles and Practice*. 6th ed. Philadelphia: Mosby; 2003.

9

MUSCULOSKELETAL SYSTEM

9-A. Shoulder Pain

Fracture
Contusion
Acromial-clavicular joint separation or injuries
Rotator cuff tendonitis, rupture or impingement syndrome
Bursitis
Bicipital tendonitis (long head)
Referred pain
    Diaphragmatic irritation
        Biliary disease
        Myocardial infarction, angina, pericarditis
        Blood or gas in peritoneal or pleural cavity
        Subphrenic abscess
        Splenic rupture
        Neoplasm
        Lower lobe pleuropulmonary inflammatory disease
    Apical lung cancer (Pancoast syndrome)
    Cervical radiculopathy and brachial neuritis
Osteoarthritis
Infectious, rheumatoid, or crystalline arthritis
Arthritis associated with collagen vascular disease
Anterior or posterior shoulder instability
Shoulder-hand syndrome
Neoplasm, primary or metastatic

Local arterial, venous, or lymphatic occlusion
Adhesive capsulitis
Carpal tunnel syndrome
Thoracic outlet syndromes
    Cervical and first rib syndromes, scalenus anterior syndrome
    Hyperabduction syndrome
    Costoclavicular syndrome
Psychogenic pain
Sleep dysesthesias
Postural
Congenital or developmental abnormalities

References

1. Harris R. See Bibliography, 1, pp. 475–504.
2. Mercier L. See Bibliography, 2, pp. 48–74.

9-B. Back Pain

Functional, mechanical causes: postural imbalance
    Anteroposterior (e.g., pregnancy)
    Lateral (e.g., scoliosis, unequal leg lengths)
Trauma
    Lumbar strain or sprain
    Lumbosacral disc herniation
    Vertebral fracture (compression or other)
    Subluxation of facet joints
Osteoarthritis, spondylosis
Rheumatoid arthritis
Fibromyalgia
Polymyalgia rheumatica
Spondylitis, or sacroiliitis, or both
    Ankylosing spondylitis
    Colitic (enteropathic) spondylitis
    Psoriatic arthritis
    Behçet syndrome, Reiter syndrome
    Familial Mediterranean fever
    Syphilis, ochronosis
Spinal stenosis
    Congenital, degenerative
    Iatrogenic (after laminectomy, fusion, or chemonucleolysis)
    Posttraumatic
    Paget disease
    Renal osteodystrophy

- Spinal or vertebral tumor
  - Benign (e.g., hemangioma, meningioma, osteoid osteoma)
  - Malignant
    - Primary (e.g., multiple myeloma, ependymoma, osteogenic sarcoma)
    - Metastatic
      - Breast, prostate, lung
      - Kidney, thyroid, gastrointestinal tract
      - Non-Hodgkin or Hodgkin lymphoma
      - Leukemic
- Infection (e.g., disc space, vertebral osteomyelitis, epidural abscess)
  - Bacteria, *Brucella*, spirochetes
  - Herpes zoster, parasites
  - Mycobacteria, fungi
- Congenital causes
  - Facet hypertrophy, spondylolysis, spondylolisthesis
  - Spina bifida, transitional vertebrae
- Hyperparathyroidism
- Osteomalacia (e.g., vitamin D–resistant rickets)
- Osteoporosis (primary, endocrine, nutritional, or drugs)
- Osteogenesis imperfecta
- Scheuermann disease (epiphysitis)
- Radium poisoning
- Referred pain
  - Vascular disease (abdominal aortic aneurysm, Leriche syndrome)
  - Hip pain
  - Pelvic or prostatic inflammation or tumor, endometriosis
  - Retroperitoneal hematoma/tumor, renal vein thrombosis
  - Renal stones, infection, tumor
  - Polycystic kidney disease
  - Abdominal disease (e.g., intestinal, pancreatic, gallbladder)
  - Cardiopulmonary (pulmonary emboli, pneumonia, pleuritis, angina)
- Hemoglobinopathies (e.g., sickle cell, myelofibrosis)
- Psychoneurotic (hysteria or malingering)

References

1. Harris R. See Bibliography, 2, pp. 118–151.
2. Broder J, Snarski J. Back pain in the elderly. *Clin Geriatric Med.* 2007;23:271–289.

3. Baker R, Patel D. Lower back pain in the athlete: common conditions and treatment. *Prim Care Clin Office Pract.* 2005;32:201–229.

9-C. Myalgias

Fibrositis
Connective tissue disease
- Polymyalgia rheumatica
- Rheumatoid arthritis
- Polymyositis, dermatomyositis
- Lupus erythematosis
- Polyarteritis nodosa
- Scleroderma

Systemic infection
- Viral illnesses [e.g., influenza, Coxsackie virus, rabies, human immunodeficiency virus (HIV)]
- Dengue fever, poliomyelitis, tularemia
- Trichinosis, glanders, leptospirosis
- Typhoid fever, malaria, brucellosis

Rhabdomyolysis (see 9-D)
Drugs (e.g., amphotericin B, chloroquine, oral contraceptives, fibrates)
Hypothyroidism, hyperparathyroidism
Congenital enzyme deficiency [e.g., phosphorylase (McArdle disease), phosphofructokinase]
Polyneuropathy (e.g., Guillain-Barré disease)
Ischemic atherosclerotic disease (e.g., intermittent claudication)

References

1. Goldman L. Chapter 461. See Bibliography, 3.
2. Wortmann RL. Chapter 80. See Bibliography, 1.

9-D. Muscle Weakness

Acute or Subacute[1]

Electrolyte abnormality
- Hyperkalemia, hypokalemia
- Hypercalcemia, hypermagnesemia
- Hypophosphatemia

Rhabdomyolysis
- Extreme muscle exertion, prolonged seizures
- Hyperthermia

- Extensive crush injury or muscle infarction
- Influenza
- Hypokalemia, hypophosphatemia
- Alcoholic myopathy
- Snake venoms
- Industrial toxin ingestion
- Familial myoglobinuria
- Metabolic myopathies (e.g., McArdle disease)

Polymyositis, dermatomyositis
Infections
- Viral (e.g., influenza, Coxsackie virus, rabies, poliomyelitis, herpes zoster)
- Trichinosis, toxoplasmosis, cysticercosis, schistosomiasis, trypanosomiasis
- Botulism, diphtheria
- Leprosy

Peripheral neuropathy (see 10-N)
Thyrotoxicosis
Corticosteroid therapy
Organophosphorous poisoning

Chronic

Progressive muscular dystrophies
- Oculopharyngeal
- Duchenne
- Facioscapulohumeral
- Limb-girdle
- Myotonic

Endocrine disorders
- Hyperthyroidism or hyperthyroidism
- Hyperparathyroidism
- Vitamin D deficiency (e.g., vitamin D–deficient rickets)
- Corticosteroid therapy
- Cushing syndrome, Addison disease
- Acromegaly

Connective tissue disease
- Lupus erythematosus
- Rheumatoid arthritis
- Polymyositis, dermatomyositis
- Sjögren syndrome
- Mixed connective tissue disease

Alcoholic myopathy
Chronic polymyopathy
    Glycogen storage diseases (e.g., McArdle disease)
    Central core disease
Mitochondrial myopathy
    Lipid metabolism disorders (e.g., carnitine deficiency)
    Familial periodic paralysis with progressive myopathy
Progressive neural-muscular atrophy
    Amyotrophic lateral sclerosis
    Multiple sclerosis
    Peroneal muscular atrophy (Charcot-Marie-Tooth disease)
    Chronic peripheral neuropathy [e.g., arsenic, lead, nutritional (see 10-N)]

Intermittent or Transient, or Both

Electrolyte abnormality
    Hypokalemia, hyperkalemia
    Hypophosphatemia
    Hypercalcemia, hypermagnesemia
    Hyperkalemic from sodium channel disorders
    Hypokalemic periodic paralysis (calcium channel disorders)
Drugs
    Aminoglycosides (neomycin, streptomycin, kanamycin or polymyxin B)
    Steroids
    Vincristine, zidovudine, cyclosporine
    Chloroquine, bretylium
    Clofibrate, statins, niacin
Myasthenia gravis
Eaton-Lambert syndrome
Acute thyrotoxic myopathy
Thyrotoxic periodic paralysis

References

1. Harris R. See Bibliography, 1, pp. 387–391.
2. Goldman L. Chapter 420. See Bibliography, 3.

[1]Developing over days to weeks (see section on intermittent or transient, or both).

9-E. Polyarticular Arthritis

Rheumatoid arthritis[1]
Juvenile rheumatoid arthritis[1]

- Rheumatic fever[1]
- Ankylosing spondylitis[1]
- Collagen vascular diseases
  - Lupus erythematosus[1]
  - Scleroderma[1]
  - Polymyositis, dermatomyositis[1]
  - Mixed connective tissue disease
  - Polyarteritis nodosa (rare)[1]
  - Henoch-Schönlein purpura (rare)[1]
  - Wegener granulomatosis (rare)[1]
  - Other vasculitides (rare; e.g., allergic granulomatosis)[1]
  - Polymyalgia rheumatica[1]
- Immunologically mediated diseases
  - Serum sickness[1]
  - Hypergammaglobulinemic purpura[1]
  - Hyper gammaglobulinemia[1]
  - Alpha-interferon induced
  - Mixed cryoglobulinemia (rare)[1]
- Systemic diseases
  - Sjögren syndrome[1]
  - Reiter syndrome[1]
  - Psoriasis[1]
  - Behçet syndrome[1]
  - Inflammatory bowel disease (ulcerative colitis, regional enteritis)[1]
- Intestinal bypass[1]
- Pancreatic disease (carcinoma, pancreatitis)
- Whipple disease[1]
- Amyloidosis
- Sarcoidosis[1]
- Hematologic disorders
  - Leukemia[1]
  - Lymphoma[1]
  - Multiple myeloma[1]
  - Hemophilia
  - Hemoglobinopathies (especially sickle cell anemia, thalassemia)[1]
- Storage disease (e.g., Gaucher disease, Fabry disease, hyperlipoproteinemia)[1]
- Ochronosis
- Hemochromatosis, Wilson disease
- Acromegaly, hypothyroidism
- Renal transplantation

Degenerative joint disease
Trauma
Neuropathic arthropathy (e.g., tabes dorsalis, diabetes mellitus, syringomyelia)
Joint tumor (e.g., hemangioma, sarcoma)
Infection
- Bacterial (especially gonococcal, staphylococcal, pneumococcal)
- Viral (especially hepatitis B, mumps, rubella, arboviruses, *Parvovirus*, retrovirus)
- Tuberculosis
- Fungal (candida associated with central venous line or hyperalimentation)
- Rickettsial (Lyme disease)
- Parasitic

Gout or pseudogout[1]
Hypertrophic osteoarthropathy
Radiation
Relapsing polychondritis[1]
Acute tropical polyarteritis[1]
Nonarticular rheumatism
- Bursitis, periarthritis[1]
- Tendonitis, tenosynovitis[1]
- Epicondylitis, myositis, fibrositis, fasciitis

References

1. Langford CA. Vasculitis in the geriatric population. *Rheum Dis Clin North Am*. 2007;33:177–195.
2. Sergent J. Polyarticular arthritis. See Bibliography, 1.
3. Fagan HB. Approach to the patient with acute swollen/painful joint. *Clin Fam Pract*. 2005;7:305–319.

[1]Usually inflammatory (i.e., joints painful, swollen, stiff, often erythematous, and warm).

9-F. Monoarticular (Oligoarticular) Arthritis

Juvenile rheumatoid arthritis
Ankylosing spondylitis
Rheumatoid arthritis (rare)
Systemic diseases
- Psoriasis
- Behçet syndrome

- Inflammatory bowel disease (ulcerative colitis, regional enteritis)
- Pancreatic disease (carcinoma, pancreatitis)
- Whipple disease
- Familial Mediterranean fever
- Hematologic disorders
  - Leukemia
  - Lymphoma
  - Bleeding/clotting disorders (hemophilia, von Willebrand disease, anticoagulant use)
  - Hemoglobinopathies (especially sickle cell anemia, thalassemia)
- Storage diseases (e.g., Gaucher, Fabry)
- Acromegaly
- Amyloidosis

Degenerative joint disease
Trauma
Neuropathic arthropathy (e.g., tabes dorsalis, diabetes mellitus, syringomyelia)
Joint tumors (e.g., pigmented villonodular synovitis, hemangioma, sarcoma)
Infection
- Bacterial (e.g., gonococcal, staphylococcal, pneumococcal)
- Viral (hepatitis B, rubella, mumps)
- Tuberculous
- Fungal, rickettsial, parasitic

Gout or pseudogout
Loose joint body or foreign body
Palindromic rheumatism
Radiation
Relapsing polychondritis
Nonarticular rheumatism (see 9-E)

References

1. Mercier L. Chapter 14. See Bibliography, 2.
2. Maury E, Flores R. Acute monoarthritis: diagnosis and management. *Prim Care Clin Office Pract*. 2006;33:779–793.

9-G. Characteristics of Synovial Fluid

	Normal	Noninflammatory	Inflammatory	Purulent	Hemorrhagic
Color	Clear to pale yellow	Xanthochromic	Xanthochromic to white	White	—
Clarity	Transparent	Transparent	Translucent to opaque	Opaque	—
Viscosity	High	High	Low	Low[a]	—
Mucin clot	Good	Good to fair	Fair to poor	Poor	—
Spontaneous clot	None	Often	Often	Often	—
WBCs/mm^3	<150	<3,000	3,000–50,000	>50,000	—
% Polymorphs	<25	<25	>70	>90	—
Glucose (mg/dL)	Nearly equal to blood	Nearly equal to blood	>25, lower than blood	>50, lower than blood	—
Culture	Negative	Negative	Negative	Often positive	—

Conditions in which findings are likely to occur	—	Osteoporosis Trauma Neuropathic arthropathy Chronic or subacute crystal synovitis SLE Scleroderma Polymyalgia rheumatica Erythema nodosum Polyarteritis nodosa Amyloidosis	Rheumatoid arthritis Connective tissue diseases (SLE, PSS, DM/PM) Viral arthritis Ankylosing spondylitis Seronegative spondyloarthropathies (Reiter syndrome, psoriatic arthritis, inflammatory bowel disease arthritis)	Bacterial arthritis Tuberculous arthritis	Trauma Anticoagulation Neuropathic arthropathy: Charcot joints Joint tumor (pigmented villonodular synovitis or hemangioma) Hematologic disorders (especially hemophilia, sickle cell trait or disease) Joint prosthesis

DM/PM dermatomyositis/polymyositis; PSS, progressive systemic sclerosis; SLE, systemic lupus erythematosis; WBCs, white blood cells.
[a] May be high in infection with coagulase-positive *Staphylococcus*.
Group designations from Ropes MW, Bauer W. *Synovial Fluid Changes in Joint Diseases*. Cambridge, MA: Harvard University Press; 1953. Table modified from Koopman WL. *Arthritis and Allied Conditions*. 15th ed. Philadelphia: Lippincott Williams & Wilkins; 2005 and from Klippel JH, ed. *Primer on Rheumatic Diseases*. 12th ed. Atlanta: Arthritis Foundation; 2001.

Reference

1. Harris R. Chapter 46. See Bibliography, 1.

9-H. Clubbing

Usually with Hypertrophic Osteoarthropathy

Neoplasm
- Intrathoracic
  - Lung, pleura
  - Mediastinum (Hodgkin disease)
  - Thymus
- Esophagus, stomach, intestine, liver

Lung abscess, empyema
HIV
Chronic interstitial pneumonitis
Pneumoconiosis
Sarcoidosis
Bronchiectasis
Tuberculosis
Cystic fibrosis
Idiopathic, hereditary (pachydermoperiostosis)

Usually without Hypertrophic Osteoarthropathy

Genetic
Subacute bacterial endocarditis
Cyanotic congenital heart disease
Chronic liver disease (e.g., biliary cirrhosis)
Intestinal disorders
- Ulcerative colitis, regional enteritis
- Celiac sprue, steatorrhea
- Bacterial or amebic dysentery
- Tuberculosis, intestinal

Hyperparathyroidism
Graves disease (thyroid acropachy)
Occupational trauma (e.g., jackhammer operation)

Unilateral

Aneurysm of aorta or of subclavian, innominate, or brachial artery
Shoulder subluxation
Hemiplegia
Axillary or apical lung tumor

Unidigital

Median nerve injury
Sarcoidosis
Tophaceous gout

References

1. Spicknall K, Zirwas MJ, English JC 3rd. Clubbing: an update on diagnosis, differential diagnosis, pathophysiology and clinical relevance. *J Am Acad Dermatol*. 2005;52:1020–1029.
2. Mason R. *Murray and Nadel's Textbook of Respiratory Medicine*. Philadelphia: Saunders; 2005.
3. Tosti A, Iorizzo M, Piraccini BM, Starace M. The nail in systemic disease. *Dermatol Clin*. 2006;24:341–347.

9-I. Raynaud Phenomenon

Raynaud disease
Chronic arterial disease
    Atherosclerosis, thromboangiitis obliterans
    Thrombosis, embolism
Pulmonary veno-occlusive disease or primary pulmonary hypertension
Collagen vascular diseases
Occupational exposure
    Vibration (e.g., pneumatic tools)
    Percussion (e.g., typing)
    Vinyl chloride polymerization
Drugs, toxins
    Heavy metals (lead, arsenic, thallium)
    Methysergide, ergot compounds
    Beta-adrenergic blockers
    Chemotherapy (bleomycin, vinblastine, cisplatin)
Hematologic disorders
    Dysproteinemias (e.g., multiple myeloma, Waldenström macroglobulinemia)
    Polycythemia vera, essential thrombocythemia
    Leukemia
    Cryoglobulinemia
    Cold agglutinin phenomenon
Neurologic disorders
    Peripheral neuropathy
    Hemiplegia
    Intervertebral disc herniation

- Spinal cord tumor
- Multiple sclerosis
- Transverse myelitis
- Syringomyelia
- Carpal tunnel syndrome

Thoracic outlet syndrome
Posttraumatic reflex sympathetic dystrophy
After frostbite injury
Acromegaly
Myxedema

References

1. Harris R. See Bibliography, 1, pp. 1218–1219.
2. Westerberg D, Lawrence J. Approach to the patient with Raynaud's phenomenon. *Clin Fam Pract.* 2005;7:321–334.

9-J. Osteomalacia

Vitamin D deficiency (diet, insufficient sun exposure, malabsorption due to pancreatic insufficiency, small intestine disease, postgastrectomy)
Disordered vitamin D metabolism (hereditary or acquired)
- Chronic renal failure
- Anticonvulsant therapy
- Chronic liver disease (biliary cirrhosis)

Vitamin D–dependent rickets (peripheral resistance to vitamin D)
Chronic acidosis (e.g., distal renal tubular acidosis, ureterosigmoidostomy)
Phosphate depletion
Impaired renal tubular phosphate reabsorption
- Familial X-linked hypophosphatemia
- Fanconi syndrome (hereditary or acquired)
- Tumor phosphaturia
- Neurofibromatosis
- Neonatal (transient)
- Intoxications (cadmium, lead, aluminum)

Osteopetrosis
Fluorosis, hyperphosphatasia
Magnesium-dependent conditions
Parenteral hyperalimentation
Calcium deficiency due to bisphosphonates
Renal transplantation
Tumor-associated renal disease

References

1. Harris R. See Bibliography, 1, pp. 1645–1647.
2. Raisz LG, et al. Metabolic bone disease. See Bibliography, 5.
3. Williams SE, Seidner DL. Metabolic bone disease in GI illness. *Gastroenterol Clin North Am*. 2007;36:161–190.

9-K. Osteoporosis[1]

Aging (especially postmenopause)
Immobilization
Nutritional causes
- Calcium or vitamin D deficiency, or both
- Malnutrition, malabsorption
- Postgastrectomy
- Pregnancy and lactation
- Total parenteral nutrition
- Scurvy
- Aluminum-containing antacids

Corticosteroid excess (Cushing syndrome or disease, or steroid therapy)
Hypogonadism (e.g., Klinefelter syndrome, Turner syndrome, early oophorectomy)
Thyrotoxicosis
Acromegaly
Hyperparathyroidism
Hypopituitarism
Diabetes mellitus
Inherited bone matrix abnormalities
- Homocystinuria
- Marfan syndrome
- Ehlers-Danlos syndrome
- Osteogenesis imperfecta
- Menkes syndrome

Rheumatoid arthritis
Ankylosing spondylitis
Malignancy, especially:
- Lymphoma, leukemia
- Multiple myeloma, Waldenström macroglobulinemia
- Systemic mastocytosis
- Carcinomatosis

Chronic heparin therapy
Smoking

Chronic acidosis (renal tubular acidosis, metabolic acidosis secondary to high-protein diet)
Alcoholism, hepatic insufficiency, cirrhosis (alcoholic or other)
Methotrexate, chronic anticonvulsant therapy
Chronic renal failure with renal osteodystrophy
Paget disease (with predominantly lytic lesions)
Riley-Day syndrome
Menkes syndrome, Down syndrome
Female distance runners

References

1. Simon L. Osteoporosis. *Rheum Dis Clin North Am*. 2007;33:149–176.
2. Gennari L, Bilezikian J. Osteoporosis in men. *Endocrinol Metab Clin North Am*. 2007;36:399–419.

[1]Low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and increased fracture risk.

9-L. Antibodies to Nuclear or Cytoplasmic Antigens

Disease	Antibodies Most Commonly Associated
Systemic lupus erythematosus	Anti–native (double-stranded) DNA Anti–single-stranded DNA Anti-histone (e.g., drug-induced lupus) Anti-ribosome (anti-snRNP; e.g., anti-P) Anti-Ro (anti–SS-A) Anti-La (anti–SS-B) Anti–RNA polymerase (anti-RNAP) Anti-Ku
Progressive systemic sclerosis/ scleroderma/ CREST variant	Anti-centromere Anti–topoisomerase I (Scl-70) Anti–RNA polymerase (anti RNAP) Anti–tRNA synthetase Anti–MA I

(continued)

9-L. Antibodies to Nuclear or Cytoplasmic Antigens (continued)

Disease	Antibodies Most Commonly Associated
Polymyositis	Myositis-specific autoantibodies (MSAs) Anti–tRNA synthetases (anti–Jo 1) Anti-snRNP Anti–PM-Scl
Mixed connective tissue disease	Anti–U1 snRNP Sm and SR proteins
Sjögren syndrome	Anti-Ro (anti–SS-A) Anti-La (anti–SS-B)
Hypercoagulable state	Anticardiolipin (aCL)

References

1. Peng S, Craft J. Antinuclear antibodies, pp. 161–173. See Bibliography, 1.
2. Salzman B, et al. See Bibliography, 6.
3. Greidinger E, Hoffman R. Autoantibodies in the pathogenesis of mixed connective tissue disease. *Rheum Dis Clin North Am*. 2005;31:437–450.

9-M. Positive Rheumatoid Factor

Rheumatoid arthritis
Aging (>70 years)
Systemic lupus erythematosus
Progressive systemic sclerosis
Dermatomyositis, polymyositis
Mixed connective tissue disease
Infections
- Syphilis
- Influenza, viral hepatitis, cytomegalovirus
- Acquired immunodeficiency disease (AIDS)
- Infectious mononucleosis, rubella
- Subacute bacterial endocarditis, periodontal disease
- Bacterial bronchitis, tuberculosis, leprosy
- Parasitic (e.g., schistosomiasis, kala-azar)
- Lyme disease
- After extensive immunizations

Sjögren syndrome (with or without arthritis)
Lymphoma
Waldenström macroglobulinemia, mixed cryoglobulinemia
Pneumoconiosis (e.g., silicosis, asbestosis)
Sarcoidosis, interstitial fibrosis (idiopathic)
Multiple transfusions
Renal transplantation

References

1. Harris R. See Bibliography, 1, pp. 151–157.
2. Salzman B. See Bibliography, 6.

9-N. Systemic Lupus Erythematosus Criteria[1]

Immunologic disorder: positive antinuclear antibody, anti-DNA antibodies, anti-Sm and anti-RNP antibodies, positive phospholipids antibodies, or false-positive serologic test for syphilis
Proteinuria >0.5 g/day or cellular casts in urine (red cell, hemoglobin, granular, tubular, mixed)
Facial erythema (butterfly rash)
Serositis: pleuritis or pericarditis, or both
Discoid lupus erythematosis
Hematologic disorder: hemolytic Coombs-positive anemia, leukopenia (WBC $<4{,}000/mm^3$), lymphopenia ($<1{,}500/mm^3$), or thrombocytopenia ($<100{,}000/mm^3$)
Photosensitivity, oral ulcers
Nonerosive arthritis
Psychosis or seizures, or both

References

1. Tan E, Cohen AS, Fries JF, at al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1982;25:1271–1277.
2. Hochberg MC. Updating the American College of Rheumatology revised criteria. *Arthritis Rheum*. 1997;40:1725.
3. Harris R. See Bibliography, 1, pp. 1105–1123.

[1]Diagnosis of systemic lupus may not be certain on initial presentation and might be classified as probable if four or more of these criteria are present.

Bibliography

1. Harris E. *Kelley's Textbook of Rheumatology*. 7th ed. Philadelphia: WB Saunders; 2005.
2. Mercier L. *Practical Orthopedics*. 5th ed. St. Louis: Mosby; 2000.
3. Goldman L, Ausiello D. *Cecil's Textbook of Medicine*. 22nd ed. Philadelphia: WB Saunders; 2004.
4. American College of Rheumatology. Practice support guidelines. Available at: http://www.rheumatology.org/practice/qmc/guidelines.asp.
5. Larsen PR, et al. *Williams Textbook of Endocrinology*. 10th ed. Philadelphia: WB Saunders; 2003.
6. Salzman B, et al. A primary care approach to the use and interpretation of common rheumatologic tests. *Clin Fam Pract*. 2005;7:335–359.

10
NERVOUS SYSTEM

10-A. Dizziness and Vertigo

Dizziness

Hyperventilation
Anxiety, psychosomatic causes
Hypoxia
Metabolic or endocrine disorder
Anemia
Infection (e.g., septicemia)
Visual disturbances
    Incorrect spectacles
    Sudden extraocular muscle paresthesia with diplopia
Hypotension (especially orthostatic) (see 2-J)
Hypertension (see 2-D)
Cardiac arrhythmia or collapse (see 2-N)
Peripheral neuropathy (see 10-N)
Myelopathy (e.g., cervical spondyloses)
Concussion or other significant cerebral insult
Aging (presbycusis or presbyastasis)
Syncope of any cause (e.g., aortic stenosis) (see 10-D)
Drugs

True Vertigo

Infection
    Labyrinthitis (bacterial, viral, syphilitic)
    Chronic otitis media with middle ear fistula

- Vestibular neuronitis or neuropathy
- Herpes zoster oticus

Vascular disorders
- Vertebrobasilar insufficiency or occlusion
- Vascular malformations
- Labyrinthine or internal auditory artery occlusion or spasm
- Migraine
- Hemorrhage into labyrinthine system, brainstem, or cerebellum (e.g., secondary to bleeding diathesis, leukemia, hypertension)

Ménière disease

Benign positional vertigo of Bárány

Drugs and toxins
- Alcohol
- Quinine
- Aminoglycoside antibiotics (especially streptomycin, gentamicin)
- Salicylates
- Benzene
- Arsenic
- Arsine

Trauma
- Temporal bone fracture
- Labyrinthine concussion
- Postsurgical (inner ear area)
- Perilymphatic fistula

Tumor, especially:
- Acoustic neuroma
- Cholesteatoma
- Epidermoid carcinoma
- Metastatic carcinoma (especially breast, kidney, lung, stomach)
- Glomus body tumor

Other
- Unusual head or neck positions including craniovertebral junction disorders
- Cerumen impaction
- Motion sickness
- Space sickness
- Multiple sclerosis
- Extraocular muscle palsy
- Syringobulbia
- Tabes dorsalis

Friedreich ataxia
Encephalitis
Seizure aura or temporal lobe seizure
Psychogenic

References

1. Deafness, dizziness, and disorders of equilibrium. See Bibliography, 2.
2. Daroff RB, Carlson MD. Syncope, faintness, dizziness and vertigo. See Bibliography, 1.

10-B. Headache and Facial Pain

Muscle contraction (tension)
Migraine
Cluster (histamine) headache
Idiopathic
Nonmigrainous causes
Effort (physical activity)
Vasomotor rhinitis
Coital
Cough (e.g., Arnold-Chiari syndrome)
Cold stimulus
Fever, infectious (especially influenza, Q-fever)
Hypertension, especially "malignant"
Hypotension
Hypoxia or hypercapnia, or both (e.g., chronic obstructive pulmonary disease, pulmonary infiltrative disease, sleep apnea syndrome, high altitude) (see 11-M)
Anemia
Atypical angina
Postseizure
Post–lumbar puncture
Endocrine causes
Hypoglycemia
Hypothyroidism
Hyperthyroidism
Adrenal insufficiency
Premenstrual syndrome
Polycystic ovary syndrome
Drugs and toxins
Erectile dysfunction agents
Theophylline

- Caffeine and caffeine withdrawal
- Nitrates
- Nitrites (e.g., hot dogs)
- Dextroamphetamines
- Ephedrine
- Oral contraceptives
- Monoamine oxidase inhibitors plus catecholamines
- Monosodium glutamate (MSG)
- Histamine
- Steroid, alcohol, and other substance withdrawal
- Disulfiram (Antabuse) plus alcohol
- Lead
- Benzene
- Carbon monoxide
- Carbon tetrachloride
- Insecticides
- Dialysis

Intracranial causes

- Acute ischemic cerebrovascular disorder
- Intracranial hemorrhage
- Tumor
- Unruptured arteriovenous malformation
- Cerebral venous thrombosis
- Aneurysm (with or without hemorrhage)
- Epi- or subdural hematoma
- Encephalitis, brain abscess
- Pseudotumor cerebri
- Posttraumatic
- High or low cerebrospinal fluid (CSF) pressure
- Related to intrathecal injections
- Pituitary apoplexy or adenoma
- Other lesions (e.g., sarcoidosis)
- Arnold-Chiari malformation
- Meningeal irritation or inflammation
- Infection (e.g., bacterial, viral, tuberculous, fungal)
- Carcinomatous infiltration
- Intrathecal injection
- Postsubarachnoid hemorrhage
- Vasculitis (e.g., polyarteritis nodosa)
- Cranial and neck causes
  - Cranial bone lesions
  - Nose (e.g., craniopharyngioma)

- Sinuses (trauma, inflammation)
- Ears (external, middle, internal)
- Eyes (inflammation, trauma, increased intraocular pressure, poor refraction)
- Teeth, jaws (infection, trauma, temporomandibular joint malocclusion)
- Cervical spine, ligaments, muscles (e.g., trauma, cervical spondylosis, ankylosing spondylitis, tumor)
- Temporal arteritis

Psychogenic, psychiatric (e.g., depression)
Systemic diseases
- Infectious mononucleosis
- Systemic lupus erythematosus
- Hashimoto thyroiditis
- Inflammatory bowel disease
- Acquired immunodeficiency syndrome (AIDS)–related illnesses
- Erythrocyanotic headache
  - Mastocytosis
  - Carcinoid tumors
  - Serotonin secretory tumor
  - Some pancreatic islet cell tumors
  - Pheochromocytoma

Facial pain
- Trigeminal neuralgia
- Raeder paratrigeminal syndrome
- Glossopharyngeal neuralgia
- Herpes zoster
- Tolosa-Hunt syndrome
- Temporomandibular joint pain
- Migrainous neuralgia
- Dental, sinus, or nasal pain
- Trochlear pain
- Carotidynia
- Otalgia, occipital neuralgia

Atypical facial pain
- Burning mouth syndrome
- Neck-tongue syndrome
- Reflex sympathetic dystrophy (RSD)
- Superolaryngeal neuralgia
- Nervus intermedius neuralgia
- Third occipital nerve headache
- Idiopathic

References

1. Headache and other craniofacial pains. See Bibliography, 2.
2. Raskin NH. Headache. See Bibliography, 1.
3. Raskin NH, Green MW. Headache. See Bibliography, 3.

10-C. Paresthesias

Peripheral neuropathy (see 10-N), especially associated with:
- Diabetes mellitus
- Amyloid
- Alcoholism
- Carcinomatosis
- Thiamine deficiency
- Paclitaxel and docetaxel

Peripheral nerve entrapment, compression, trauma (e.g., ulnar nerve compression, thoracic duct outlet syndrome, carpal tunnel syndrome) (see 10-O)

Atherosclerotic peripheral vascular disease

Spinal cord disease
- Spinal cord or nerve root compression
- Multiple sclerosis
- Tabes dorsalis
- Subacute combined degeneration of spinal cord (pernicious anemia, vitamin B_{12} deficiency)
- Strachan syndrome

Cortical or thalamic lesions

Metabolic disturbance
- Hypocalcemia
- Respiratory alkalosis
- Hemodialysis

References

1. Paresthesias, pain and dysesthesias. See Bibliography, 2.
2. Rowland LP. Diagnosis of pain and paresthesia, p. 29. See Bibliography, 3.

10-D. Syncope

Neurologic or Mechanical Causes, or Both

Mediated by vagal stimulation or autonomic insufficiency, or both
- Vasovagal reaction (often associated with strong emotion or pain)

- Prolonged recumbency or inactivity
- Peripheral neuropathy with autonomic involvement (e.g., diabetes, amyloidosis, tabes dorsalis, Guillain-Barré syndrome) (see 10-N)
- Drugs (e.g., nitrates, antihypertensive agents, ganglionic blockers, alcohol)
- Carotid sinus syncope
- Severe pain
- Swallow syncope
- Stretch syncope
- Bowel stimulation or defecation syncope
- Airway stimulation (e.g., suctioning)
- Eyeball pressure
- Glossopharyngeal neuralgia
- Syringomyelia
- Shy-Drager syndrome
- Sympathectomy
- Primary autonomic insufficiency
- Parkinson disease

Seizure
Head or spinal cord trauma
Reduced venous return to heart
- Hypovolemia
- Hypotension (especially orthostatic) (see 2-J)
- Valsalva maneuver
- Cough
- Voluntary forced expiration against closed glottis
- Weight lifting
- Micturition

Cardiopulmonary Causes

Cardiac arrhythmias (see 2-N)
- Bradyarrhythmias (e.g., sick sinus syndrome)
- Tachyarrhythmias (especially ventricular fibrillation, ventricular tachycardia, paroxysmal atrial tachycardia)
- Atrioventricular block

Pulmonary embolism (submassive or massive)
Myocardial infarction with cardiogenic shock
Pericardial tamponade
Aortic stenosis
Pulmonic stenosis
Primary pulmonary hypertension

Congenital heart disease
Cardiomyopathies (see 2-G)
Shock (see 2-J)
Atrial myxoma or thrombus
Prosthetic valve thrombosis or obstruction

Cerebrovascular Causes (see 10-L)

Atherosclerotic disease of carotid and/or cerebral vessels
(especially vertebral-basilar insufficiency)
Subclavian steal
Takayasu or other arteritis
Hypertensive encephalopathy
Cervical spine abnormalities (e.g., cervical spondylosis)
Intracerebral or subarachnoid hemorrhage

Metabolic Causes

Anemia
Hypoxia
Hyperventilation
Hypoglycemia
Adrenal insufficiency
Heat stroke
Other severe metabolic derangements

Psychological Causes

Anxiety, hysteria

Unknown

References

1. Hirsch L J, Ziegler DK, Pedley TA. Syncope, seizures and their mimics, p. 13. See Bibliography, 3.
2. Faintness and syncope. See Bibliography, 2.

10-E. Deafness

Sensorineural (Inner Ear)

Aging (presbycusis)
Prolonged exposure to loud noise
Drugs
- Salicylates
- Aminoglycoside antibiotics (especially neomycin, amikacin)
- Erythromycin (intravenous)
- Furosemide
- Quinine

- Cisplatin, carboplatin
- Vancomycin (intravenous)

Infection
- Meningitis
- Chronic middle or inner ear infection
- Labyrinthitis
  - Bacterial
  - Viral (e.g., mumps)
  - Syphilis (usually congenital)
- Herpes zoster oticus
- Measles vaccination
- Scarlet fever
- *Mycoplasma pneumoniae* infection

Autoimmune disease (e.g., polyarteritis nodosa, Cogan syndrome)
Ménière disease
Fractures of temporal bone
Cochlear otosclerosis
Tumor or infection of eighth nerve or cerebellopontine angle
- Acoustic neuroma
- Cholesteatoma
- Lymphoma
- Carcinoma

Eighth nerve infarction
Multiple sclerosis
Sarcoidosis
Meningeal hemosiderosis
Vogt-Koyanagi-Harada disease
Postoperative [e.g., post–coronary artery bypass graft (CABG)]
Hereditary or congenital causes (e.g., congenital rubella, Alport syndrome)
Any central auditory pathway lesion (e.g., small strokes, multiple sclerosis)

Conductive

Cerumen impaction and foreign bodies
Otosclerosis
Eustachian tube obstruction
Chronic otitis media, cholesteatoma
Trauma (including temporal bone fracture, bleeding into middle ear)
Mucopolysaccharidoses
Neoplasm
Central (e.g., temporal lobe disease)

Hysterical

References

1. Deafness, dizziness, and disorders of equilibrium. See Bibliography, 2.
2. Storper IS. Dizziness and hearing loss, p. 32. See Bibliography, 3.

10-F. Ataxia

Symmetric and Progressive Cerebellar Signs

Acute (hours to days)
- Toxic
  - Paclitaxel, docetaxel
  - Alcohol
  - Fluorouracil
  - Lithium
  - Phenytoin
  - Barbiturates
  - Carbamazepine
- Heatstroke
- Viral cerebellitis
- Seizure disorder
- Postinfection syndrome
- Hypoglycemia
- Hyponatremia
- Hypoxic encephalopathy
- Cranial trauma

Subacute (days to weeks)
- Toxic
  - Arsenic-bismuth
  - Mercury
  - Lead
  - Glue and paint sniffing
  - Toluene exposure
  - Spray painting
  - Chemotherapeutics
  - Thallium
  - Organophosphates
- Alcoholic nutritional (e.g., vitamin B_1 and B_{12} deficiency)
- Lyme disease
- Miscellaneous infections (e.g., viral, toxoplasmosis)

Chronic (months to years)
- Prion disorder (e.g., contaminated growth hormone)
- Paraneoplastic syndrome

Hypothyroidism
Anti-gliadin antibody syndrome
Tabes dorsalis
Inherited ataxias
Meningovascular syphilis
Vitamin E deficiency
Phenytoin toxicity
Immune mediated (e.g., gluten-sensitive enteropathy)

Focal and Ipsilateral Cerebellar Signs

Acute (hours to days)
Cerebellar hemorrhage
Thrombosis or embolism
Epi- or subdural hematoma
Infarction
Vasculitis
Cerebellar abscess
Subacute (days to weeks)
Acute multiple sclerosis
Primary or metastatic neoplasm
AIDS–related progressive multifocal leukoencephalopathy or lymphoma
Chronic (months to years)
Stable gliosis due to stroke or demyelinating plaque
Dandy-Walker or Arnold-Chiari malformations

References

1. Bressman SB, Saunders-Pullman R J, Rosenberg RN. Hereditary ataxias, p. 783. See Bibliography, 3.
2. Rosenberg AN. Ataxic disorders. See Bibliography, 1.

10-G. Acute Confusional State or Coma, or Both

Usually No Lateralizing Signs, Normal Brainstem Reflexes

Drug withdrawal after chronic intoxication, especially:
Alcohol
Barbiturates
Other sedatives
Drug intoxication, especially:
Atropine
Amphetamines

- Barbiturates and other neuroleptics
- Bromides
- Caffeine
- Carbon monoxide
- Corticosteroids
- Lithium
- Metoclopramide
- Narcotics
- Scopolamine
- Tricyclic antidepressants

Infectious illness, especially:

- Septicemia
- Meningitis
- Pneumonia
- Typhoid fever
- Creutzfeldt-Jakob disease (CJD) (late stages)
- Rheumatic fever
- Progressive multifocal leukoencephalopathy

Central nervous system disorders

- Subdural hematoma
- Cerebrovascular disease (especially involving parietal or temporal lobes or upper brainstem)
- Viral encephalitis (nonherpetic)
- Subarachnoid hemorrhage
- Acute hydrocephalus
- Head trauma (e.g., concussion)
- Seizures and postictal state
- Fat embolism
- Migraine
- Primary neuronal or glial disorders (e.g., CJD)
- Carcinomatosis meningitis
- Acute toxic encephalopathy (e.g., Reye syndrome)

Hysterical coma or catatonia

Metabolic causes

- Pancreatitis
- Hyperviscosity syndrome
- Adrenal insufficiency
- Hyponatremia or hypernatremia
- Hypocalcemia or hypercalcemia
- Hypomagnesemia or hypermagnesemia
- Hypophosphatemia or hyperphosphatemia
- Hypokalemia or hyperkalemia
- Hypoxia (e.g., postresuscitative)

Hypercarbia
Congestive heart failure, shock, and other hypoperfusion states (see 2-J)
Hypoglycemia or hyperglycemia
Hepatic encephalopathy
Vitamin or other nutritional deficiency
Uremia
Hypothyroidism or hyperthyroidism
Wernicke disease
Porphyria
Severe metabolic acidosis or alkalosis (e.g., methanol or ethylene glycol)
Severe hyperthermia or hypothermia
Hypo-osmolality or hyperosmolality
Hypertensive encephalopathy
Febrile illness
Acute psychosis (e.g., postoperative, postpartum)
Pre-existing dementia with superimposed stress (see 10-H)

Usually with Lateralizing Signs, and/or Abnormal Brainstem Reflexes

Hemorrhage, intracerebral, cerebellar, or pontine
Large cerebral, thalamic, cerebellar, or brainstem infarction with edema (e.g., basilar artery thrombosis)
Herpes virus encephalitis
Fat embolism
Subdural or epidural hematoma or empyema
Tumor (especially with edema)
Brain abscess with edema
Vasculitis with infarction
Metabolic encephalopathy with pre-existing focal lesion
Pituitary apoplexy
Thrombotic thrombocytopenic purpura (TTP)
Focal seizure or postictal state
Intravascular lymphoma
Acute hemorrhagic leukoencephalitis
Contusion, head trauma
Demyelination
Encephalitis (e.g., herpes)
Migraine of basilar artery
Multiple intracerebral artery emboli due to infective or marantic endocarditis
Severe drug overdose

References

1. Coma and related disorders of consciousness: introduction. See Bibliography, 2.
2. Ropper AH. Acute confusional states and coma. See Bibliography, 1.

10-H. Dementia[1]

Degenerative diseases
- Alzheimer disease
- Cerebral arteriosclerosis, multiple infarct dementia
- Binswanger dementia
- Pick disease (frontal temporal dementia)
- Parkinson disease
- Korsakoff's psychosis
- Demyelinating disease [e.g., multiple sclerosis, Schilder disease (diffuse cerebral sclerosis)]
- Amyotrophic lateral sclerosis (ALS)
- Progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome)
- Dementia with Lewy bodies
- Shy-Drager syndrome
- Cortical basal degeneration
- Parkinson dementia complex of Guam

Metabolic causes
- Hypoxic encephalopathy
- Pulmonary, renal, or hepatic failure
- Mitochondrial encephalopathies
- Hypoglycemia
- Hypocalcemia (e.g., hypoparathyroidism)
- Pernicious anemia, subacute combined degeneration of the spinal cord
- Heavy metal intoxication
- Pellagra
- Myxedema
- Cushing disease and adrenal insufficiency
- Chronic barbiturate intoxication
- Bromide intoxication
- Dialysis dementia
- Other drugs and medications

Infectious causes
- Brain abscess
- Chronic meningoencephalitis (e.g., cryptococcosis, neurosyphilis)

- Viral encephalitis (especially herpes simplex)
- AIDS
- Progressive multifocal leukoencephalopathy
- CJD and other prion disorders
- Subacute sclerosing panencephalitis (SSPE)

Intracranial tumor
Sarcoidosis
Head trauma (e.g., contusion, hemorrhage, subdural hematoma)
Whipple disease
Acute intermittent porphyria
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Paraneoplastic dementia
Recurrent, nonconvulsive seizures
Vasculitis
Myoclonic epilepsy
Normal-pressure hydrocephalus
Hereditary diseases

- Huntington chorea
- Wilson and Leigh disease
- Mitochondrial mutations
- Lipid storage diseases (e.g., Tay-Sachs, leukodystrophies)
- Mucopolysaccharidoses
- Hereditary ataxia (some)
- Adult Down syndrome with Alzheimer dementia

Pseudodementias

- Depression
- Hypomania
- Schizophrenia
- Hysteria

References

1. Bird TD. Alzheimer's disease and other dementias: introduction. See Bibliography, 1
2. Dementia and the amnesic (Korsakoff) syndrome with comments on the neurology of intelligence and memory. See Bibliography, 2.
3. Small SA, Mayeux R. Alzheimer disease and related dementias, p. 771. See Bibliography, 3.

[1]Deterioration of intellectual and cognitive functions with little or no disturbance of consciousness or perception.

10-I. Tremor

Tremor at rest (present at rest, decreased with movement)
- Parkinson disease
- Postencephalitic parkinsonism
- Wilson disease
- Phenothiazines (tardive dyskinesia)
- Metoclopramide
- Selective serotonin reuptake inhibitor (SSRI) antidepressants
- Brain tumor
- Mercury poisoning

Action tremor (present with movement, decreased at rest)
- Physiologic (anxiety, fatigue)
- Essential (senile or familial, or both)
- Cerebellar disease
- Withdrawal from alcohol or opiates, barbiturates, benzodiazepines
- Charcot-Marie-Tooth disease
- Orthostatic tremor
- Meningoencephalitis (e.g., viral, paretic neurosyphilis)
- Hyperthyroidism
- Fever
- Pheochromocytoma
- Hypoglycemia
- Parkinson disease (rarely)
- Carcinoid syndrome
- Dystonic tremor
- Drugs
  - Bromide and bismuth intoxications
  - Bronchodilators, beta-agonists
  - Lithium
  - Steroids
  - Thyroid preparations
  - Tricyclic antidepressants
  - Valproic acid
  - Xanthines (e.g., coffee, tea)

Ataxic or intension tremor (increased at terminal phase of voluntary movement) (see 10-F)
- Cerebellar disease
- Multiple sclerosis
- Vascular midbrain and subthalamic lesions
- Polyneuropathy

References

1. Delong MR, Juncos JL. Parkinson's disease and other movement disorders. See Bibliography, 1.
2. Fahn S. Involuntary movements, p. 48. See Bibliography, 3.
3. Tremor, myoclonus, focal dystonias, and tics. See Bibliography, 2.

10-J. Choreoathetosis

Hereditary diseases, especially:
- Wilson disease and variants
- Huntington disease and variants (HDL 1-3)
- Neuroacanthocytosis
- Ataxia telangiectasia
- Lesch-Nyhan disease
- Dentatorubropallidoluysian atrophy
- Lipid storage disease (e.g., Niemann-Pick)
- Dystonia musculorum deformans
- Hallervorden-Spatz disease
- Leigh disease
- Kufs disease
- Ataxia telangiectasia
- Hereditary nonprogressive chorea

Drugs, especially:
- Anticholinergics
- "Atypical" antipsychotics (e.g., clozapine, risperidone, and dopamine agonists such as bromocriptine)
- Cocaine
- Dihydroxyphenylalanine
- Estrogens (e.g., oral contraceptives)
- Haloperidol
- L-Dopa
- Phenothiazines
- Phenytoin

Postinfectious
- Rheumatic fever (Sydenham chorea)
- Diphtheria
- Rubella
- Pertussis
- Encephalitis

Pregnancy (chorea gravidarum)
Multiple sclerosis

Hypoxic encephalopathy
Hyperosmolar nonketotic hyperglycemic encephalopathy
Senile essential chorea
"Postpump" after cardiac surgery
Hypoparathyroidism
Hyperthyroidism
Non-Wilsonian hepatocerebral degeneration
    (posthepatic coma)
AIDS
    Toxoplasmosis
    Lymphoma
    Progressive multifocal leukoencephalopathy
Paraneoplastic or neoplastic
Lupus erythematosus
Periarteritis nodosa
Antiphospholipid syndrome
Acute disseminated encephalomyelitis (postinfectious,
    postvaccinal)
Corticostriatospinal degeneration
Subthalamic infarct or hemorrhage (hemiballism)
Polycythemia vera

References

1. Fahn S. Sydenham and other forms of chorea, p. 807. See Bibliography, 3
2. Abnormalities of movement and posture due to disease of the basal ganglia. See Bibliography, 2.

10-K. Seizures (Exclude Syncope) (see 10-D)

Central Nervous System and Vascular Causes

Cerebrovascular disease (see 10-L)
    Old infarction
    Thrombosis
    Embolism
    Hemorrhage (intracerebral or subarachnoid)
    Epi- or subdural hematoma
    Vasculitis (especially lupus erythematosus, polyarteritis
        nodosa, mixed connective tissue disease)
    Thrombophlebitis
    Arteriovenous malformation
Brain tumor (especially metastatic tumor, meningioma,
    astrocytoma)

Cerebral infection
- Encephalitis
- Meningitis (especially bacterial)
- Brain abscess
- Human immunodeficiency virus (HIV) encephalopathy
- Subdural empyema
- Neurosyphilis
- CJD

Head trauma
Hypoxic encephalopathy
Reduced cerebral blood flow (e.g., hypotension, Stokes-Adams syndrome, carotid sinus syncope)
Hypertensive encephalopathy
Eclampsia
Alzheimer disease
Pick disease
Multiple sclerosis

Metabolic Causes

Fever
Alcohol withdrawal
Barbiturate withdrawal
Benzodiazepine reversal with flumazenil
Drugs, toxins
- Acyclovir, ganciclovir
- Amphetamines
- Arsenic
- Bupropion
- Camphor
- Cocaine
- Cyclosporine
- Cycloserine
- Digitalis
- Ergot
- Erythropoietin
- Heroin
- Interferon
- Isoniazid
- Lead
- Lidocaine
- Lithium
- Meperidine
- Mercury

- Methylphenidate
- Muromonab (OKT3)
- Penicillins and β-lactam antibiotics
- Phencyclidine
- Phenothiazines
- Physostigmine, other anticholinergics
- Quinolones
- Radiographic contrast
- Salicylates
- Strychnine
- Tacrolimus
- Thallium
- Theophylline
- Tramadol
- Tricyclic antidepressants
- Vincristine

Hypoglycemia
Hyperglycemia
Hyponatremia
Hypernatremia (or rapid correction of hypernatremia)
Hypocalcemia
Hypomagnesemia
Alkalosis (respiratory or metabolic)
Uremia
Dialysis disequilibrium
Hepatic failure
Reye syndrome
Thyrotoxicosis
Hypothyroidism
Pyridoxine deficiency
Pellagra

Congenital or Inherited Diseases

Congenital infection
- Toxoplasmosis
- Cytomegalovirus
- Syphilis
- Rubella (maternal)
- HIV

Neonatal hypoxia or trauma, kernicterus, or pyridoxine (B_6) deficiency
Down syndrome

Lipid storage disease (e.g., Gaucher disease)
Tuberous sclerosis
Sturge-Weber disease
Phenylketonuria
Acute intermittent porphyria
Argininosuccinic aciduria

Idiopathic Epilepsy

Generalized
- Tonic-clonic (grand mal)
- Absence (petit mal)
  - With loss of consciousness only
  - Complex, with brief tonic, clonic, or automatic movements
- Lennox-Gastaut syndrome
- Juvenile myoclonic epilepsy
- Infantile spasms (West syndrome)
- Atonic

Partial or focal
- Simple (without loss of consciousness or alteration in psychic functioning)
  - Motor—frontal lobe origin (e.g., Jacksonian)
  - Somatosensory or special sensory (e.g., olfactory)
  - Autonomic (e.g., flushing)
  - Pure psychic (e.g., hallucination)
- Complex (with impaired consciousness)
  - Beginning as simple partial seizure and progressing to impairment of consciousness
  - With impairment of consciousness at onset
  - With automatisms

Special epileptic syndromes
- Myoclonus and myoclonic seizures
- Reflex epilepsy
- Acquired aphasia with convulsive disorder
- Febrile and other seizures of childhood and infancy

Hysterical

References

1. Bazil CW, Morrell MJ, Pedley TA. Epilepsy, p. 990. See Bibliography, 3.
2. Lowenstein DH. Seizures and epilepsy. See Bibliography, 1.
3. Epilepsy and other seizure disorders. See Bibliography, 2.

10-L. Cerebrovascular Disease

Thrombosis or Vascular Occlusion, or Both

Thrombosis, atherosclerotic
Hypotension in presence of atherosclerotic carotid disease
    (e.g., hypovolemia, Stokes-Adams attack, myocardial infarction)
Infectious
    Subacute bacterial meningitis
    Meningovascular syphilis
    Tuberculous meningitis
    Fungal meningitis
    Protozoan and parasitic meningitis (e.g., malaria, trichinosis, schistosomiasis)
    HIV related
Noninfectious (e.g., vasculitis)
    Systemic lupus erythematosus
    Polyarteritis nodosa
    Sjögren syndrome
    Necrotizing arteritis
    Granulomatous arteritis (e.g., Wegener)
    Lymphomatoid granulomatosis
    Takayasu disease
    Behçet syndrome
Cerebral thrombophlebitis and/or venous sinus thrombosis
    (usually associated with infection of ear, sinus, face, or meninges)
Oral contraceptives
Hematologic disorders
    Sickle cell disease
    Factor C or S deficiency
    Polycythemia vera
    TTP
    Thrombocytosis
    Hyperproteinemic or hyperviscosity states
    Hypercoagulable state
    Antiphospholipid antibodies
    Diffuse intravascular coagulation
Carotid artery trauma
Radiation
Closed head trauma
Eclampsia
Postarteriographic

Cocaine, heroin, and amphetamine use
Dissecting aneurysm of carotid artery (e.g., secondary to cystic medial necrosis or dissecting aortic aneurysm)
Pressure secondary to intracerebral hematoma
Migraine syndrome
Fibromuscular dysplasia
Fabry disease
Homocystinuria
Moyamoya disease
Binswanger disease
Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS)

Embolism

Atrial arrhythmias (especially atrial fibrillation—usually with rheumatic valvular or atherosclerotic cardiovascular disease)
Rheumatic and other valvular heart disease, especially mitral stenosis
Myocardial infarction with mural thrombus
Cardiac surgery complications
Prosthetic heart valve or other intracardiac device
Cardiomyopathy (see 2-G)
Endocarditis
  Bacterial
  Nonbacterial (e.g., associated with carcinomatosis or systemic lupus erythematosus)
Congenital heart disease
Atherosclerotic embolism from other arteries
  Aorta or carotid arteries (e.g., secondary to carotid massage or arteriography)
  Vertebral or basilar arteries
Pulmonary vein thrombosis (especially septic or tumor emboli)
Fat embolism
Tumor embolism
Air embolism
Venous thromboembolism with cardiac or pulmonary right-to-left shunt (paradoxical embolism)
Left atrial myxoma
Trichinosis

Hemorrhage

Hypertension (including hypertensive encephalopathy)
Aneurysm (ruptured or unruptured)
    Saccular ("berry")
    Fusiform (atherosclerotic)
    Mycotic
Arteriovenous malformation, ruptured or unruptured
Cavernous angioma
Hemorrhagic disorders (e.g., thrombocytopenia, thrombocytosis, coagulopathy, disseminated intravascular coagulation, anticoagulant therapy)
Intracranial trauma (e.g., acute extradural or subdural hematoma, intracerebral hemorrhage)
Postneurosurgical
Hemorrhage into tumor
Dural arteriovenous fistula
Hemorrhagic infarction
Connective tissue disease (especially lupus erythematosus and polyarteritis nodosa)
Cerebral amyloid angiopathy
Moyamoya disease

References

1. Cerebrovascular diseases. See Bibliography, 2.
2. Sacco RL. Pathogenesis, classification, and epidemiology of cerebrovascular disease, p. 275. See Bibliography, 3.
3. Smith WS, Johnston C, Easton JD. Cerebrovascular diseases: introduction. See Bibliography, 1.

10-M. Weakness, Paresis, and Paralysis

Acute Paraparesis or Paraplegia

Cerebral
    Anterior cerebral artery ischemia
    Superior sagittal sinus thrombosis
    Central venous thrombosis
    Acute hydrocephalus
Spinal cord disease
    Hemorrhage (e.g., warfarin)
    Embolism or thrombosis (e.g., decompression sickness)
    Trauma
        Blunt
        Penetrating

- Electrical
- Irradiation
- Infarct (e.g., aortic dissection)
- Myelitis of any cause (e.g., infection)
- Infection (e.g., epidural abscess, polio)
- Tumor
- Herniated disc (e.g., cauda equina syndrome)
- Arteriovenous malformation or other vascular anomaly

Subacute-Chronic

- Guillain-Barré syndrome
- Myopathy, including rhabdomyolysis
- Spondylosis
- ALS
- Other peripheral neuropathies (see 10-N)
- Multiple sclerosis
- Subacute combined degeneration (vitamin B_{12} deficiency)
- Parasagittal meningioma
- Chronic hydrocephalus

Generalized Weakness

- Tetany
- Tetanus
- Botulism
- Black widow spider bite
- Metabolic
  - Thyroid and adrenal dysfunction
  - Hypo- and hypercalcemia
  - Hypo- and hyperkalemia
  - Hypo- and hypernatremia
  - Hypomagnesemia
  - Hypophosphatemia
- Major organ failure, especially:
  - Cardiac
  - Pulmonary
  - Hepatic
  - Renal
- Multiple sclerosis
- Parkinson disease
- Myasthenia gravis (episodic)
- Lambert-Eaton myasthenic syndrome
- Transient ischemic attack of brainstem
- Transient global cerebral ischemia

Metabolic muscle disease
Depression
Chronic fatigue syndrome
Psychogenic
Malingering
Deconditioning
Drugs (e.g., beta-blocker)

Hemiplegia or Hemiparesis

Cerebrovascular accident (see 10-L)
- Thrombosis
- Embolism
- Hemorrhage
- Arteriovenous malformation

Migraine syndrome
Head trauma (e.g., brain contusion, subdural or epidural hematoma)
Todd paralysis
Brain tumor (primary or metastatic)
Infection (e.g., brain abscess, encephalitis, subdural empyema, meningitis)
Nonketotic hyperosmolar coma
Hypertensive encephalopathy
Vasculitis
Demyelinating disease (e.g., acute necrotizing myelitis)
AIDS neurologic syndromes (see 12-H)
Hereditary disease (e.g., leukodystrophies)
Congenital, perinatal injury
Sarcoidosis
Neurofibromatosis and other unusual lesions

References

1. Motor paralysis. See Bibliography, 2.
2. Olney RK. Weakness, disorders of movement, and imbalance: introduction. See Bibliography, 1.
3. Rowland LP. Syndromes caused by weak muscles, p. 52. See Bibliography, 3.

10-N. Peripheral Neuropathy

Primary Motor, Acute (May Have Sensory Involvement)

Guillain-Barré syndrome
Acute pandysautonomic neuropathy
Infectious mononucleosis

Porphyria (three types, rare)
Diphtheria
Arsenic
Toxins (e.g., organophosphorous compounds, inhalants, thallium, and vaccine for rabies, typhoid, smallpox)
Tick paralysis
Polio
Lambert-Eaton myasthenic syndrome
Hereditary spinal-muscular atrophy
Hexosaminidase A deficiency
West Nile virus and enterovirus
Critical illness
Vasculitis
Paraneoplastic syndrome
ALS (lower motor neurons)

Sensorimotor, Subacute

Alcoholism with associated nutritional deficiency
Beriberi and other vitamin deficiencies (B_2, B_3, B_6, B_{12}, E)
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
Diphtheria
Critical illness
Drugs, toxins, especially
- Acrylamide
- Allopurinol
- Amiodarone
- Amitriptyline
- Arsenic
- Carbon monoxide
- Carboplatin and cisplatin
- Chloramphenicol
- Clioquinol
- Colchicine
- Dapsone
- Didanosine
- Diketonic hevacarbon (solvent)
- Disulfiram
- Docetaxel
- Doxorubicin
- Ethambutol
- Ethionamide

- Flecainide
- Gold
- Hydralazine
- Indomethacin
- Industrial solvents (e.g., nitrous and ethylene oxides)
- Isoniazid
- L-Tryptophan
- Lead, inorganic
- Lithium
- Mercury
- Metronidazole (chronic use)
- Misonidazole
- Neuromuscular blockers (prolonged use)
- Nitrofurantoin
- Nucleosides (ddC, ddI)
- Organophosphates
- Paclitaxel
- Pantothenic acid
- Perhexiline maleate
- Phenytoin
- Platinum
- Podophyllin
- Pyridoxine
- Sodium cyanate
- Statins
- Stavudine
- Suramin
- Thalidomide
- Thallium
- Vincristine
- Zalcitabine

Diabetes mellitus
Hypoglycemia, especially with insulinoma
Spondylotic neoplastic polyradiculopathy
Atherosclerosis
Vasculitis (e.g., polyarteritis nodosa, systemic lupus erythematosus, Wegener granulomatosis, rheumatoid arthritis)
Sarcoidosis
Paraneoplastic, including lymphoid disorders (e.g., Castleman disease)
Subacute asymmetric idiopathic polyneuritis

Nonsystemic vasculitic neuropathy
Subacute inflammatory demyelinating polyneuropathy

Sensorimotor, Chronic
Carcinoma, lymphoma, leukemia
Amyloidosis
Paraproteinemia (especially multiple myeloma, macroglobulinemia, cryoglobulinemia)
Uremia
Vasculitis (e.g., polyarteritis nodosa)
Beriberi
Alcoholism
Drugs, toxins
Burning feet syndrome
Diabetes mellitus
Lyme disease
Mixed cryoglobulinemia
HIV infection
Polycythemia vera (rare)
Ischemia
Herpes zoster
Sjögren syndrome
Sarcoidosis
Connective tissue disease (especially systemic lupus erythematosus)
Chronic obstructive pulmonary disease (severe)
Leprous neuritis
Acromegaly
Primary biliary cirrhosis (rare)
Myxedema
Celiac sprue
CIDP
Liver disease (rare)
Major hereditary diseases
- Charcot-Marie-Tooth disease
- Hereditary sensory and autonomic neuropathies (e.g., Riley-Day syndrome)
- Dejerine-Sottas disease
- Hereditary neuropathy with lability to pressure palsies
- Refsum disease
- Familial amyloid
- Fabry disease
- Abetalipoproteinemia and Tangier disease

Metachromatic leukodystrophy
Ataxia telangiectasia

Autonomic Neuropathy

Diabetes
Autonomic paralysis of tetraplegia and paraplegia
Alcoholic
Peripheral neuropathy with dysautonomia (e.g., amyloidosis)
Post–thoracolumbar sympathectomy
Acute autonomic crisis (e.g., cocaine)
Guillain-Barré syndrome
Pandysautonomia
Lambert-Eaton myasthenic syndrome
Idiopathic orthostatic hypotension (IOH)
Horner and stellate ganglion syndromes

References

1. Disorders of the autonomic nervous system, respiration, and swallowing. See Bibliography, 2.
2. Asbury AK. Approach to the patient with peripheral neuropathy: introduction. See Bibliography, 1.
3. Brannagan TH III, Weiner LH, Latov N. Acquired neuropathies, p. 748. See Bibliography, 3.

10-O. Carpal Tunnel Syndrome

Idiopathic
Fibrosis or tenosynovitis of flexor tendons
Fracture (e.g., Colles)
Occupational trauma (e.g., jackhammer or keyboard operation)
Degenerative arthritis
Wrist ganglion or benign tumor
Pregnancy
Congestive heart failure (with edema)
Amyloidosis (e.g., multiple myeloma)
Rheumatoid arthritis
Scleroderma
Systemic lupus erythematosus
Diabetes mellitus
Hypothyroidism

Tuberculosis, other granulomatous diseases (e.g., leprosy, sarcoidosis)
Gout
Paget disease
Acromegaly
Mucopolysaccharidoses
Eosinophilic fasciitis

References

1. Asbury AK. Mononeuropathy. See Bibliography, 1.
2. Diseases of the peripheral nerves. See Bibliography, 2.

10-P. Typical Cerebrospinal Fluid Characteristics in Various Diseases

Condition	Pressure (cm H_2O)	WBCs/mm^3	Predominant Type of Cells	Glucose (mg/dL)	Protein (mg/dL)	Other
Normal	5–20	<5	100% lymphocytes	50–75% of serum value	<50	
Meningitis						
Bacterial	Usually ↑	100–200,000	85–95% neutrophils	<40, or <40% of blood glucose	45–500	Positive bacterial culture, gram's stain, counter-immunoelectrophoresis, enzyme-linked immunosorbent assay, polymerase chain reaction (PCR) and others
Viral	Normal to ↑	10–500	Lymphocytes (sometimes neutrophils early)	Normal, occasionally ↓ in mumps and herpes simplex	50–200	Viral cultures sometimes positive

Tuberculosis	↑	50–500	Lymphocytes (occasionally neutrophils early)	<40	100–200	Positive mycobacterial culture or Ziehl–Neelsen stain, or both, positive PCR
Fungal (± abscess)	Normal to ↑	25–1,000	Lymphocytes	20–40	25–500+	Antibody, antigen, and fungal preps are often useful
Neurosyphilis (meningovascular or	Normal to ↑	200–3,000 (acute) 10–50 (chronic)	Lymphocytes	Normal	40–200	↑ γ-Globulins, positive serologic tests (VDRL test usually, fluorescent treponemal antibody absorption test)
Herpes encephalitis	Normal to ↑↑	20–1,000	Lymphocytes (neutrophils early)	Normal, sometimes ↓	50–100	RBCs, xanthochromia PCR for herpes, DNA sometimes positive, culture positive <10%

(continued)

10-P. Typical Cerebrospinal Fluid Characteristics in Various Diseases (continued)

Condition	Pressure (cm H_2O)	WBCs/mm^3	Predominant Type of Cells	Glucose (mg/dL)	Protein (mg/dL)	Other
Brain abscess[a]	↑ to ↑↑	65–300 (may be >50,000 if ruptured into ventricles)	10–80% neutrophils	Normal	45–200	Lumbar puncture usually contraindicated, cultures rarely positive
Neoplasm[a]	Usually ↑	<100	Lymphocytes	40–80	50–1,000	Positive cytology occasionally
Cerebral hemorrhage	Usually ↑	↑	Lymphocytes RBCs 50–200+, higher if ventricular rupture of blood	Normal, occasionally ↓	50–200	↑↑ RBCs, xanthochromia or gross blood
Guillain-Barré syndrome	Normal	Normal (sometimes 10–100 lymphocytes)	Lymphocytes	<80	50–1,000	Protein may be normal in first few days

Multiple sclerosis	Normal or ↑	<100 (usually <20)	Lymphocytes	Normal	<100	↑ γ-Globulins (>12% of total protein): ↑ myelin basic protein, oligoclonal bands may be present
Subarachnoid hemorrhage	↑	Slight increase in WBCs	RBCs >7,500 mm^3	Normal	50–4,000	Distinguish from "traumatic" tap by xanthochromia of spun specimen or clearing of blood in consecutive tubes

↓, decreased; ↑, increased; ↑↑, greatly increased; WBC, white blood cells; RBCs, red blood cells; VDRL, venereal disease research laboratory.

[a]If this diagnosis is suspected, lumbar puncture is contraindicated, at least until after computed tomography has been performed.

10-Q. Dermatome Chart

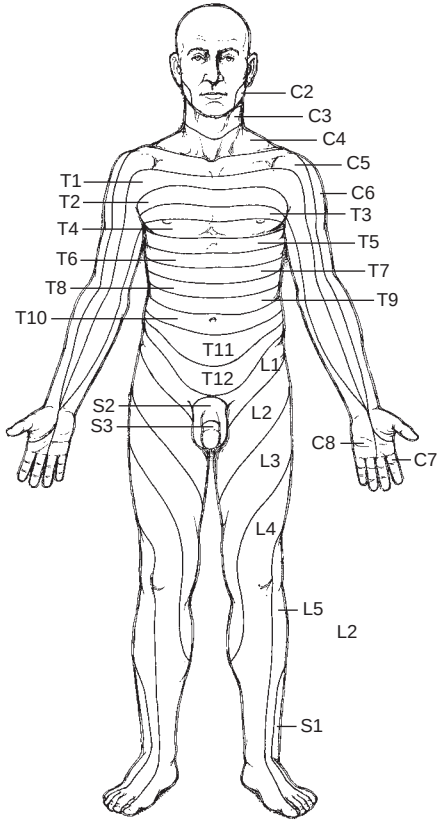

FIGURE 10-1. Dermatome chart. (From *Stedman's Medical Dictionary.* 27th ed. Baltimore: Lippincott Williams & Wilkins; 2000.)

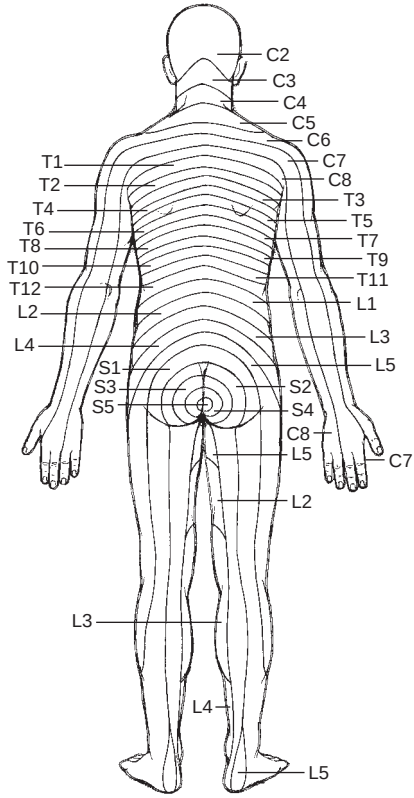

FIGURE 10-1. (continued)

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3. Rowland LP, ed. *Merritt's Textbook of Neurology*. 11th ed. Baltimore: Lippincott Williams & Wilkins; 2005.

11

RESPIRATORY SYSTEM

11-A. Cough

Acute

Viral upper respiratory infection
- Pharyngitis
- Rhinitis
- Tracheobronchitis
- Bronchiolitis

Gastroesophageal reflux

Bacterial and other infections
- Pneumonia
- Sinusitis, especially maxillary
- Lung abscess
- *Bordetella pertussis*

Asthma

Inhalation of irritants (environmental, occupational)
- Smoke/smog
- Noxious fumes
- Extremely hot or cold air

Pulmonary edema

Pulmonary embolism

Aspiration pneumonia

Foreign body inhalation

Laryngeal inflammation

External or middle ear disease
Acute pleural, pericardial, mediastinal, or diaphragmatic inflammation

Chronic

(May have more than one etiology)
Postnasal drip syndrome
- Perennial or seasonal allergic rhinitis
- Vasomotor rhinitis
- Chronic bacterial sinusitis
- Allergic fungal sinusitis (e.g., *Aspergillus* spp.)
- Nonallergic rhinitis
  - Medication abuse (legal or illegal)
  - Pregnancy
  - Environmental irritants

Asthma
Gastroesophageal reflux
Bronchiectasis
Neoplasms (especially endobronchial or laryngeal), malignant or benign
Lung abscess
Interstitial lung disease
Recurrent aspiration (hiatal hernia or achalasia)
Drug induced
- Angiotensin-converting enzyme (ACE) inhibitors
- Beta-blockers, selective and nonselective
- Amiodarone

Chronic pulmonary edema
Mitral stenosis
Psychogenic/habit cough
Chronic laryngeal inflammation or tumor
Chronic pneumonia, especially tuberculosis and fungal
Cystic fibrosis
External and middle ear disease, chronic
Bronchogenic/mediastinal cyst
Zenker diverticulum
Aortic aneurysm
Irritation of vagal afferent nerve
Osteophytes
Pacemaker wires
Chronic pleural, pericardial, mediastinal, or diaphragmatic inflammation

References

1. Tilles S. See Bibliography, 1.
2. Irwin RS. Diagnosis and management of cough. *Chest*. 2006;129:25S–27S.
3. Prakash U. Uncommon causes of cough. *Chest*. 2006;129:206S–219S.

11-B. Dyspnea

Acute

Pleuropulmonary causes
- Obstructive lung disease [chronic obstructive pulmonary disease (COPD) and asthma]
- Acute tracheobronchitis
- Pneumonitis
- Pulmonary edema and congestion
- Pulmonary thromboembolism/vasculitis
- Pneumothorax
- Pleurisy and/or pleural effusion
- Gastric or other fluid aspiration
- Noxious gas inhalation (including carbon monoxide)
- Upper airway obstruction/foreign body aspiration
- Collapse of lung segment(s)
- Angioedema
- Chest trauma-pulmonary contusion, rib fractures

Nonpulmonary causes
- Psychogenic causes (e.g., anxiety)
- Acute neuromuscular dysfunction
- Decreased inspired oxygen tension (e.g., at high altitude)
- Shock
- Fever
- Acute anemia
- Increased intracranial pressure
- Metabolic acidosis
- Cardiac tamponade
- Thoracic burn with eschar formation

Chronic

Pleuropulmonary causes
- Chronic obstructive diseases—emphysema, asthma
- Chronic bronchitis
- Cystic fibrosis

Pulmonary edema (see 11-L)
Interstitial fibrosis (any cause)
Chronic pneumonia
Pulmonary vascular disease
    Recurrent pulmonary emboli
    Pulmonary hypertension
    Arteriovenous malformation
Malignancy—primary lung tumors or metastatic disease to the lung
Respiratory muscle disease
    Phrenic nerve dysfunction
    Neuromuscular disease
        Guillain-Barré syndrome
        Myasthenia gravis
        Muscular dystrophy
        Poliomyelitis
Chest wall abnormalities
    Pectus excavatum
    Kyphoscoliosis
Pleural disease
    Effusion
    Fibrothorax
    Pulmonary or metastatic neoplasm
Bronchiectasis
Alveolar filling disease
    Lipoid pneumonia
    Pulmonary alveolar proteinosis
Lung resection
Upper airway obstruction
Nonpulmonary causes
    Anemia, abnormal hemoglobins
    Obesity
    Psychogenic disorders
    Abdominal mass (e.g., tumor, pregnancy)
    Ascites
    Metabolic acidosis
    Thyroid disease
    Arteriovenous shunt
    Congenital heart disease

References

1. Shiber J, Santana J. Dyspnea. *Med Clin North Am.* 2006;90:453–479.

2. Sarkar S, Amelung P. Evaluation of the dyspneic patient in the office. *Prim Care Clin Office Pract.* 2006;33:643–657.

11-C. Wheezing

Asthma

Allergic sensitization, viral trigger
Exercise or cold induced
Drug induced
- Aspirin, indomethacin
- Beta-blockers
- Sulfites, tartrazine
- Acetylcysteine

Other Etiologies

Anaphylaxis
Upper airway/tracheal obstruction
- Extrinsic
  - Thyroid enlargement, tumor, hemorrhage
  - Lymphoma
  - Edema of, or hemorrhage into, subcutaneous tissues of the neck
  - Retropharyngeal edema, hemorrhage, abscess
  - Mediastinal tumor or hemorrhage
  - Esophageal cancer
  - Vascular compression (aortic aneurysm, congenital anomalies)
- Intrinsic
  - Epiglottitis
  - Foreign body
  - Tracheal fracture, stricture, tumor, or tracheomalacia
  - Laryngeal tumor, trauma, edema, spasm
  - Vocal cord dysfunction or paralysis
  - Amyloidosis
- Functional
  - Laryngeal dyskinesia

Peripheral airway obstruction
- Bronchitis, acute or chronic
- Bronchiolitis
- Bronchiectasis
- Cystic fibrosis
- Pneumonia

Pulmonary embolism

Pulmonary edema (cardiogenic or noncardiogenic)
Aspiration of foreign body or gastric contents
Irritant inhalants (e.g., toluene, sulfur dioxide)
Pulmonary infiltrate with eosinophilia
    Löffler syndrome
    Tropical eosinophilia
    Chronic eosinophilic pneumonia
    Bronchopulmonary aspergillosis
    Polyarteritis nodosa
Angioedema
    Idiopathic
    Hereditary angioneurotic edema
Carcinoid syndrome

References

1. Tilles S. See Bibliography, 1.
2. Nowak R, Tokarski G. Chapter 27. See Bibliography, 2.
3. Mathur SK, Busse WW. Asthma: diagnosis and management. *Med Clin North Am*. 2006;90:39–60.

11-D. Hemoptysis[1]

Pseudohemoptysis

Blood of upper gastrointestinal origin
Upper airway lesions
Epistaxis
Gingival bleeding
Oropharyngeal carcinoma
Laryngeal carcinoma or other lesions
Hereditary hemorrhagic telangiectasia
Airway trauma

Tracheobronchial Sources

Bronchitis, acute or chronic
Bronchiectasis
Bronchogenic carcinoma
Bronchial adenoma
Foreign body
Endobronchial metastatic neoplasm
Bronchial trauma
Cystic fibrosis
Bronchiolithiasis
Amyloidosis

Pulmonary Parenchymal Sources

Pneumonia (bacterial, tuberculosis)
Pulmonary embolism/infarction
Neoplasm
Lung abscess
Fungal infections (especially aspergilloma)
Lung contusion or laceration
Goodpasture syndrome
Wegener granulomatosis
Idiopathic pulmonary hemosiderosis
Inhalation injury (toxic or heated gases)
Sequestration
Bronchogenic cyst
Parasitic infestation (e.g., *Paragonimus westermani*)
Pulmonary endometriosis
Pulmonary Kaposi sarcoma

Cardiac or Vascular Disorders

Pulmonary edema
Severe mitral stenosis
Aortic aneurysm
Primary pulmonary hypertension
Arteriovenous malformation
Eisenmenger syndrome
Pulmonary vasculitis
Collagen vascular diseases (lupus)
Behçet syndrome
Pulmonary veno-occlusive disease
Pulmonary telangiectasia

Hematologic Disorders

Coagulopathy, congenital or acquired (anticoagulant therapy)
Thrombocytopenia

References

1. Bidwell J, Pachner R. Hemoptysis: diagnosis and management. *Am Fam Physician*. 2005;72:1253–1260.
2. Hanley ME, Welsh CH. Hemoptysis. In: *Current Diagnosis and Treatment in Pulmonary Medicine*. New York: McGraw-Hill; 2003.

[1]Five percent to 15% of patients remain undiagnosed despite extensive evaluation.

11-E. Cyanosis[1]

Central Cyanosis

Arterial desaturation
- Decreased inspired oxygen tension, high altitude
- Pulmonary disease
  - Alveolar hypoventilation
  - Ventilation-perfusion mismatch
  - Impaired oxygen diffusion
- Anatomic (right to left) shunt
  - Congenital heart disease
  - Pulmonary arteriovenous fistulas
  - Other intrapulmonary shunts
- Hemoglobin abnormalities
  - Carbon monoxide intoxication
  - Cyanide toxicity
  - Sulfhemoglobinemia
  - Methemoglobinemia
    - Drug induced (e.g., lidocaine, dapsone, sulfonamides, benzocaine)
  - Hemoglobin with low affinity for oxygen (e.g., hemoglobin Kansas)
  - Hemoglobin M

Pseudocyanosis

Polycythemia vera
Argyria
Hemochromatosis

Peripheral Cyanosis

Reduced cardiac output, shock
Cold exposure (including Raynaud phenomenon)
Arterial obstruction
Venous stasis and/or obstruction

References

1. Bocock J, Kolodizwk J. Chapter 30. See Bibliography, 2.
2. Kasper D, et al. Hypoxia and cyanosis. In: *Harrison's Principles of Internal Medicine*. 16th ed. New York: McGraw-Hill; 2005.
3. Lichtman MA, et al. Methemoglobin and other causes of cyanosis. In: *Williams Hematology*. 7th ed. New York: McGraw-Hill; 2006.

[1]Indicates ≥5 g of unsaturated hemoglobin or ≥1.5 g of methemoglobin present.

11-F. Pleuritic Pain[1]

Chest Wall Disease

Bony thorax
- Costochondritis (Tietze syndrome)
- Rib fracture or tumor
- Fractured cartilage
- Periostitis or periosteal hematoma
- Xiphoidalgia
- Thoracic spondylitis due to arthritis, infection

Soft tissues
- Infection
- Muscle spasm (intercostals or pectoral)
- Myositis or fibromyositis

Neural structures
- Intercostal neuritis
- Herpes zoster
- Neurofibromatosis

Pleuropulmonary Disease[2]

Infectious pleuritis, especially viral
Pulmonary embolism and infarction
Pneumonia
Pneumothorax
Trauma
Neoplasm (primary or metastatic)
Immune-mediated disease
- Systemic lupus erythematosus
- Post–cardiac injury syndrome
- Rheumatoid disease
- Vasculitis
- Drug induced

Diaphragmatic irritation
- Pancreatitis
- Abscess (subphrenic, splenic, and hepatic)

Asbestosis
Uremic pleuritis, renal capsular hematoma
Radiation pleuritis
Familial polyserositis
Middle lobe syndrome

Mediastinal Disease

Pneumomediastinum
Mediastinitis
Esophageal perforation
Esophageal variceal sclerotherapy
Pericarditis
Tumor, primary or metastatic

References

1. English J, Leslie K. See Bibliography, 3.
2. Kass S, Williams PM, Reamy BV. Pleurisy. *Am Fam Physician*. 2007;75:1357–1364.
3. Butler K, Swencki S. Chest pain: a clinical assessment. *Radiol Clin North Am*. 2006;44:165–179.

[1]Pleuritic pain is defined as pain accentuated by breathing, coughing, or sneezing.

[2]Most of the disorders that cause exudative effusions also cause pleuritic pain. See next section for a more complete list.

11-G. Pleural Effusion: Exudate

Infection
- Bacterial
  - Empyema (see 11-J)
  - Parapneumonic effusion
- Tuberculosis
- Viral
- Fungal
- Parasitic (amebiasis, echinococcosis, paragonimiasis)
- Mycoplasma, actinomycosis, nocardiosis
- Rickettsiae (Q-fever)

Neoplasm
- Lung[1]
- Breast[1]
- Lymphoma, leukemia[1]
- Ovarian neoplasm (Meigs syndrome)
- Metastasis (sarcoma, melanoma)
- Kaposi sarcoma
- Primary pleural malignancy (mesothelioma)

Thromboembolic disease
- Pulmonary embolism
- Pulmonary infarction

- Immune-mediated diseases
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Churg-Strauss syndrome
  - Drug-induced lupus
  - Wegener granulomatosis
  - Sarcoidosis
  - Post–cardiac injury syndrome
  - Sjögren syndrome
  - Familial Mediterranean fever
- Intra-abdominal disorders
  - Pancreatitis
  - Esophageal perforation
  - Intra-abdominal abscesses (e.g., hepatic, splenic, subphrenic)
  - Esophageal variceal sclerotherapy
  - Post–abdominal surgery, postpartum state
- Drug-induced pleural disease
  - Nitrofurantoin
  - Amiodarone
  - Methotrexate
  - Interleukin-2
  - Ovarian hyperstimulation syndrome
- Inhalation of inorganic dusts (asbestosis)

Hemothorax

- Traumatic
  - Penetrating or nonpenetrating trauma
  - Iatrogenic
- Nontraumatic
  - Malignancy, especially metastatic
  - Anticoagulant therapy for pulmonary emboli
  - Spontaneous
    - Secondary to bleeding disorder (hemophilia, thrombocytopenia)
    - Rupture of intrathoracic vessel or aneurysm
    - Ruptured pancreatic pseudocyst
    - Thoracic endometriosis
    - Idiopathic
  - Pulmonary emboli
- Yellow nail syndrome
- Uremic pleuritis
- Radiation pleuritis

Myxedema
Spontaneous pneumothorax
Trapped lung
Postpartum pleural effusion
Amyloidosis
Ovarian hyperstimulation

Chylothorax

Traumatic
- Penetrating or nonpenetrating trauma
- Surgery, iatrogenic

Malignancy (causes 50% of chylothoraces)
- Lymphoma (accounts for 75% of malignant chylothoraces)
- Metastatic malignancy
- Kaposi sarcoma in acquired immunodeficiency syndrome (AIDS)

Thrombosis of superior vena cava/subclavian vein
Idiopathic
Congenital
Pulmonary lymphangioleiomyomatosis
Pseudochylothorax

References

1. English J, Leslie K. See Bibliography, 3.
2. Light R. See Bibliography, 4.
3. Light R. *Pleural Diseases*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2001.

[1]Causes 75% of malignant pleural effusions.

11-H. Pleural Effusion: Transudate

Cardiac disease
- Congestive heart failure
- Fluid overload
- Constrictive pericarditis
- Obstruction of superior vena cava or azygos vein

Renal disease
- Nephrotic syndrome
- Acute glomerulonephritis
- Urinary tract obstruction
- Peritoneal dialysis

Liver disease (cirrhosis with ascites)
Thromboembolic disease[1]
Meigs syndrome[1]
Myxedema[1]
Sarcoidosis
Severe malnutrition (with hypoalbuminemia)
Iatrogenic (e.g., venous catheter in pleural space)
After lung transplantation
Cerebrospinal fluid leak
    After ventriculopleural shunting
    After trauma or surgery to the thoracic spine

References

1. Light R. See Bibliography, 4.
2. Husain AN, Kumar V. Chapter 15. See Bibliography, 5.

[1]Most are exudates.

11-I. Pleural Effusion: Exudate versus Transudate[1,2]

Characteristics of an exudative effusion:
    Pleural fluid–serum protein ratio >0.5
    Pleural fluid lactate dehydrogenase (LDH) greater than two thirds of the upper limit of normal for serum LDH
    Pleural fluid–serum LDH ratio >0.6

References

1. Light R. See Bibliography, 3.
2. Nicoll D, et al. *Pocket Guide to Diagnostic Tests*. 4th ed. New York: McGraw-Hill; 2004.

[1]An exudate will have one or more of these three characteristics; a transudate will not have any of these characteristics.
[2]Diuretics can alter protein levels and cause misclassification of transudates associated with congestive heart failure.

11-J. Empyema

Pulmonary Causes

Pneumonia (anaerobic > aerobic bacteria)
Bronchial obstruction (tumor or foreign body)
Hematogenous spread of infection
Bronchopleural fistula
Ruptured abscess

Spontaneous pneumothorax
Bronchiectasis
Rheumatoid disease

Mediastinal Causes
Esophageal perforation
Abscess
Lymph node infection
Osteomyelitis
Pericarditis

Subdiaphragmatic Causes
Abscess (hepatic, pancreatic, splenic, or retrogastric)
Peritonitis

Direct Inoculation
Postoperative
    Infected hemothorax
    Leaky bronchial stump (postlobectomy or postpneumonectomy)
Penetrating chest trauma
    Foreign body in pleural space
Iatrogenic inoculation (thoracentesis or chest tube)

References
1. English J, Leslie K. See Bibliography, 3.
2. Shields T. *General Thoracic Surgery*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2005:819–859.
3. Light R. *Pleural Diseases*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2001.

11-K. Pneumothorax

Primary spontaneous pneumothorax
Secondary spontaneous pneumothorax
    Obstructive pulmonary disease (COPD or asthma)
Malignancy
    Primary lung carcinoma
    Pleural metastatic disease
Infectious disease
    Lung abscess
    Tuberculosis
    Pneumocystis carinii in patients with AIDS

Pulmonary infarction
Diffuse lung disease
- Idiopathic pulmonary fibrosis
- Eosinophilic granuloma
- Scleroderma
- Rheumatoid disease
- Tuberous sclerosis
- Sarcoidosis
- Lymphangioleiomyomatosis
- Idiopathic pulmonary hemosiderosis
- Alveolar proteinosis
- Xanthomatosis
- Biliary cirrhosis

Pneumoconiosis
- Silicosis
- Berylliosis

Congenital disease
- Cystic fibrosis
- Marfan syndrome

Catamenial pneumothorax
Neonatal pneumothorax
Iatrogenic pneumothorax
Traumatic pneumothorax
- Penetrating thoracic trauma
- Barotrauma
- Sudden chest compression
- Blunt abdominal trauma
- Drug abuse (attempted injection in subclavian/internal jugular vein)

References

1. Baumann M. Management of spontaneous pneumothorax. *Clin Chest Med*. 2006;27:369–381.
2. Putukian M. Pneumothorax and pneumomediastinum. *Clin Sports Med*. 2004;23:443–453.

11-L. Pulmonary Edema

Elevated Microvascular Pressure

Cardiogenic (see 2-F, Left Heart Failure)
Volume overload (especially when associated with low plasma oncotic pressure)

Neurogenic
- Head trauma
- Intracerebral hemorrhage
- Postictal

Pulmonary venous obstruction
- Chronic mediastinitis
- Anomalous pulmonary venous return
- Congenital pulmonary venous stenosis
- Idiopathic veno-occlusive disease

High-altitude pulmonary edema (mixed hydrostatic and inflammatory reaction)

Normal Microvascular Pressure (Adult Respiratory Distress Syndrome)

Infection
- Sepsis
- Pneumonia
  - Bacterial
  - Viral
  - *Mycoplasma*
  - Fungal
  - *P. carinii*
  - Legionnaires' disease
  - Miliary tuberculosis
  - Toxic shock syndrome
  - Malaria

Liquid aspiration
- Gastric contents
- Water (near-drowning, fresh and salt water)
- Hypertonic contrast media
- Ethyl alcohol

Shock, especially septic (see 2-J)

Multiple trauma and burns

Hematologic disorders
- Diffuse intravascular coagulation
- Transfusion-related leukoagglutinins
- Leukemia
- Thrombotic thrombocytopenic purpura

Inhaled toxic gases
- Oxygen (high concentration)
- Smoke, ozone
- Nitrogen dioxide
- Sulfur dioxide

Chlorine, phosgene
Metallic oxides, acid fumes
Carbon monoxide
Hydrocarbons
Cadmium, ammonia
Embolism (thrombus, fat, air, or amniotic fluid)
Acute pancreatitis
Drug overdose (narcotics, aspirin)
Drug-induced lung injury (see 11-N)
Immunologic injury (Goodpasture, lupus)
Associated with high negative pleural pressure
Postthoracentesis
Post–expansion of pneumothorax
Acute bronchial asthma
Complete upper airway obstruction (e.g., hanging)
Pulmonary lymphatic obstruction
Fibrotic and inflammatory disease (e.g., silicosis)
Lymphangitic carcinomatosis
Post–lung transplant
Acute radiation pneumonitis
Pulmonary contusion
Post–cardiopulmonary bypass
Diabetic ketoacidosis
Circulating vasoactive substance (e.g., histamine)
Dextran
Eclampsia

References

1. Mattu A, Martinez JP, Kelly BS. Modern management of cardiogenic pulmonary edema. *Emerg Med Clin North Am*. 2005;23:1105–1125.
2. Gallagher S, Hackett P. High-altitude illness. *Emerg Med Clin North Am*. 2004;22:329–355.
3. Rogers R. Acute congestive heart failure in the emergency department. *Cardiol Clin*. 2006;24:115–123.

11-M. Respiratory Failure

Central Nervous System Disorders

Drug intoxication (sedatives, tranquilizers, analgesics, or anesthetics)
Herbal drugs of abuse

Vascular disorders, hypoperfusion states
- Intracranial infarction or bleeding (especially brainstem)
- Shock (see 2-J)

Disorders of the central respiratory controller
- Primary alveolar hypoventilation
- Obstructive sleep apnea syndrome

Trauma
- Spinal cord injury
- Head injury
- Increased intracranial pressure

Infection
- Viral encephalitis
- Bulbar poliomyelitis

Status epilepticus
Myxedema

Neuromuscular Disorders

Peripheral nerve and anterior horn cell disorders
- Guillain-Barré syndrome
- Poliomyelitis
- Amyotrophic lateral sclerosis

Myoneural junction disorders
- Myasthenia gravis
- Tetanus
- Curare-like drugs
- Anticholinesterase drugs

Muscular disorders
- Muscle weakness due to, for example, hypophosphatemia or hypokalemia
- Muscle fatigue
- Polymyositis, dermatomyositis
- Muscular dystrophies
- Myotonia

Chest Wall and Pleural Disorders

Kyphoscoliosis
Chest trauma
- Flail chest, multiple rib fractures
- Postthoracotomy

Pleural disorders
- Large pleural effusions (see 11-G, 11-H)
- Tension pneumothorax
- Massive fibrosis

Pulmonary Disorders

Airflow limitation, chronic
- Pulmonary emphysema
- Chronic bronchitis
- Asthma, especially status asthmaticus

Alveolar disorders
- Pneumonia
- Aspiration pneumonitis
- Pulmonary edema (see 11-L)

Airway obstruction, acute
- Foreign body
- Upper airway obstruction (see 11-C)
- Epiglottitis
- Respiratory burns

Interstitial disorders
- Fibrosing alveolitis
- Interstitial fibrosis and other diffuse disorders (see 11-N)
- Extensive neoplasms

Vascular disorders
- Pulmonary embolus (especially thrombus, fat)
- Obliterative vasculitis (primary pulmonary hypertension, scleroderma)

References

1. Lee-Chiong T, Matthay R. Drug-induced pulmonary edema and acute respiratory distress syndrome. *Clin Chest Med.* 2004;25:95–104.
2. Richardson WH 3rd, Slone CM, Michels JE. Herbal drugs of abuse: an emerging problem. *Emerg Med Clin North Am.* 2007;25:435–457.

11-N. Interstitial Lung Disease

Interstitial Disease of Known Etiology

Inorganic dusts
- Silica
- Silicates, especially asbestos, talc, kaolin, diatomaceous earth
- Aluminum (powered aluminum, bauxite)
- Antimony
- Carbon (coal, granite, beryllium)
- Mixed dusts
- Metal dusts, especially titanium, tungsten, cadmium

Organic dusts (hypersensitivity pneumonitis)
- Farmer's lung
- Humidifier lung
- Bagassosis
- Many others (see reference 2)

Gases (oxygen, sulfur dioxide, chlorine gas)
Fumes
- Oxides of zinc, cadmium, copper, and others
- Mercury, toluene diisocyanate

Aerosols (fats, pyrethrum, Bordeaux mixture)
Drugs
- Chemotherapeutic agents
  - Busulfan
  - Bleomycin
  - Cyclophosphamide
  - Methotrexate
  - Nitrosoureas
  - Procarbazine
  - Mitomycin
- Antibiotics (nitrofurantoin, sulfonamides, penicillin)
- Drugs causing drug-induced lupus
- Diphenylhydantoin
- Amiodarone
- Gold salts

Poisons (Paraquat)
Infections
Radiation injury (acute or chronic)
Graft-versus-host reaction
Chronic pulmonary edema
Chronic uremia
Adult respiratory distress syndrome (see 11-L)

Other Interstitial Diseases

Idiopathic pulmonary fibrosis
Sarcoidosis
Collagen vascular disease/autoimmune disease
- Rheumatoid arthritis
- Progressive systemic sclerosis
- Systemic lupus erythematosus
- Polymyositis/dermatomyositis
- Sjögren syndrome

Vasculitis
- Wegener granulomatosis
- Lymphoid granulomatosis
- Churg-Strauss syndrome
- Hypersensitivity vasculitis
- Overlap syndromes

Eosinophilic lung disease
Idiopathic pulmonary hemosiderosis
Goodpasture syndrome
Lymphangioleiomyomatosis
Amyloidosis
Bronchocentric granulomatosis
Inherited disorders
- Familial interstitial fibrosis
- Tuberous sclerosis
- Neurofibromatosis
- Hermansky-Pudlak syndrome
- Niemann-Pick disease
- Gaucher disease

Liver disease
- Chronic active hepatitis
- Primary biliary cirrhosis

Bowel disease
- Whipple disease
- Ulcerative colitis
- Crohn disease
- Weber-Christian disease

References

1. Glazer C, Newman L. Occupational interstitial lung disease. *Clin Chest Med*. 2004;25:467–478.
2. Raghu G, Brown K. Interstitial lung disease: clinical evaluation and keys to an accurate diagnosis. *Clin Chest Med*. 2004;25:409–419.
3. Selman M. Hypersensitivity pneumonitis: a multifaceted deceiving disorder. *Clin Chest Med*. 2004;25:531–547.

11-O. Pulmonary Hypertension

Pulmonary Arterial Hypertension (Precapillary)

Alveolar hypoxemia with vasoconstriction
Most causes of respiratory failure (see 11-M)

- Chronic obstructive lung disease
  - Chronic bronchitis/bronchiolitis
  - Emphysema
  - Asthma
  - Cystic fibrosis
  - Bronchiectasis
- Alveolar disorders
  - Pneumonia and aspiration pneumonia
  - Pulmonary edema (see 11-L)
  - Chronic alveolar filling disorders
- Upper airway obstruction (see 11-C)
- Alveolar hypoventilation
  - Neuromuscular disorders (see 10-D)
  - Central nervous system disorders (see 11-M)
  - Obesity
  - Primary alveolar hypoventilation
  - Obstructive sleep apnea syndrome
- Chest wall and pleural disorders
  - Chest deformity
    - Kyphoscoliosis
    - Thoracoplasty
    - Poliomyelitis
    - Muscular dystrophy
  - Pleural disease (especially fibrothorax)
- High-altitude pulmonary hypertension
- Restriction of the vascular bed
  - Extrinsic
    - Diffuse interstitial disease (see 11-N)
    - Neoplasm (metastatic and alveolar cell carcinoma)
  - Intrinsic
    - Pulmonary thromboembolic disease
      - Emboli such as fat, amniotic fluid, foreign material such as talc
      - Parasitic (schistosomiasis, filariasis)
    - Pulmonary arteritis
      - Raynaud syndrome
      - Scleroderma, CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome
      - Rheumatoid disease, lupus
      - Polymyositis, dermatomyositis
      - Takayasu disease
      - Granulomatous arteritis

- Toxin-induced pulmonary vascular injury
  - Intravenous drug use, cocaine
  - L-tryptophan
  - Anorexic agents
- Thrombosis due to sickle cell disease
- Human immunodeficiency virus–associated pulmonary hypertension

Increased flow
- Patent ductus arteriosus
- Atrial septal defect (Eisenmenger physiology)
- Ventricular septal defect
- Sinus of Valsalva aneurysm

Decreased flow
- Tetralogy of Fallot

Destruction of vascular bed (e.g., emphysema)
Primary pulmonary hypertension

Pulmonary Venous Hypertension (Postcapillary)

Cardiac disease
- Left ventricular failure (see 2-F)
- Mitral valve disease
  - Mitral stenosis
  - Mitral insufficiency, papillary muscle rupture
- Left atrial obstruction
  - Myxoma or other tumor
  - Supravalvular stenotic ring
  - Thrombus
- Cor triatriatum

Pericardial disease
- Pericardial tamponade
- Restrictive pericarditis

Pulmonary venous disease
Mediastinal neoplasm or granuloma
Mediastinal fibrosis
Mediastinitis
Anomalous pulmonary venous return
Congenital pulmonary venous stenosis
Idiopathic pulmonary veno-occlusive disease

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11-P. Mediastinal Masses by Predominant Compartment

Anterior

Substernal thyroid
Thymoma
Lymphoma
Germinal cell neoplasm (e.g., dermoid)
Ascending aortic aneurysm
Parathyroid tumor
Mesenchymal neoplasm (e.g., lipoma or fibroma)
Hematoma
Bronchogenic cyst

Middle

Lymphoma
Metastatic neoplasm (pulmonary or extrapulmonary)
Sarcoid lymphadenopathy
Infectious granulomatous disease
Bronchogenic cyst
Vascular dilatation
    Superior vena cava
    Azygos vein
    Pulmonary artery
Aortic arch aneurysm
Vascular anomaly
Pleuropericardial cyst
Lymph node hyperplasia
Mononucleosis-associated lymphadenopathy
Primary or tracheal neoplasm
Hematoma

Anterior Costophrenic Angle

Pleuropericardial cyst or tumor
Foramen of Morgagni hernia
Fat pad
Diaphragmatic lymph node enlargement
        (e.g., lymphoma)
Pulmonary parenchymal mass
Cardiac aneurysm

Posterior

Neurogenic tumor
Meningocele
Esophageal lesion (tumor, hiatal hernia, diverticulum, megaesophagus)
Bochdalek hernia
Thoracic spine lesion (neoplasm, fracture with hematoma, infection)
Extramedullary hematopoiesis
Descending aortic aneurysm
Mediastinal abscess
Pancreatic pseudocyst
Lymph node hyperplasia
Hematoma
Cystic lesion (neurogenic, gastroenteric, thoracic duct, bronchogenic)

Diffuse Mediastinal Widening

Bronchogenic carcinoma
Mediastinal hemorrhage
Granulomatous mediastinitis (idiopathic, tuberculosis, histoplasmosis)
Mediastinal lipomatosis
Pneumomediastinum
Acute mediastinitis

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11-Q. Solitary Pulmonary Nodule

Neoplasm
- Bronchogenic carcinoma
- Metastatic malignancy
- Hamartoma
- Bronchial adenoma
- Lymphoma
- Amyloidosis
- Plasmacytoma

Infection
- Tuberculosis
- Histoplasmosis
- Aspergillosis (mucoid impaction)
- Cryptococcosis
- *Dirofilaria immitis*

Immune disorders
- Rheumatoid nodule
- Wegener granulomatosis

Developmental disorders
- Bronchogenic cyst
- Arteriovenous fistula
- Sequestration
- Bronchial atresia

Pulmonary infarction
Lipoid pneumonia
Hematoma

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11-R. Solitary Pulmonary Nodule: Distinguishing Benign from Malignant Lesions

	Benign	Malignant
Clinical Findings		
Age[a]	<40	>45
Symptoms	Absent	Present
History	Tuberculosis exposure Histoplasmosis exposure Nonsmoker Mineral oil use	Smoker Extrathoracic malignancy Prior malignancy
X-ray findings		
Size	<2 cm	>2 cm
Border[a]	Smooth, well-defined	Ill-defined, lobulated

11-R. Solitary Pulmonary Nodule: Distinguishing Benign from Malignant Lesions (continued)

Calcification[a]	Laminated, "popcorn" or multiple punctuate	Rare, eccentric if present
Doubling time[a]	<1 or >16 months	1–16 months
Other findings	CT: low density, high fat	Erosion of adjacent rib

CT, computed tomography.
[a]These factors are most important in distinguishing benign from malignant lesions.

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11-S. Elevated Hemidiaphragm

Pseudoelevation

Subpulmonic effusion
Diaphragmatic neoplasm

True Elevation

Intrathoracic conditions
- Lobar or segmental atelectasis
- Pneumonia
- Pulmonary infarction
- Rib fracture
- Pleurisy
- Paralysis or paresis due to phrenic nerve dysfunction
- Bronchogenic carcinoma or mediastinal malignancy
- Surgical or nonsurgical trauma

Neurologic disorders
- Myelitis, encephalitis
- Herpes zoster
- Poliomyelitis
- Serum sickness following tetanus antitoxin
- Diphtheria

Extrinsic pressure
- Substernal thyroid
- Aortic aneurysm

Infection
- Pneumonia, tuberculosis
- Empyema or pleuritis
- Infection of the neck or cervical spine

Eventration
Traumatic rupture of the diaphragm
Radiation therapy
- Intra-abdominal pathology
- Subphrenic or hepatic abscess
- Pancreatitis
- Other mass lesions, especially malignancy
- Splenic infarct

Idiopathic

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11-T. Factors Associated with an Increased Risk of Postoperative Pulmonary Complications

General Factors

Cigarette smoking (especially ≥10 pack-years or ≥10 cigarettes daily)
Older age + concomitant illness (not age alone)
Alcohol abuse
Dependent functional status

Surgical Factors

Thoracic surgery (especially with resection of functional lung)
Emergency surgery, trauma
Perioperative blood transfusions
Upper abdominal surgery
Anesthesia time >3 hours, anesthesia type
Neuromuscular blockade

Pulmonary Factors

Pulmonary function tests have variable predictive value
Preoperative hypoxia by pulse oximetry (hypoxemia not a reliable indicator)
Arterial blood gases ($PaCO_2$ >45 mm Hg)
Acute respiratory infections
Obstructive sleep apnea
Chronic bronchitis
Asthma/chronic obstructive lung disease
Hemoglobin level >16 g/dL
Blood urea nitrogen (BUN) >30 g/dL and serum albumin <3.0 g/dL
Unable to climb ≤3 flights of stairs
Myasthenia gravis
Spinal cord injury

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12

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

12-A. Infection and Fever

Infections

Bacterial

- *Streptococcus pneumoniae* [including penicillin-resistant *S. pneumoniae* (PRSP)]
- *Salmonella* spp. (especially, *Salmonella enteritidis* and *Salmonella typhimurium*)
- *Haemophilus influenzae*
- *Staphylococcus aureus* [including methicillin-resistant *S. aureus* (MRSA)]
- *Pseudomonas aeruginosa*
- *Moraxella catarrhalis*
- *Rhodococcus equi*
- *Nocardia* spp.
- *Legionella* spp.

Syphilis

- *Listeria*
- *Bartonella henselae* or *Bartonella quintana*
- *Campylobacter* spp.
- *Shigella* spp.
- *Clostridium difficile*
- *Chlamydia* spp.
- *Borrelia burgdorferi*

Viral
- Human immunodeficiency virus (HIV) (especially acute infection)
- Cytomegalovirus (CMV)
- Herpes simplex virus (HSV), types I and II
- Epstein-Barr virus (EBV)
- Varicella-zoster virus (VZV)
- Hepatitis A, B, C
- Human papilloma virus (HPV)
- Measles virus
- Papovavirus, especially JC virus
- Human herpesvirus 6 (HHV-6)

Protozoa
- *Pneumocystis jiroveci* (*carinii*)
- *Toxoplasma gondii*
- *Cryptosporidium parvum*
- *Microsporidia* spp., especially *Enterocytozoon bieneusi*, *Encephalitozoon* spp.
- *Isospora belli*
- *Giardia lamblia*
- *Entamoeba histolytica*
- *Babesia microti*
- *Cyclospora cayetanensis*

Nematode
- *Strongyloides stercoralis*

Fungal
- *Cryptococcus neoformans*
- *Candida* spp.
- *Histoplasma capsulatum*
- *Coccidioides immitis*
- *Aspergillus* spp.
- Mucormycosis
- *Fusarium* spp.
- *Blastomyces* spp.

Mycobacterium
- *Mycobacterium tuberculosis*
- *Mycobacterium avium* complex
- *Mycobacterium chelonae*
- *Mycobacterium fortuitum*
- *Mycobacterium kansasii*
- *Mycobacterium marinum*, *Mycobacterium scrofulaceum*

Mycobacterium genavense, *Mycobacterium gordonae*, *Mycobacterium simiae*
Mycobacterium xenopi, *Mycobacterium celatum*
Malignancies
Lymphoma, especially non-Hodgkin lymphoma (NHL), central nervous system (CNS) lymphoma, Hodgkin disease
Kaposi sarcoma
Squamous cell cancer (especially of skin, anus)
Cervical and anal intraepithelial neoplasia (CIN, AIN)
Solid organ tumors (see 8-A)
Metastatic cancer
Carcinomatosis
Drugs
Trimethoprim and sulfamethoxazole (TMP/SMX) (Bactrim, Septra)
Sulfonamides
Dapsone
Phenytoin
Penicillins
Amphotericin B
Barbiturates
Clindamycin
Interferon
Pentamidine
Cephalosporins
Carbamazepine
Tuberculosis (TB) drugs [especially isoniazid (INH), rifampin, and streptomycin]
Salicylates
Bleomycin
Methotrexate

Other

Vaccinations
Adrenal insufficiency

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12-B. Primary HIV Infection: Signs and Symptoms

Fever/rash (exanthem—including face, trunk, palms, soles)/fatigue
Headache/lymphadenopathy (generalized)/pharyngitis
Myalgias and arthralgias/nausea, vomiting, anorexia, diarrhea
Night sweats/oral, esophageal, and genital ulcers/weight loss
Oral, esophageal, and vaginal candidiasis
Leukopenia/thrombocytopenia
Meningitis/encephalopathy/encephalitis/radiculopathy/cranial nerve palsies (VII)—rare

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12-C. Differential Diagnosis of Primary HIV Infection

Acute viral syndrome
Infectious mononucleosis
Secondary syphilis
Acute viral hepatitis
Influenza
Acute toxoplasmosis
Acute parvovirus B19 infection
Aseptic meningitis
Acute CMV (cytomegalovirus) infection
Acute rheumatic fever
Adverse drug/medication reaction
Streptococcal pharyngitis

12-D. Ocular Complications

Retinitis
- CMV: usually unilateral initially, painless, progressive loss of vision
- Toxoplasmosis: chorioretinitis with or without CNS involvement
- VZV: rapid loss of vision (can be associated with trigeminal zoster lesions)
- HSV: can cause acute retinal necrosis syndrome or progressive outer retinal necrosis (PORN); associated with pain, keratitis, and iritis; associated with oral, mucocutaneous lesions
- Fungal (especially *C. neoformans* and *H. capsulatum*)
- *Treponema pallidum*
- Idiopathic

Uveitis
- *T. pallidum*
- *Mycobacterium* spp.
- VZV
- Drugs, especially rifabutin, cidofovir

Optic neuritis
- *T. pallidum*
- *C. neoformans*

Choroiditis
- *P. jiroveci* (*carinii*): can mimic CMV retinitis
- *Mycobacterium* spp.

Other
HIV retinopathy: seen in 50–75% of patients

Fungal endophthalmitis (*Candida* spp.)
Herpes zoster virus (HZV) ophthalmicus
Fungal or bacterial corneal ulcers
Kaposi sarcoma (conjunctivae, lid, orbit)
NHL (lid/retina)
Molluscum contagiosum (conjunctivae, lid)
HSV keratitis
Reiter syndrome (conjunctivitis, arthritis, urethritis, or cervicitis)
VZV blepharitis, conjunctivitis, keratitis

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12-E. Hematologic Complications

Red Blood Cell Disorders

Etiologies of anemia
- HIV infection
- *M. avium* complex infection
- Parvovirus B19 infection
- Drugs, especially:
  - TMP/SMX
  - Sulfonamides
  - Interferon or ribavirin
  - Azidothymidine (AZT)
  - Ganciclovir
  - Pentamidine
  - Dideoxycytidine (ddC, zalcitabine)
  - Lamivudine (3TC, Epivir)
  - Dapsone (especially in patients with glucose-6-phosphate dehydrogenase deficiency)
- Iron deficiency anemia

Autoimmune hemolytic anemia (AIHA)
Vitamin B_{12} deficiency
Blood loss
Bone marrow infiltration with infection (especially CMV, *M. avium* complex)
Bone marrow infiltration with malignancy (especially lymphoma)
Hypersplenism
Thrombotic thrombocytopenic purpura (TTP)

White Blood Cell Disorders

Etiologies of neutropenia or leukopenia
HIV infection
Drugs, especially:
ddC (zalcitabine)
3TC (Epivir)
TMP/SMX
Ganciclovir
AZT (Retrovir)
Bone marrow infiltration with infection (especially CMV, *M. avium* complex)
Bone marrow infiltration with malignancy (especially lymphoma)
Hypersplenism

Platelet Disorders

Etiologies of thrombocytopenia
HIV infection
CMV
Parvovirus B19
Fungal infections (especially *Cryptococcus* and *Histoplasma*)
M. tuberculosis and *M. avium* complex disseminated infections
Lymphoma
Hepatitis B and C
HHV-6
TTP

Drugs Causing Multiple Hematologic Abnormalities in HIV Infection

Zidovudine (Retrovir or AZT)
Ganciclovir
TMP/SMX

Sulfonamides
Interferon-α or ribavirin, or both
Pyrimethamine
3TC (Epivir)
Antineoplastic chemotherapy
Dapsone
Didanosine (ddI)
ddC (zalcitabine)
Amphotericin B
Pentamidine
Fluconazole
Rifabutin
Clarithromycin

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12-F. Malignant Complications

Kaposi sarcoma
Lymphoma, especially NHL, primary CNS lymphoma, Hodgkin disease
Cervical cancer
Squamous cell cancer of the skin
Anogenital neoplasia

Squamous cell carcinoma of the anus
Basal cell cancer of the skin
Seminoma

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12-G. Gastrointestinal Complications

Oral or Oropharynx

Infections

Candida spp.: thrush, cheilitis, leukoplakia
HSV (HSV I, HSV II): painful clusters of blisters/vesicles on erythematous base (oral cavity, lips, palate, tongue, or adjacent skin) can ulcerate
CMV: usually secondary to disseminated infection
EBV: oral hairy leukoplakia (small painless ulcers or vesicles on palate, tongue, gingival, lateral borders of tongue; can alter taste); EBV DNA polymerase chain reaction (PCR) can be positive
Cryptococcus spp.: painless oral ulcers
Histoplasma spp.: painless oral/palate ulcers
Bacterial infections, especially gingivitis, necrotizing ulcerative periodontal disease
Aphthous ulcers (acute ulcers can be seen in primary HIV infection); recurrent: superficial painful ulcers of oral mucosa can cause dysphagia, hoarseness

Squamous cell cancer: usually affects tongue
Kaposi sarcoma: HHV-8 associated; red, violaceous lesions
Lymphoma: poorly demarcated lesions
VZV (trigeminal dermatome)
Human papilloma virus: single or multiple papilliform painless lesions/oral warts
Bacillary epithelioid angiomatosis: can mimic Kaposi sarcoma (biopsy for diagnosis)
Secondary syphilis: mucous patches, aphthous ulcers, erosions

Esophagus

Infections
Candida spp.: most common cause of dysphagia in HIV-positive patients
CMV: most common cause of odynophagia in HIV-positive patients
Acute HIV infection: dysphagia
HSV: causes odynophagia, can be associated with oral ulcers
Idiopathic-aphthous ulcers: odynophagia

Colitis

Infections
Campylobacter spp. (*Campylobacter jejuni*, *Campylobacter coli*, *Campylobacter upsaliensis*): watery or bloody diarrhea with fever, + fecal white blood cells (WBCs)
C. difficile: watery diarrhea with fever, + fecal WBCs
CMV: bloody diarrhea with fever, + fecal WBCs
Salmonella spp. (*S. enteritidis*, *S. typhimurium*): watery diarrhea with fever, + fecal WBCs
Shigella spp.: watery diarrhea with fever, + fecal WBCs
M. avium complex: associated with disseminated infection
C. parvum: watery diarrhea, associated with nausea, vomiting, fever, − fecal WBCs
Microsporidia spp.: watery diarrhea, − fecal WBCs
I. belli: watery diarrhea, usually no fever, − fecal WBCs
Escherichia coli (enteroadherent): watery diarrhea
E. coli (enterotoxigenic): watery diarrhea, nausea, vomiting, − fecal WBCs
G. lamblia: watery diarrhea, nausea, bloating, weight loss, − fecal WBCs

E. histolytica: bloody diarrhea
HSV
C. cayetanensis: watery diarrhea
Microsporidia spp.: watery diarrhea
T. gondii
Viruses (rotavirus, adenovirus, astrovirus): watery diarrhea

Hepatobiliary Tract

Infections
- *C. parvum*
- CMV
- *M. avium* complex
- *M. tuberculosis*
- Chronic viral hepatitis, especially B and C
- *B. henselae*, *B. quintana*
- Kaposi sarcoma
- *Candida* spp.

Drugs
- TMP/SMX
- INH
- Rifampin
- Didanosine (ddI, Videx)
- Zidovudine (AZT, Retrovir)
- Pyrazinamide
- Pentamidine
- Doxycycline
- Nevirapine (especially if patient is hepatitis C positive)
- Ritonavir
- Fluconazole
- Fosamprenavir (Lexiva)
- Atazanavir (Reyataz)
- Lopinavir/ritonavir (Kaletra)
- Macrolides

Granulomatous Hepatitis

Infections
- Mycobacteria (*M. tuberculosis*, *M. avium* complex)
- *H. capsulatum*
- *C. neoformans*
- *C. immitis*
- CMV
- *P. jiroveci* (*carinii*)

Sclerosing Cholangitis

Infections
- *C. parvum*
- *Microsporidia* spp.
- CMV

Pancreatitis

Infections
- CMV
- HIV
- *C. parvum*
- *C. neoformans*

Other
- Kaposi sarcoma
- Lymphoma
- Hyperlipidemia

Drugs
- Pentamidine
- Didanosine (ddI, Videx)
- Zalcitabine (ddC, Hivid)
- TMP/SMX
- Lopinavir/ritonavir (Kaletra)
- Abacavir (Ziagen)
- Stavudine (Zerit)
- Didanosine and stavudine
- Zalcitabine and pentamidine

Proctitis

Infections
- HSV
- *Neisseria gonorrhoeae* (GC)
- HPV
- Condylomata
- *T. pallidum* (syphilis)
- *Chlamydia trachomatis*
- *C. parvum*
- *Microsporidia* spp.
- *M. avium* complex
- CMV

Other
- Kaposi sarcoma
- Squamous cell cancer of the anorectum

Hepatotoxicity

Lactic acidosis/hepatic steatosis: especially due to nucleoside reverse transcriptase inhibitors (stavudine and nucleoside reverse transcriptase inhibitors in combination; i.e., stavudine and didanosine)

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12-H. Central Nervous System Manifestations

Meningitis

Infections

- Acute HIV infection (aseptic, early presentation, may relapse)
- Bacteria, especially *S. pneumoniae* (including PRSP), *Neisseria meningitides*, *H. influenzae*
- *Listeria monocytogenes*
- *Salmonella* spp.
- Fungal, especially *C. neoformans*, *H. capsulatum*, *Candida* spp., *Aspergillus* spp., Mucormycosis, *C. immitis*
- Spirochetes, especially *T. pallidum* (syphilis), *B. burgdorferi*
- Mycobacteria, especially *M. tuberculosis*, *M. avium* complex, *M. kansasii*

Other

- Malignancy, especially lymphoma

Encephalitis

Infections
- HIV (acute encephalitis early in course, encephalopathy late in illness)
- HSV I
- CMV
- HSV II
- *T. gondii*
- Papovavirus (JC virus) [progressive multifocal leukoencephalopathy (PML)]
- HHV-6

Space-Occupying Lesions

Infections
- *T. gondii*
- *C. neoformans*
- Pyogenic brain abscesses
- *Nocardia asteroides*
- *Salmonella* spp.
- *L. monocytogenes*
- *S. pneumoniae*
- *M. tuberculosis* (tuberculomas)
- *Aspergillus* spp.
- *Streptococcus mitis*
- *Staphylococcus epidermidis*

Other
- Malignancy, especially CNS lymphoma, Kaposi sarcoma, metastatic cancer
- JC virus, PML

Myelitis

Infections
- HIV
- CMV
- HSV
- VZV
- *T. pallidum* (syphilis)
- *T. gondii*
- *M. tuberculosis*

Other
- Idiopathic

Infarction, Hemorrhage, Transient Ischemic Attack, Cardiovascular Accident

Infections
- *T. pallidum* vasculitis (syphilis)
- *T. gondii*
- *C. neoformans*
- VZV vasculitis
- *M. tuberculosis*
- *Aspergillus* spp.

Other
- Marantic endocarditis
- Anticardiolipin antibody
- Thrombocytopenia
- Idiopathic

Neurotoxicity: drugs
- Zidovudine (AZT, Retrovir): myopathy
- Efavirenz (Sustiva): nightmares, vivid dreams, sleep disturbances
- Didanosine (ddI, Videx)/stavudine (d4T, Zerit)/zalcitabine (ddC, Hivid)/zidovudine (AZT, Retrovir): dose-dependent myopathy, sensory distal polyneuropathy
- Dapsone/vincristine: distal sensory and motor neuropathy
- Metronidazole/INH/cisplatin: peripheral neuropathy

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12-I. Pulmonary Complications

Infections

Pneumonia or pneumonitis

- Bacterial
  - *S. pneumoniae* (including PRSP): 100 times more common in HIV-positive patients
  - *H. influenzae*: more common in HIV-positive patients
  - *S. aureus* (including MRSA): usually 2/2 bacteremia, tricuspid valve endocarditis in intravenous drug users
  - *P. aeruginosa*: rare, except when CD4 <50, use of steroids, chemotherapy, neutropenia
  - *E. coli*
  - *Legionella* spp.: may be health care acquired
  - *M. pneumoniae*: rare
  - *C. pneumoniae*
  - Other gram-negative bacilli
  - *Nocardia* spp., especially *asteroides*: can see associated brain lesions
  - *R. equi*: CD4 <100 usually associated with bacteremia
- Mycobacteria, especially *M. tuberculosis* (CD4 >200, usually upper lobe infiltrates/cavitary disease; CD4 <50, usually lower lobe infiltrates, disseminated/extrapulmonary disease), *M. avium* complex (can be asymptomatic colonizer or pathogen), and *M. kansasii* (most common non-TB mycobacteria causing pulmonary infections: nodules, cavitary infiltrates)
- Viral, especially influenza A, B (predisposes patients to bacterial superinfection with *S. pneumoniae*, *H. influenzae*, *S. aureus*)

Fungal, especially *C. neoformans* (CD4 <100 usually associated with meningitis, fever, cough, dyspnea, diffuse interstitial pulmonary infiltrates; can be confused with *P. carinii* pneumonia; need lumbar puncture to rule out meningitis; serum antigen

positive in 90% of cases), *H. capsulatum* (CD4 <100, pneumonia is associated with disseminated infection, fever, cough, skin lesions, hepatosplenomegaly, bone marrow suppression, diffuse interstitial or reticulonodular infiltrates), *C. immitis* (indolent course; cough, fever, dyspnea, ± cutaneous lesions, meningitis, joint involvement, diffuse pulmonary infiltrates), *Aspergillus* spp. (especially *fumigatus*) (CD4 <50, associated with neutropenia, steroid use, marijuana use, broad-spectrum antibiotics, structural lung abnormalities, hemoptysis, fever, cavitary pulmonary infiltrates), *Penicillium marneffei* (indolent course, fever, weight loss, associated skin lesions: disseminated), *Blastomyces dermatitidis*

Protozoal, especially *P. jiroveci* (*carinii*), *T. gondii*

Viral, especially CMV, HSV, adenovirus, VZV (pulmonary infection can be associated with skin lesions)

Malignancies

Kaposi sarcoma: nodular infiltrates, usually have cutaneous or mucosal lesions

Lymphoma, especially NHL, Hodgkin disease: pulmonary nodules, masses, pleural effusions

Bronchogenic carcinoma

Metastatic carcinoma

Other

Pulmonary emboli

Septic pulmonary emboli

Primary pulmonary hypertension

Pneumothorax (especially associated with *P. carinii* pneumonia)

Nonspecific interstitial pneumonitis

Bronchiectasis

Emphysema

Pulmonary hypertension (increased incidence in HIV-positive patients)

Lymphocytic interstitial pneumonitis (rare)

Drugs: abacavir (hypersensitivity reaction involving lungs: mimics bronchitis/pneumonia), associated with rash, fatigue, gastrointestinal symptoms, arthralgias

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12-J. Dermatologic Manifestations

Superficial Cutaneous Infections

Molluscum contagiosum: multiple lesions on face, periorbital region
HSV I and II: ulcerative lesions
Cutaneous HPV
Condyloma
Candidiasis: oral or vaginal, recurrent or refractory infection
Folliculitis: plaquelike lesions, progress to botryomycosis
VZV: can be disseminated
Bacterial skin infections, especially *S. aureus* (including MRSA), most common cutaneous bacterial pathogen: folliculitis, cellulites, pyomyositis, botryomycosis, necrotizing fasciitis
Dermatophytosis
Sarcoptes scabiei (crusted Norwegian scabies): hyperkeratotic crusted lesions on palms, soles, trunk
Mycobacteria, especially *M. tuberculosis*, *M. avium* complex, *M. marinum*, *M. kansasii*, *Mycobacterium haemophilum* (*M. tuberculosis*/*M. avium* complex skin lesions: papules, pustules, lymphadenitis)
Cutaneous *P. carinii*: friable red nodules/papules on head, ears, nares (rare)
Impetigo: seen in inguinal, axillary, intertriginous locations

Systemic Infections with Dermatologic Manifestations

Acute HIV infection: erythematous exanthem of trunk and upper extremities, associated with fever, pharyngitis, headache, myalgias, arthralgias, lymphadenopathy, fatigue

Reiter syndrome [usually human leukocyte antigen (HLA) B27 positive, oligoarticular arthritis, urethritis, keratoderma blennorrhagicum, conjunctivitis, balanitis]
P. carinii infection: friable red nodules/papules on head, nares, ears (rare)
T. pallidum (syphilis)
Bartonella spp. (*henselae/quintana*): subcutaneous nodules, red violaceous papules (can be multiple) associated with fever, weight loss, fatigue, malaise, night sweats, headache, endocarditis (rare)
Bacillary angiomatosis: subcutaneous/dermal red-purple nodules (dry or draining), single or multiple; and can involve liver, spleen, brain, bone, lung, gastrointestinal tract, lymph nodes, cervix
C. neoformans: verrucous lesions, erythematous papules/nodules, cellulitis
H. capsulatum: cutaneous, oral, palate lesions/ulcers; erythematous macules, nodules = erythema nodosum, erythema multiforme
P. marneffei: umbilicated papules on face/upper trunk/extremities/genitalia, associated with fever, anemia, weight loss, night sweats, lymphadenopathy; note: lesions can look like molluscum contagiosum
M. tuberculosis: skin lesions/papules/pustules/lymphadenitis (draining or nondraining) seen in disseminated TB (cervical, axillary, inguinal nodes)
M. avium complex: nodules/ulcers/pustule/abscesses (dry or draining) seen in disseminated infection
R. equi: deep tissue abscesses
Nocardia spp./*Actinomyces* spp.: chronic draining sinuses, usually overlying thick plaque
Burkholderia cepacia: abscesses/nodular skin lesions

Noninfectious Dermatologic Manifestations

Seborrheic dermatitis: orange, yellow plaque with scale located in scalp region, eyebrows, nasolabial folds, hairline, beard, mustache area; occurs in approximately 50% of HIV-positive patients
Psoriasis: more severe in HIV-positive patients; may be more refractory to therapy; unusual locations (axillae, scalp, groin rather than knees and elbows)
Eosinophilic pustular folliculitis: multiple urticarial papules (may coalesce into plaques)

Atopic dermatitis
Ichthyosis, acquired: more severe in HIV-positive patients
Porphyria cutanea tarda
Hyperpigmentation: seen in patients on clofazimine
Photodermatitis

Cutaneous Malignancies

Kaposi sarcoma (associated with HHV-8): pink, violaceous, red, brown macules/plaques/nodules on mucous membranes, skin (especially lower extremities and face), genitalia, gastrointestinal tract, pulmonary (endobronchial), lymphatics
B-cell lymphoma
T-cell lymphoma (human T-lymphotropic virus I): multiple skin lesions, lytic bone lesions (rare), tropical spastic paraparesis
Invasive squamous cell cancer: intraepithelial neoplasia (cervix in females, anorectal mucosa in males)
Anogenital neoplasia: cervical and anal carcinomas (HPV associated with carcinomas, especially HPV types 16, 18, and 31)
Basal cell cancer of the skin

Other

Drug reactions, especially pruritus, erythema multiforme, Stevens-Johnson syndrome, morbilliform rash: abacavir (Ziagen), nevirapine (Viramune), efavirenz (Sustiva), amprenavir (Agenerase), delavirdine (Rescriptor), enfuvirtide (Fuzeon)
Fixed drug eruptions, especially penile ulcers secondary to foscarnet
Eosinophilic pustular folliculitis (may be 2/2 allergic reaction, mites)
Toxic epidermal necrolysis: nevirapine (Viramune), abacavir (Ziagen)
Photosensitivity: saquinavir (Fortovase), doxycycline
Hypersensitivity reaction (potentially fatal): abacavir (Ziagen); do not rechallenge with drug
Porphyria cutanea tarda
Vitiligo
TTP
Bullous pemphigoid
Sicca syndrome

Polyarteritis nodosa
Cutaneous leukocytoclastic vasculitis
Alopecia/premature graying of hair: more common in HIV-positive patients
Aphthous ulcers

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12-K. Immune Reconstitution Syndrome

Highly active antiretroviral therapy (HAART): successful in reducing HIV-1 RNA and increasing CD4 lymphocyte counts
Opportunistic infections and mortality in HIV patients have decreased dramatically
Improvement in immune system function may be associated with paradoxical worsening/recrudescence of underlying opportunistic infections = immune reconstitution syndrome
Immune reconstitution syndrome
- Presentation varies by infectious pathogen
- *M. tuberculosis*: fever, lymphadenopathy, pulmonary infiltrate, pleural effusions, CNS TB meningitis, abscesses; therapy = continue HAART, begin TB therapy, steroids
- CMV: immune recovery uveitis (usually in patients with history of CMV retinitis), CMV viremia, colitis, pancreatitis, pneumonitis; therapy = steroids +/− CMV therapy
- *M. avium* complex: lymphadenitis (focal or diffuse), usually painful and associated w/ fever, +/− abdominal pain and hepatosplenomagaly and negative blood cx. Lymph node bx/cx is + AFB/*M. avium* complex; therapy = *M. avium* complex rx.

M. avium complex osteomyelitis (rare): therapy = MAC treatment
C. neoformans: meningitis with cerebrospinal fluid pleocytosis, hearing loss, lymphadenitis
Hepatitis C: Acute hepatitis, worsening cirrhosis, cryoglobulinemia
HSV/VZV: mucocutaneous lesions: reactivation of local lesions; therapy = acyclovir, famciclovir
M. tuberculosis: pulmonary TB: fever, pulmonary infiltrates, lymphadenopathy, psoas abscesses, CNS tuberculomas; therapy = HAART and TB treatment (steroids for treatment of severe symptoms)

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