

Table 435-1

Antiarrhythmic Drugs Commonly Used in Pediatric Patients, by Class

DRUG	INDICATIONS	DOSING	SIDE EFFECTS	DRUG INTERACTIONS	DRUG LEVEL
CLASS IA: INHIBITS NA⁺ FAST CHANNEL, PROLONGS REPOLARIZATION					
Quinidine	SVT, atrial fibrillation, atrial flutter, VT. In atrial flutter, an AV node blocking drug (digoxin, verapamil, propranolol) must be given first to prevent 1:1 conduction	Oral: 30-60 mg/kg/24 hr divided q6h (sulfate) or q8h (gluconate) In adults, 10 mg/kg/day divided q6h Max dose: 2.4g/24 hr	Nausea, vomiting, diarrhea, fever, cinchonism, QRS and QT prolongation, AV nodal block, asystole, syncope, thrombocytopenia, hemolytic anemia, SLE, blurred vision, convulsions, allergic reactions, exacerbation of periodic paralysis	Enhances digoxin, may increase PTT when given with warfarin	2-6 µg/mL
Procainamide	SVT, atrial fibrillation, atrial flutter, VT	Oral: 15-50 mg/kg/24 hr divided q4h Max dose: 4 g/24 hr IV: 10-15 mg/kg over 30-45 min load followed by 20-80 µg/kg/min Max dose: 2 g/24 hr	PR, QRS, QT interval prolongation, anorexia, nausea, vomiting, rash, fever, agranulocytosis, thrombocytopenia, Coombs-positive hemolytic anemia, SLE, hypotension, exacerbation of periodic paralysis, proarrhythmia	Toxicity increased by amiodarone and cimetidine	4-8 µg/mL With NAPA <40 µg/mL
Disopyramide	SVT, atrial fibrillation, atrial flutter	Oral: <2 yr: 20-30 mg/kg/24 hr divided q6h or q12h (long-acting form); 2-10 yr: 9-24 mg/kg/24 hr divide q6h or q12h (long-acting form); 11 yr: 5-13 mg/kg/24 hr divided q6h or q12h (long-acting form) Max dose: 1.2 g/24 hr	Anticholinergic effects, urinary retention, blurred vision, dry mouth, QT and QRS prolongation, hepatic toxicity, negative inotropic effects, agranulocytosis, psychosis, hypoglycemia, proarrhythmia		2-5 µg/ml
CLASS IB: INHIBITS NA⁺ FAST CHANNEL, SHORTENS REPOLARIZATION					
Lidocaine	VT, VF	IV: 1 mg/kg repeat q 5 min 2 times followed by 20-50 µg/kg/min (max dose: 3 mg/kg)	CNS effects, confusion, convulsions, high grade AV block, asystole, coma, paresthesias, respiratory failure	Propranolol, cimetidine, increases toxicity	1-5 µg/mL
Mexiletine	VT	Oral: 6-15 mg/kg/24 hr divided q8h	GI upset, skin rash, neurologic	Cimetidine	0.8-2 µg/mL
Phenytoin	Digitalis intoxication	Oral: 3-6 mg/kg/24 hr divided q12h Max dose: 600 mg IV: 10-15 mg/kg over 1 hr load	Rash, gingival hyperplasia, ataxia, lethargy, vertigo, tremor, macrocytic anemia, bradycardia with rapid push	Amiodarone, oral anticoagulants, cimetidine, nifedipine, disopyramide, increase toxicity	10-20 µg/mL
CLASS IC: INHIBITS NA⁺ CHANNEL					
Flecainide	SVT, atrial tachycardia, VT	Oral: 6.7-9.5 mg/kg/24 hr divided q8h In older children, 50-200 mg/m ² /day divided q12h	Blurred vision, nausea, decrease in contractility, proarrhythmia	Amiodarone increases toxicity	0.2-1 µg/mL
Propafenone	SVT, atrial tachycardia, atrial fibrillation, VT	Oral: 150-300 mg/m ² /24 hr divided q6h	Hypotension, decreased contractility, hepatic toxicity, paresthesia, headache, proarrhythmia	Increases digoxin levels	0.2-1 µg/mL

Continued

2252 Part XX ◆ The Cardiovascular System

Table 435-1 Antiarrhythmic Drugs Commonly Used in Pediatric Patients, by Class—cont'd

DRUG	INDICATIONS	DOSING	SIDE EFFECTS	DRUG INTERACTIONS	DRUG LEVEL
CLASS II: β-BLOCKERS					
Propranolol	SVT, long QT	Oral: 1-4 mg/kg/24 hr divided q6h Max dose 60 mg/24 hr IV: 0.1-0.15 mg/kg over 5 min Max IV dose: 10 mg	Bradycardia, loss of concentration, school performance problems bronchospasm, hypoglycemia, hypotension, heart block, CHF	Coadministration with disopyramide, flecainide or verapamil may decrease ventricular function	
Atenolol	SVT	Oral: 0.5-1 mg/kg/24 hr once daily or divided q12h	Bradycardia, loss of concentration, school performance problems	Coadministration with disopyramide, flecainide or verapamil may decrease ventricular function	
Nadolol	SVT, long QT	Oral: 1-2 mg/kg/24 hr given once daily	Bradycardia, loss of concentration, school performance problems bronchospasm, hypoglycemia, hypotension, heart block, CHF	Coadministration with disopyramide, flecainide or verapamil may decrease ventricular function	
CLASS III: PROLONGS REPOLARIZATION					
Amiodarone	SVT, JET, VT	Oral: 10 mg/kg/24 hr in 1-2 divided doses for 4-14 days; reduce to 5 mg/kg/24 hr for several weeks; if no recurrence, reduce to 2.5 mg/kg/24 hr IV: 2.5-5 mg/kg over 30-60 min, may repeat 3 times, then 2-10 mg/kg/24 hr continuous infusion	Hypothyroidism or hyperthyroidism, elevated triglycerides, hepatic toxicity, pulmonary fibrosis	Digoxin (increases levels), flecainide, procainamide, quinidine, warfarin, phenytoin	0.5-2.5 mg/L
CLASS IV AND MISCELLANEOUS MEDICATIONS					
Digoxin	SVT (not WPW), atrial flutter, atrial fibrillation	Oral/load instructions: Premature: 20 µg/kg Newborn: 30 µg/kg >6 mo: 40 µg/kg Give $\frac{1}{2}$ total dose followed by $\frac{1}{4}$ q8-12h × 2 doses Maintenance: 10 µg/kg/24 hr divide q12h Max dose: 0.5 mg IV: $\frac{3}{4}$ PO dose Max dose: 0.5 mg	PAC, PVC, bradycardia, AV block, nausea, vomiting, anorexia, prolongs PR interval	Quinidine Amiodarone, verapamil, increase digoxin levels	1-2 mg/mL
Verapamil	SVT (not WPW)	Oral: 2-7 mg/kg/24 hr divided q8h Max dose: 480 mg IV: 0.1-0.2 mg/kg q 20 min × 2 doses Max dose: 5-10 mg	Bradycardia, asystole, high degree AV block, PR prolongation, hypotension, CHF	Use with β-blocker or disopyramide exacerbates CHF, increases digoxin level and toxicity	
Adenosine	SVT	IV: 50-300 µg/kg by need rapid IV push Begin with 50 µg/kg and increase by 50-100 µg/kg/dose Max dose: 18 mg	Chest pain, flushing, dyspnea, bronchospasm, atrial fibrillation, bradycardia, asystole		

AV, atrioventricular; CHF, congestive heart failure; CNS, central nervous systems; GI, gastrointestinal; IV, intravenous; JET, junctional ectopic tachycardia; NAPA, N-acetyl procainamide; PAC, premature atrial contraction; PTT, partial thromboplastin time; PVC, premature ventricular contraction; SLE, systemic lupus erythematosus-like illness; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

2258 Part XX ♦ The Cardiovascular System

Table 435-2 Diagnosis of Tachyarrhythmias: Electrocardiographic Findings

	HEART RATE (BEATS/MIN)	P WAVE	QRS DURATION	REGULARITY
Sinus tachycardia	<230	Always present, normal axis	Normal	Rate varies with respiration
Atrial tachycardia	180-320	Present Abnormal P wave morphology and axis	Normal or prolonged (with aberration)	Usually regular but ventricular response may be variable because of Wenckebach conduction
Atrial fibrillation	120-180	Fibrillatory waves	Normal or prolonged (with aberration)	Irregularly irregular (no 2 R-R intervals alike)
Atrial flutter	Atrial: 250-400 Ventricular response variable: 100-320	Sawtoothed flutter waves	Normal or prolonged (with aberration)	Regular ventricular response (e.g., 2:1, 3:1, 3:2, and so on)
Junctional tachycardia	120-280	Atrioventricular dissociation with no fusion, and normal QRS capture beats	Normal or prolonged (with aberration)	Regular (except with capture beats)
Ventricular tachycardia	120-300	Atrioventricular dissociation with capture beats and fusion beats	Prolonged for age	Regular (except with capture beats)

Table 435-3 Inherited Channel Mutations in Long and Short QT Syndromes

CHROMOSOME	GENE	PROTEIN	ION CURRENT AFFECTED	TRIGGER	SPECIAL FEATURES/ OCCURRENCE
LQTS TYPE					
1	11p15.5	KCNQ1	KvLQT1 (Kv7.1)	I_{K_s}	Exercise (swimming), emotion
2	7q35-36	KCNH2	HERG, (Kv11.1)	I_{K_r}	Rest, emotion, exercise (acoustic, postpartum), surprise (sudden loud noise)
3	3p24-21	SCN5A	Nav1.5	I_{Na}	Rest, sleep, emotion
4	4q24-27	ANK2	Ankyrin-B	$I_{Na-K}, I_{Na-Ca}, I_{Na}$	Exercise
5	21q22	KCNE1	MinK	I_{K_s}	Exercise, emotion
6	21q22	KCNE2	MIRP1	I_{K_r}	Rest, exercise
7	17q23	KCNJ2	Kir2.1	I_{K_1}	Rest, exercise
8	12p13.3	CACNA1C	Cav1.2	I_{Ca}	Exercise, emotion
9	3p25.3	CAV3	Caveolin-3	I_{Na}	Nonexertional, sleep
10	11q23.3	SCN4B	NaVβ4	I_{Na}	Exercise, postpartum
11	7q21-22	AKAP9	Yotiao	I_{K_s}	Poorly characterized
12	2q11.2	SNTA1	Syntrophin α1	I_{Na}	Poorly characterized
13	11q24	KCNJ5	Kir3.4	I_{K_r}	Poorly characterized
SHORT QT SYNDROME TYPE					
1	7q35-36	KCNH2	HERG (Kv11.1)	I_{K_r}	Exercise, rest (acoustic)
2	11p15.5	KCNQ1	KvLQT1 (Kv7.1)	I_{K_s}	—
3	17q23	KCNJ2	Kir2.1	I_{K_1}	Sleep
4	12p13.3	CACNA1C	Cav1.2	I_{Ca}	—
5	10p12.33	CACNB2b	CaV β2b	I_{Ca}	—
JERVELL AND LANGE-NIELSEN SYNDROME TYPE					
1	11p15.5	KCNQ1	KvLQT1 (Kv7.1)	I_{K_s}	Exercise (swimming), emotion
2	21q22	KCNE1	MinK	I_{K_s}	Exercise (swimming), emotion

From Morita H, Wu J, Zipes DP: The QT syndromes: long and short, Lancet 372:750-762, 2008, p. 751, Table 1.

Table 435-4 Acquired Causes of QT Prolongation*

DRUGS
Antibiotics—erythromycin, clarithromycin, azithromycin, telithromycin, trimethoprim/sulfamethoxazole, fluoroquinolones [†]
Antifungal agents [†] —fluconazole, itraconazole, ketoconazole
Antiprotozoal agents—pentamidine isethionate
Antihistamines—astemizole, terfenadine (Seldane; Seldane has been removed from the market for this reason)
Antidepressants—tricyclics such as imipramine (Tofranil), amitriptyline (Elavil), desipramine (Norpramin), and doxepin (Sinequan)
Antipsychotics—haloperidol, risperidone, phenothiazines such as thioridazine (Mellaril) and chlorpromazine (Thorazine), selective serotonin uptake inhibitors
Antiarrhythmic agents
Class 1A (sodium channel blockers)—quinidine, procainamide, disopyramide
Class III (prolong depolarization)—amiodarone (rare), bretylium, dofetilide, N-acetyl-procainamide, sotalol
Lipid-lowering agents—probucol
Antianginals—bepridil
Diuretics (through K ⁺ loss)—furosemide (Lasix), ethacrynic acid (bumetanide [Bumex])
Opiates—methadone, oxycodone
Oral hypoglycemic agents—glibenclamide, glyburide
Organophosphate insecticides
Motility agents—cisapride, domperidone
Vasodilators—prenylamine
Other drugs—Ondansetron, HIV protease inhibitors, Chinese herbs
ELECTROLYTE DISTURBANCES
Hypokalemia—diuretics, hyperventilation
Hypocalcemia
Hypomagnesemia
UNDERLYING MEDICAL CONDITIONS
Bradycardia—complete atrioventricular block, severe bradycardia, sick sinus syndrome
Myocardial dysfunction—anthracycline cardiotoxicity, congestive heart failure, myocarditis, cardiac tumors
Endocrinopathy—hyperparathyroidism, hypothyroidism, pheochromocytoma
Neurologic—encephalitis, head trauma, stroke, subarachnoid hemorrhage
Nutritional—alcoholism, anorexia nervosa, starvation

*A more exhaustive updated list of medications that can prolong the QTc interval is available at the University of Arizona Center for Education and Research of Therapeutics website (www.aczert.org).

[†]Combinations of quinolones plus azoles increase the risk of prolonged QT intervals.

From Park MY: Pediatric cardiology for practitioners, ed 5, Philadelphia, 2008, Mosby/Elsevier, p. 433, Box 24-1.

Table 434-1 Extracardiac Complications of Cyanotic Congenital Heart Disease and Eisenmenger Physiology

PROBLEM	ETIOLOGY	THERAPY
Polycythemia	Persistent hypoxia	Phlebotomy
Relative anemia	Nutritional deficiency	Iron replacement
CNS abscess	Right-to-left shunting	Antibiotics, drainage
CNS thromboembolic stroke	Right-to-left shunting or polycythemia	Phlebotomy
Low-grade DIC, thrombocytopenia	Polycythemia	None for DIC unless bleeding, then phlebotomy
Hemoptysis	Pulmonary infarct, thrombosis, or rupture of pulmonary artery plexiform lesion	Embolization
Gum disease	Polycythemia, gingivitis, bleeding	Dental hygiene
Gout	Polycythemia, diuretic agent	Allopurinol
Arthritis, clubbing	Hypoxic arthropathy	None
Pregnancy complications: abortion, fetal growth retardation, prematurity increase, maternal illness	Poor placental perfusion, poor ability to increase cardiac output	Bed rest, pregnancy prevention counseling
Infections	Associated asplenia, DiGeorge syndrome, endocarditis	Antibiotics
	Fatal RSV pneumonia with pulmonary hypertension	Ribavirin; RSV immunoglobulin (prevention)
Failure to thrive	Increased oxygen consumption, decreased nutrient intake	Treat heart failure; correct defect early; increase caloric intake
Protein-losing enteropathy	S/P Fontan; high right-sided pressures	Oral budesonide or sildenafil
Chylothorax	Injury to thoracic duct	Medium chain triglyceride diet Octreotide Surgical ligation of thoracic duct
Psychosocial adjustment	Limited activity, cyanotic appearance, chronic disease, multiple hospitalizations	Counseling

CNS, central nervous system; DIC, disseminated intravascular coagulation; RSV, respiratory syncytial virus; S/P, status post (after).

Table 436-1

Potential Causes of Sudden Death in Infants, Children, and Adolescents

SIDS AND SIDS "MIMICS"

- SIDS
- Long QT syndromes*
- Inborn errors of metabolism
- Child abuse
- Myocarditis
- Ductal-dependent congenital heart disease

CORRECTED OR UNOPERATED CONGENITAL HEART DISEASE

- Aortic stenosis
- Tetralogy of Fallot
- Transposition of great vessels (postoperative atrial switch)
- Mitral valve prolapse
- Hypoplastic left-heart syndrome
- Eisenmenger syndrome

CORONARY ARTERIAL DISEASE

- Anomalous origin*
- Anomalous tract (tunneled)
- Kawasaki disease
- Periarteritis
- Arterial dissection
- Marfan syndrome (rupture of aorta)
- Myocardial infarction

MYOCARDIAL DISEASE

- Myocarditis
- Hypertrophic cardiomyopathy*
- Dilated cardiomyopathy
- Arrhythmogenic right ventricular dysplasia
- Lyme carditis

CONDUCTION SYSTEM ABNORMALITY/ARRHYTHMIA

- Long QT syndromes*
- Brugada syndrome
- Proarrhythmic drugs
- Preexcitation syndromes
- Heart block
- Commotio cordis
- Idiopathic ventricular fibrillation
- Arrhythmogenic right ventricular dysplasia
- Catecholaminergic polymorphic ventricular tachycardia
- Heart tumor

MISCELLANEOUS

- Pulmonary hypertension
- Pulmonary embolism
- Heat stroke
- Cocaine and other stimulant drugs or medications
- Anorexia nervosa
- Electrolyte disturbances

SIDS, sudden infant death syndrome.

*Common.

Table 437-1

Bacterial Agents in Pediatric Infective Endocarditis

COMMON: NATIVE VALVE OR OTHER CARDIAC LESIONS

- Viridans group streptococci (*Streptococcus mutans*, *Streptococcus sanguinis*, *Streptococcus mitis*)
- Staphylococcus aureus*
- Group D streptococcus (enterococcus) (*Streptococcus bovis*, *Streptococcus faecalis*)

UNCOMMON: NATIVE VALVE OR OTHER CARDIAC LESIONS

- Streptococcus pneumoniae*
- Haemophilus influenzae*
- Coagulase-negative staphylococci
- Abiotrophia defectiva* (nutritionally variant streptococcus)
- Coxiella burnetii* (Q fever)*
- Neisseria gonorrhoeae*
- Brucella**
- Chlamydia psittaci**
- Chlamydia trachomatis**
- Chlamydia pneumoniae**
- Legionella**
- Bartonella**
- Tropheryma whipplei** (Whipple disease)
- HACEK group†
- Streptobacillus moniliformis**
- Pasteurella multocida**
- Campylobacter fetus*
- Culture negative (6% of cases)

PROSTHETIC VALVE

- Staphylococcus epidermidis*
- Staphylococcus aureus*
- Viridans group streptococcus
- Pseudomonas aeruginosa*
- Serratia marcescens*
- Diphtheroids
- Legionella* species*
- HACEK group†
- Fungi‡

*These fastidious bacteria plus some fungi may produce culture-negative endocarditis. Detection may require special media, incubation for more than 7 days, polymerase chain reaction on blood or valve for 16S rRNA (bacteria) or 18S rRNA (fungi), or serologic tests.

†The HACEK group includes *Haemophilus* species (*H. paraphrophilus*, *H. parainfluenzae*, *H. aphrophilus*), *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species.

‡*Candida* species, *Aspergillus* species, *Pseudallescheria boydii*, *Histoplasma capsulatum*.

Priority: blood specimen

Q fever and *Bartonella* serology
+
Determination of rheumatoid factors and antinuclear antibodies

If negative

Dedicated PCR for *Bartonella* sp and *Tropheryma whipplei*, broad range PCR for fungi

If negative

Septifast blood PCR specifically targeting streptococci and staphylococci (if previous antibiotic therapy)

Other serologies (*Mycoplasma pneumoniae*, *Legionella pneumophila*, *Brucella melitensis*) and western blot for *Bartonella* spp

Valvular specimen available

Broad range PCR for bacteria (16S rRNA) and fungi (18S rRNA)
+
Histological examination

If negative

Primer extension enrichment reaction

Autoimmunohistochemistry

Figure 437-1 Diagnostic tests applied to clinical specimens for the identification of the causative agents of blood culture-negative endocarditis. Septifast, LightCycler SeptiFast (Roche). Serum should be considered a priority specimen, with Q fever and *Bartonella* serologic analysis being routinely done. We also suggest that detection of antinuclear antibodies and rheumatoid factor should be routinely done for diagnosis of noninfective endocarditis.

Table 437-2 Manifestations of Infective Endocarditis

HISTORY	
Prior congenital or rheumatic heart disease	
Preceding dental, urinary tract, or intestinal procedure	
Intravenous drug use	
Central venous catheter	
Prosthetic heart valve	
SYMPTOMS	
Fever	
Chills	
Chest and abdominal pain	
Arthralgia, myalgia	
Dyspnea	
Malaise, weakness	
Night sweats	
Weight loss	
CNS manifestations (stroke, seizures, headache)	
SIGNS	
Elevated temperature	
Tachycardia	
Embolic phenomena (Roth spots, petechiae, splinter nail bed hemorrhages, Osler nodes, CNS or ocular lesions)	
Janeway lesions	
New or changing murmur	
Splenomegaly	
Arthritis	
Heart failure	
Arrhythmias	
Metastatic infection (arthritis, meningitis, mycotic arterial aneurysm, pericarditis, abscesses, septic pulmonary emboli)	
Clubbing	
LABORATORY	
Positive blood culture	
Elevated erythrocyte sedimentation rate; may be low with heart or renal failure	
Elevated C-reactive protein	
Anemia	
Leukocytosis	
Immune complexes	
Hypergammaglobulinemia	
Hypocomplementemia	
Cryoglobulinemia	
Rheumatoid factor	
Hematuria	
Renal failure: azotemia, high creatinine (glomerulonephritis)	
Chest radiograph: bilateral infiltrates, nodules, pleural effusions	
Echocardiographic evidence of valve vegetations, prosthetic valve dysfunction or leak, myocardial abscess, new-onset valve insufficiency	

Table 437-3 Diagnostic Approach to Uncommon Pathogens Causing Endocarditis

PATHOGEN	DIAGNOSTIC PROCEDURE
<i>Brucella</i> spp.	Blood cultures; serology; culture, immunohistology, and PCR of surgical material
<i>Coxiella burnetii</i>	Serology (IgG phase I >1 in 800); tissue culture, immunohistology, and PCR of surgical material
<i>Bartonella</i> spp.	Blood cultures; serology; culture, immunohistology, and PCR of surgical material
<i>Chlamydia</i> spp.	Serology; culture, immunohistology, and PCR of surgical material
<i>Mycoplasma</i> spp.	Serology; culture, immunohistology, and PCR of surgical material
<i>Legionella</i> spp.	Blood cultures; serology; culture, immunohistology, and PCR of surgical material
<i>Tropheryma whipplei</i>	Histology and PCR of surgical material

Table 437-6 2007 Statement of the American Heart Association (AHA): Cardiac Conditions Associated with the Highest Risk of an Adverse Outcome from Infective Endocarditis for Which Prophylaxis with Dental Procedures Is Reasonable

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous infective endocarditis
CONGENITAL HEART DISEASE (CHD)*
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired CHD with prosthetic material or device, whether placed by surgery or catheter intervention, during the 1st 6 mo after the procedure [†]
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch, or prosthetic device (which inhibit endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy

*Except for the conditions listed here, antibiotic prophylaxis is no longer recommended by the AHA for any other form of CHD.

[†]Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 mo after the procedure.

From Wilson W, Taubert KA, Gewitz M, et al: Prevention of infective endocarditis. Guidelines from the American Heart Association. Circulation 116:1736–1754, 2007.

Table 440-1 Etiology of Pericardial Disease

CONGENITAL	
Absence (partial, complete)	
Cysts	
Milibray nanism (<i>TRIM 37</i> gene mutation)	
Camptodactyly-arthropathy-coxa vara-pericarditis syndrome (<i>PRG4</i> gene mutation)	
INFECTIOUS	
Viral (coxsackievirus B, Epstein-Barr virus, influenza, adenovirus, parvovirus, HIV, mumps)	
Bacterial (<i>Haemophilus influenzae</i> , streptococcus, pneumococcus, staphylococcus, meningococcus, mycoplasma, tularemia, listeria, leptospirosis, tuberculosis, Q-fever, salmonella)	
Immune complex (meningococcus, <i>H. influenzae</i>)	
Fungal (actinomycosis, histoplasmosis)	
Parasitic (toxoplasmosis, echinococcosis)	
NONINFECTIOUS	
Idiopathic	
Systemic inflammatory diseases (acute rheumatic fever, juvenile idiopathic arthritis, systemic lupus erythematosus, mixed connective tissue disorders, systemic sclerosis, Kawasaki disease, Churg-Strauss syndrome, Behcet syndrome, sarcoidosis, familial Mediterranean fever and other recurrent fever syndromes, pancreatitis, granulomatosis with polyangiitis)	
Metabolic (uremia, hypothyroidism, Gaucher disease, very-long-chain acyl-CoA dehydrogenase deficiency)	
Traumatic (surgical, catheter, blunt)	
Lymphomas, leukemia, radiation therapy	
Primary pericardial tumors	

Table 437-4Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *Streptococcus bovis*

REGIMENT	DOSAGE* AND ROUTE	DURATION, WK	COMMENTS
Aqueous crystalline penicillin G sodium <i>or</i>	12-18 million U/24 hr IV either continuously or in 4 or 6 equally divided doses	4	Preferred in patients with impairment of 8th cranial nerve function or renal function
Ceftriaxone sodium	2 g/24 hr IV/IM in 1 dose <i>Pediatric dose</i> [†] : penicillin 200,000 U/kg per 24 hr IV in 4-6 equally divided doses; ceftriaxone 100 mg/kg per 24 hr IV/IM in 1 dose	4	
Aqueous crystalline penicillin G sodium <i>or</i>	12-18 million U/24 hr IV either continuously or in 6 equally divided doses	2	2 wk regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired 8th cranial nerve function, or <i>Abiotrophia</i> , <i>Granulicatella</i> , or <i>Gemella</i> spp. infection; gentamicin dosage should be adjusted to achieve peak serum concentration of 3-4 µg/mL and trough serum concentration of <1 µg/mL when 3 divided doses are used; nomogram used for single daily dosing
Ceftriaxone sodium <i>plus</i>	2 g/24 hr IV/IM in 1 dose	2	
Gentamicin sulfate [‡]	3 mg/kg per 24 hr IV/IM in 1 dose, or 3 equally divided doses <i>Pediatric dose</i> : penicillin 200,000 U/kg per 24 hr IV in 4-6 equally divided doses; ceftriaxone 100 mg/kg per 24 hr IV/IM in 1 dose; gentamicin 3 mg/kg per 24 hr IV/IM in 1 dose or 3 equally divided doses [§]	2	
Vancomycin hydrochloride [¶]	30 mg/kg per 24 hr IV in 2 equally divided doses not to exceed 2 g/24 hr unless concentrations in serum are inappropriately low <i>Pediatric dose</i> : 40 mg/kg per 24 hr IV in 2-3 equally divided doses	4	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain peak (1 hr after infusion completed) serum concentration of 30-45 µg/mL and a trough concentration range of 10-15 µg/mL

Minimum inhibitory concentration ≤0.12 µg/mL.

*Dosages recommended are for patients with normal renal function.

[†]Pediatric dose should not exceed that of a normal adult.[‡]Other potentially nephrotoxic drugs (e.g., nonsteroidal antiinflammatory drugs) should be used with caution in patients receiving gentamicin therapy.[§]Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of infective endocarditis exist.[¶]Vancomycin dosages should be infused during course of at least 1 hr to reduce risk of histamine-release "red man" syndrome.From Baddour LM, Wilson WR, Bayer AS, et al: *Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications*, Circulation 111:e394–**Table 439-3**

Causes of Myocarditis

INFECTIOUS		IMMUNE-MEDIATED	TOXIC
Viral	Adenovirus Parvovirus Coxsackie B virus Epstein-Barr virus Hepatitis C virus Measles virus Human herpes virus Varicella-zoster virus Human immunodeficiency virus Influenza viruses	Autoantigens	Churg-Strauss syndrome Inflammatory bowel disease Giant cell myocarditis Diabetes mellitus Sarcoidosis Systemic lupus erythematosus Thyrototoxicosis Takayasu arteritis Kawasaki syndrome Celiac disease Whipple disease
Bacterial	Mycobacteria <i>Streptococcus</i> spp. <i>Mycoplasma pneumoniae</i> <i>Treponema pallidum</i> <i>Corynebacterium diphtheriae</i> <i>Borrelia burgdorferi</i> <i>Ehrlichia</i>		Anthracyclines Cocaine Interleukin-2 Ethanol Heavy metals Spider bite Snake bite Scorpion bite Electric shock
Fungal	<i>Aspergillus</i> <i>Candida</i> <i>Coccidioides</i> <i>Cryptococcus</i> <i>Histoplasma</i>	Hypersensitivity	Granulomatosis with polyangiitis Sulfonamides Cephalosporins Diuretics Tricyclic antidepressants Dobutamine
Protozoal	<i>Trypanosoma cruzi</i> <i>Toxoplasma gondii</i> <i>Babesia</i>		
Parasitic	Schistosomiasis Larva migrans (visceral)		

Data from Feldman AM, McNamara D: Myocarditis, N Engl J Med 343:1388-1398, 2000; Magnani JW, Dec GW: Myocarditis: current trends in diagnosis and treatment, Circulation 113:876-990, 2006.

2268 Part XX ◆ The Cardiovascular System

Table 437-5 Therapy for Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

REGIMEN	DOSAGE* AND ROUTE	DURATION	COMMENTS
OXACILLIN-SUSCEPTIBLE STRAINS			
Nafcillin or oxacillin [†]	12 g/24 hr IV in 4-6 equally divided doses	6 wk	For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk
with Optional addition of gentamicin sulfate [‡]	3 mg/kg per 24 hr IV/IM in 2 or 3 equally divided doses <i>Pediatric dose</i> [§] : Nafcillin or oxacillin 200 mg/kg per 24 hr IV in 4-6 equally divided doses; gentamicin 3 mg/kg per 24 hr IV/IM in 3 equally divided doses	3-5 day	Clinical benefit of aminoglycosides has not been established
For penicillin-allergic (nonanaphylactoid-type) patients: Cefazolin	6 g/24 hr IV in 3 equally divided doses	6 wk	Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β -lactams; vancomycin should be used in these cases [§]
with Optional addition of gentamicin sulfate	3 mg/kg per 24 hr IV/IM in 2 or 3 equally divided doses <i>Pediatric dose</i> : cefazolin 100 mg/kg per 24 hr IV in 3 equally divided doses; gentamicin 3 mg/kg per 24 hr IV/IM in 3 equally divided doses	3-5 day	Clinical benefit of aminoglycosides has not been established
OXACILLIN-RESISTANT STRAINS			
Vancomycin [¶]	30 mg/kg per 24 hr IV in 2 equally divided doses <i>Pediatric dose</i> : 40 mg/kg per 24 hr IV in 2 or 3 equally divided doses	6 wk	Adjust vancomycin dosage to achieve 1 hr serum concentration of 30-45 μ g/mL and trough concentration of 10-15 μ g/mL

IE, infective endocarditis.

*Dosages recommended are for patients with normal renal function.

[†]Penicillin G 24 million U/24 hr IV in 4-6 equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration \leq 0.1 μ g/mL) and does not produce β -lactamase.[‡]Gentamicin should be administered in close temporal proximity to vancomycin, nafcillin, or oxacillin dosing.[§]Pediatric dose should not exceed that of a normal adult.[¶]For specific dosing adjustment and issues concerning vancomycin, see Table 437-4 footnotes.

From Badour LM, Wilson WR, Bayer AS, et al: Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications, Circulation 111:e394–

Table 437-7 2007 Statement of the American Heart Association (AHA): Prophylactic Antibiotic Regimens for a Dental Procedure

SITUATION	AGENT	ADULTS	CHILDREN
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin or cefazolin or ceftriaxone	2 g IM or IV 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin ^{*†} or Clindamycin or Azithromycin or clarithromycin	2 g 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone [†] or clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

IM, intramuscular; IV, intravenous.

^{*}Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.[†]Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, urticaria with penicillins or ampicillin.

From Wilson W, Taubert KA, Gewitz M, et al: Prevention of infective endocarditis. Guidelines from the American Heart Association, Circulation 116:1736–1754, 2007.

Table 439-1 Etiology of Pediatric Myocardial Disease

CARDIOMYOPATHY	
Dilated Cardiomyopathy (DCM)	
Neuromuscular diseases	Muscular dystrophies (Duchenne, Becker, limb girdle, Emery-Dreifuss, congenital muscular dystrophy, etc.), myotonic dystrophy, myofibrillar myopathy
Inborn errors of metabolism	Fatty acid oxidation disorders (trifunctional protein, VLCAD), carnitine abnormalities (carnitine transport, CPTI, CPTII), mitochondrial disorders (including Kearns-Sayre syndrome), organic acidemias (propionic acidemia)
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic DCM
Genetic syndromes	Alstrom syndrome, Barth syndrome (phospholipid disorders)
Ischemic	Most common in adults
Chronic tachyarrhythmias	
Hypertrophic Cardiomyopathy (HCM)	
Inborn errors of metabolism	Mitochondrial disorders (including Friedreich ataxia, mutations in nuclear or mitochondrial genome), storage disorders (glycogen storage disorders, especially Pompe; mucopolysaccharidoses; Fabry disease; sphingolipidoses; hemochromatosis; Danon disease)
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic HCM
Genetic syndromes	Noonan, Costello, cardiofaciocutaneous, Beckwith-Wiedemann syndrome
Infant of a diabetic mother	Transient hypertrophy
Restrictive Cardiomyopathy (RCM)	
Neuromuscular disease	Myofibrillar myopathies
Metabolic	Storage disorders
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic RCM
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic ARVC
LVNC	X-linked (Barth syndrome), autosomal dominant, autosomal recessive, mitochondrial inheritance, or sporadic LVNC
SECONDARY OR ACQUIRED MYOCARDIAL DISEASE	
Myocarditis (see also Table 439-3)	Viral: parvovirus B19, adenovirus, coxsackievirus A and B, echovirus, rubella, varicella, influenza, mumps, Epstein-Barr virus, cytomegalovirus, measles, poliomyelitis, smallpox vaccine, hepatitis C virus, human herpesvirus 6, HIV virus, or opportunistic infections Rickettsial: psittacosis, <i>Coxiella</i> , Rocky Mountain spotted fever, typhus Bacterial: diphtheria, mycoplasma, meningococcus, leptospirosis, Lyme disease, typhoid fever, tuberculosis, streptococcus, listeriosis Parasitic: Chagas disease, toxoplasmosis, <i>Loa loa</i> , <i>Toxocara canis</i> , schistosomiasis, cysticercosis, echinococcus, trichinosis Fungal: histoplasmosis, coccidioidomycosis, actinomycosis SLE, infant of mother with SLE, scleroderma, Churg-Strauss vasculitis, rheumatoid arthritis, rheumatic fever, sarcoidosis, dermatomyositis, periarteritis nodosa, hypereosinophilic syndrome (Löffler syndrome), acute eosinophilic necrotizing myocarditis, giant cell myocarditis, Kawasaki disease Beriberi (thiamine deficiency), kwashiorkor, Keshan disease (selenium deficiency) Doxorubicin (Adriamycin), cyclophosphamide, chloroquine, ipecac (emetine), sulfonamides, mesalazine, chloramphenicol, alcohol, hypersensitivity reaction, envenomations, irradiation, herbal remedy (blue cohosh)
Systemic inflammatory disease	Kawasaki disease, medial necrosis, anomalous left coronary artery from the pulmonary artery, other congenital coronary anomalies (anomalous right coronary, coronary ostial stenosis), familial hypercholesterolemia
Nutritional deficiency Drugs, toxins	Anemia, sickle cell disease, leukemia Hyperthyroidism, carcinoid tumor, pheochromocytoma
Coronary artery disease	
Hematology-oncology Endocrine-neuroendocrine	

CPTI/CPTII, carnitine palmitoyltransferase 1/2; LVNC, left ventricular noncompaction; SLE, systemic lupus erythematosus; VLCAD, very long chain acyl coenzyme A dehydrogenase.

Table 442-2 Dosage of Drugs Commonly Used for the Treatment of Congestive Heart Failure

DRUG	DOSAGE
DIGOXIN	
Digitalization ($\frac{1}{2}$ initially, followed by $\frac{1}{4}$ q12h \times 2)	Premature: 20 µg/kg Full-term neonate (up to 1 mo): 20-30 µg/kg Infant or child: 25-40 µg/kg Adolescent or adult: 0.5-1 mg in divided doses NOTE: These doses are PO; IV dose is 75% of PO dose
Maintenance digoxin	5-10 µg/kg/day, divided q12h Trough serum level: 1.5-3.0 ng/mL <6 mo old; 1-2 ng/mL >6 mo old NOTE: These doses are PO; IV dose is 75% of PO dose
DIURETICS	
Furosemide (Lasix)	IV: 0.5-2 mg/kg/dose PO: 1-4 mg/kg/day, divided qd-qid
Bumetanide (Bumex)	IV: 0.01-0.1 mg/kg/dose PO: 0.01-0.1 mg/kg/day q24-48h
Chlorothiazide (Diuril)	PO: 20-40 mg/kg/day, divided bid or tid
Spironolactone (Aldactone)	PO: 1-3 mg/kg/day, divided bid or tid
Nesiritide (B-type natriuretic peptide)	IV: 0.001-0.03 µg/kg/min
ADRENERGIC AGONISTS (ALL IV)	
Dobutamine	2-20 µg/kg/min
Dopamine	2-30 µg/kg/min
Isoproterenol	0.01-0.5 µg/kg/min
Epinephrine	0.1-1.0 µg/kg/min
Norepinephrine	0.1-2.0 µg/kg/min
PHOSPHODIESTERASE INHIBITORS (ALL IV)	
Milrinone	0.25-1.0 µg/kg/min
AFTERLOAD-REDUCING AGENTS	
Captopril (Capoten), all PO	Prematures: start at 0.01 mg/kg/dose; 0.1-0.4 mg/kg/day, divided q6-24h Infants: 1.5-6 mg/kg/day, divided q6-12h Children: 2.5-6 mg/kg/day, divided q6-12h
Enalapril (Vasotec), all PO	0.08-0.5 mg/kg/day, divided q12-24h
Hydralazine (Apresoline)	IV: 0.1-0.5 mg/kg/dose (maximum: 20 mg) PO: 0.75-5 mg/kg/day, divided q6-12h
Nitroglycerin	IV: 0.25-0.5 µg/kg/min start; increase to 20 µg/kg/min maximum
Nitroprusside (Nipride)	IV: 0.5-8 µg/kg/min
β-ADRENERGIC BLOCKERS	
Carvedilol (Coreg)	PO: initial dose 0.1 mg/kg/day (maximum: 6.25 mg) divided bid, increase gradually (usually 2 wk intervals) to maximum of 0.5-1 mg/kg/day over 8-12 wk as tolerated; adult maximal dose: 50-100 mg/day
Metoprolol (Lopressor, Toprol-XL)	PO, nonextended release form: 0.2 mg/kg/day divided bid, increase gradually (usually 2 wk intervals) to maximum dose of 1-2 mg/kg/day PO, extended release form (Toprol-XL) is given once daily; adult initial dose 25 mg/day, maximum dose is 200 mg/day

Note: Pediatric doses based on weight should not exceed adult doses. Because recommendations may change, these doses should always be double-checked. Doses may also need to be modified in any patient with renal or hepatic dysfunction.

Maintenance digitalis therapy is started \approx 12 hr after full digitalization. The daily dosage, one quarter of the total digitalizing dose, is divided in 2 and given at 12-hr intervals. The oral maintenance dose is usually 20-25% higher than when digoxin is used parenterally (see Table 442-2). The normal daily dose of digoxin for older children (>5 yr of age) calculated by body weight should not exceed the usual adult dose of 0.125-0.5 mg/24 hr.

Table 442-3 Treatment of Cardiogenic Shock*

DETERMINANTS OF STROKE VOLUME			
	Preload	Contractility	Afterload
Parameters measured	CVP, PCWP, LAP, cardiac chamber size on echocardiography	CO, BP, fractional shortening or ejection fraction on echocardiography, MV O ₂ saturation	BP, peripheral perfusion, SVR
Treatment to improve cardiac output	Volume expansion (crystalloid, colloid, blood)	β-Adrenergic agonists, phosphodiesterase inhibitors	Afterload-reducing agents: milrinone, nitroprusside, ACE inhibitors

ACE, angiotensin-converting enzyme; BP, blood pressure; CO, cardiac output (measured with a thermodilution catheter); CVP, central venous pressure; LAP, left atrial pressure (measured with an indwelling LA line); MV O₂ saturation, mixed venous oxygen saturation (measured with a central venous catheter); PCWP, pulmonary capillary wedge pressure (measured with a thermodilution catheter); SVR, systemic vascular resistance (calculated from CO and mean BP).

*The goal is to improve peripheral perfusion by increasing cardiac output, where: cardiac output = heart rate \times stroke volume.

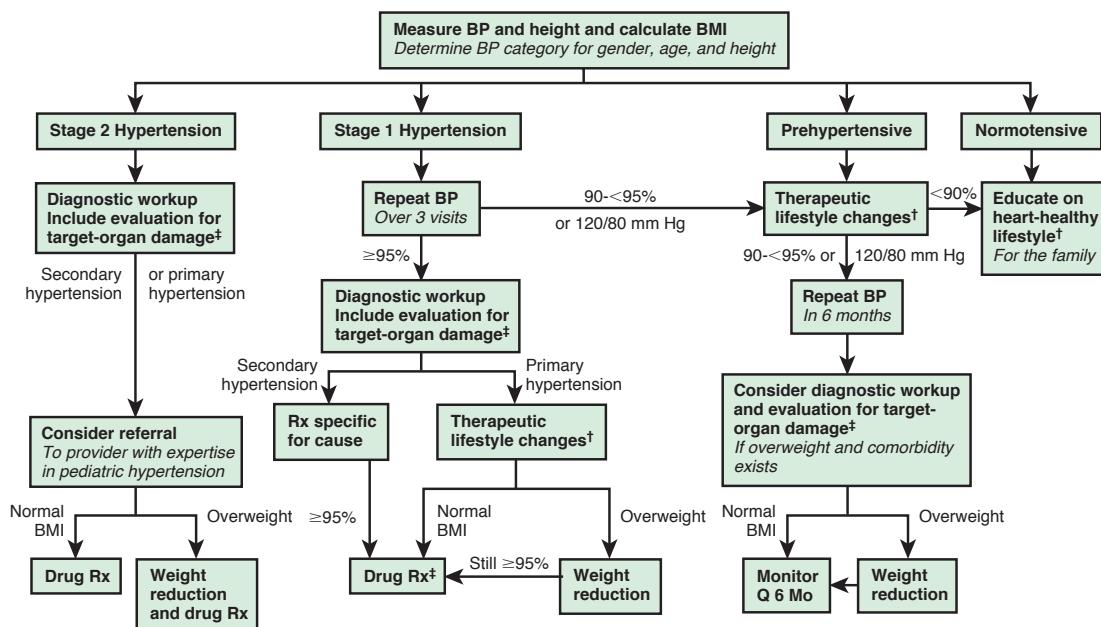


Figure 445-1 Management algorithm. BMI, body mass index; BP, blood pressure; Q, every; Rx, prescription; † diet modification and physical activity; ‡ especially if younger, very high BP, little or no family history, diabetic, or other risk factors. (From National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, Pediatrics 114[2 Suppl 4th Report]:571, 2004.)

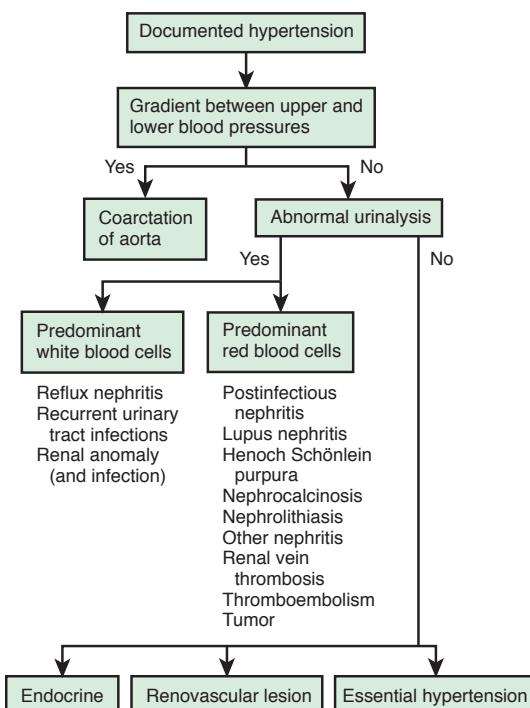


Figure 445-3 Initial diagnostic algorithm in the evaluation of hypertension. (From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, ed 2, Philadelphia, 2004, Elsevier, p. 222.)

Table 442-1 Etiology of Heart Failure

FETAL
Severe anemia (hemolysis, fetal-maternal transfusion, parvovirus B19-induced anemia, hypoplastic anemia)
Supraventricular tachycardia
Ventricular tachycardia
Complete heart block
Severe Ebstein anomaly or other severe right-sided lesions
Myocarditis
PREMATURE NEONATE
Fluid overload
Patent ductus arteriosus
Ventricular septal defect
Cor pulmonale (bronchopulmonary dysplasia)
Hypertension
Myocarditis
Genetic cardiomyopathy
FULL-TERM NEONATE
Asphyxial cardiomyopathy
Arteriovenous malformation (vein of Galen, hepatic)
Left-sided obstructive lesions (coarctation of aorta, hypoplastic left heart syndrome)
Large mixing cardiac defects (single ventricle, truncus arteriosus)
Myocarditis
Genetic cardiomyopathy
INFANT-TODDLER
Left-to-right cardiac shunts (ventricular septal defect)
Hemangioma (arteriovenous malformation)
Anomalous left coronary artery
Genetic or metabolic cardiomyopathy
Acute hypertension (hemolytic-uremic syndrome)
Supraventricular tachycardia
Kawasaki disease
Myocarditis
CHILD-ADOLESCENT
Rheumatic fever
Acute hypertension (glomerulonephritis)
Myocarditis
Thyrototoxicosis
Hemochromatosis-hemosiderosis
Cancer therapy (radiation, doxorubicin)
Sickle cell anemia
Endocarditis
Cor pulmonale (cystic fibrosis)
Genetic or metabolic cardiomyopathy (hypertrophic, dilated)

2296 Part XX ◆ The Cardiovascular System

Table 445-1 Conditions Associated with Chronic Hypertension in Children

RENAL
Chronic pyelonephritis
Chronic glomerulonephritis
Hydronephrosis
Congenital dysplastic kidney
Multicystic kidney
Solitary renal cyst
Vesicoureteral reflux nephropathy
Segmental hypoplasia (Asz-Upmark kidney)
Ureteral obstruction
Renal tumors
Renal trauma
Rejection damage following transplantation
Postirradiation damage
Systemic lupus erythematosus (other connective tissue diseases)
VASCULAR
Coarctation of thoracic or abdominal aorta
Renal artery lesions (stenosis, fibromuscular dysplasia, thrombosis, aneurysm)
Umbilical artery catheterization with thrombus formation
Neurofibromatosis (intrinsic or extrinsic narrowing of vascular lumen)
Renal vein thrombosis
Vasculitis
Arteriovenous shunt
Williams-Beuren syndrome
Moyamoya disease
Takayasu arteritis
ENDOCRINE
Hyperthyroidism
Hyperparathyroidism
Congenital adrenal hyperplasia (11β-hydroxylase and 17-hydroxylase defect)
Cushing syndrome
Primary aldosteronism
Apparent mineralocorticoid excess
Glucocorticoid remedial aldosteronism (familial aldosteronism type 1)
Glucocorticoid resistance (Chrousos syndrome)
Pseudohypaldosteronism type 2 (Gordon syndrome)
Pheochromocytoma
Other neural crest tumors (neuroblastoma, ganglioneuroblastoma, ganglioneuroma)
Liddle syndrome
Geller syndrome
CENTRAL NERVOUS SYSTEM
Intracranial mass
Hemorrhage
Residual following brain injury
Quadriplegia

Table 445-2 Conditions Associated with Transient or Intermittent Hypertension in Children

RENAL
Acute postinfectious glomerulonephritis
Anaphylactoid (Henoch-Schönlein) purpura with nephritis
Hemolytic-uremic syndrome
Acute tubular necrosis
After renal transplantation (immediately and during episodes of rejection)
After blood transfusion in patients with azotemia
Hyponatremia
After surgical procedures on the genitourinary tract
Pyelonephritis
Renal trauma
Leukemic infiltration of the kidney
Obstructive uropathy associated with Crohn disease
DRUGS AND POISONS
Cocaine
Oral contraceptives
Sympathomimetic agents
Amphetamines
Phencyclidine
Corticosteroids and adrenocorticotrophic hormone
Cyclosporine or sirolimus treatment posttransplantation
Licorice (glycyrrhizic acid)
Lead, mercury, cadmium, thallium
Antihypertensive withdrawal (clonidine, methyldopa, propranolol)
Vitamin D intoxication
CENTRAL AND AUTONOMIC NERVOUS SYSTEM
Increased intracranial pressure
Guillain-Barré syndrome
Burns
Familial dysautonomia
Stevens-Johnson syndrome
Posterior fossa lesions
Porphyria
Poliomyelitis
Encephalitis
Spinal cord injury (autonomic storm)
MISCELLANEOUS
Preeclampsia
Fractures of long bones
Hypercalcemia
After coarctation repair
White cell transfusion
Extracorporeal membrane oxygenation
Chronic upper airway obstruction

Table 445-3 Clinical Findings in Patients with Mineralocorticoid Excess

CONDITION	CLINICAL PRESENTATION
CAH: 11β-hydroxylase deficiency	Early growth spurt initially, then short adult stature, advanced bone age, premature adrenarche, acne, precocious puberty in males, amenorrhea/hirsutism/virilism in females
CAH: 17α-hydroxylase deficiency	Pseudohermaphroditism (male), sexual infantilism (female)
Apparent mineralocorticoid excess	Growth retardation/short stature, nephrocalcinosis
Liddle syndrome	Severe hypertension, hypokalemia, and metabolic alkalosis, muscle weakness
Geller syndrome	Early onset of hypertension (before age 20 years), exacerbated in pregnancy
Glucocorticoid remediable aldosteronism (GRA) (familial aldosteronism type 1)	Early onset of hypertension, presence of family history of mortality or morbidity from early hemorrhagic stroke
Pseudohypaldosteronism type 2 (Gordon syndrome)	Short stature, hyperkalemic and hyperchloremic metabolic acidosis, borderline blood pressure
Glucocorticoid resistance (children) (Chrousos syndrome)	Ambiguous genitalia, precocious puberty; women may have acne, excessive hair, oligo/anovulation, infertility

Table 445-4

Findings to Look for on Physical Examination in Patients with Hypertension

PHYSICAL FINDINGS	POTENTIAL RELEVANCE
GENERAL	
Pale mucous membranes, edema, growth retardation	Chronic renal disease
Elfin facies, poor growth, retardation	Williams syndrome
Webbing of neck, low hairline, widespread nipples, wide carrying angle	Turner syndrome
Moon face, buffalo hump, hirsutism, truncal obesity, striae, acne	Cushing syndrome
HABITUS	
Thinness	Pheochromocytoma, renal disease, hyperthyroidism
Virilization	Congenital adrenal hyperplasia
Rickets	Chronic renal disease
SKIN	
Café-au-lait spots, neurofibromas	Neurofibromatosis, pheochromocytoma
Tubers, "ash-leaf" spots	Tuberous sclerosis
Rashes	Systemic lupus erythematosus, vasculitis (Henoch-Schönlein purpura), impetigo with acute nephritis
Pallor, evanescent flushing, sweating	Pheochromocytoma
Needle tracks	Illicit drug use
Bruises, striae	Cushing syndrome
Acanthosis nigricans	Type 2 diabetes, insulin resistance
EYES	
Extraocular muscle palsy	Nonspecific, chronic, severe
Fundal changes	Nonspecific, chronic, severe
Proptosis	Hyperthyroidism
HEAD AND NECK	
Goiter	Thyroid disease
Adenotonsillar hypertrophy	Sleep disordered breathing
CARDIOVASCULAR SIGNS	
Absent or diminished femoral pulses, low leg pressure relative to arm pressure	Aortic coarctation
Heart size, rate, rhythm; murmurs; respiratory difficulty, hepatomegaly	Aortic coarctation, congestive heart failure
Bruits over great vessels	Arteritis or arteriopathy
Rub	Pericardial effusion secondary to chronic renal disease
PULMONARY SIGNS	
Pulmonary edema	Congestive heart failure, acute nephritis
Picture of bronchopulmonary dysplasia	Bronchopulmonary dysplasia-associated hypertension
ABDOMEN	
Epigastric bruit	Primary renovascular disease or in association with Williams syndrome, neurofibromatosis, fibromuscular dysplasia, or arteritis
Abdominal masses	Wilms tumor, neuroblastoma, pheochromocytoma, polycystic kidneys, hydronephrosis, dysplastic kidneys
NEUROLOGIC SIGNS	
Neurologic deficits	Chronic or severe acute hypertension with stroke
Muscle weakness	Hyperaldosteronism, Liddle syndrome
GENITALIA	
Ambiguous, virilized	Congenital adrenal hyperplasia

2300 Part XX ◆ The Cardiovascular System

STUDY OR PROCEDURE	PURPOSE	TARGET POPULATION
EVALUATION FOR IDENTIFIABLE CAUSES		
History, including sleep history, family history, risk factors, diet, and habits such as smoking and drinking alcohol; physical examination	History and physical examination help focus subsequent evaluation	All children with persistent BP ≥95th percentile
Blood urea nitrogen, creatinine, electrolytes, urinalysis, and urine culture	R/O renal disease and chronic pyelonephritis, mineralocorticoid excess states	All children with persistent BP ≥95th percentile
Complete blood count	R/O anemia, consistent with chronic renal disease	All children with persistent BP ≥95th percentile
Renal ultrasound	R/O renal scar, congenital anomaly, or disparate renal size	All children with persistent BP ≥95th percentile
EVALUATION FOR COMORBIDITY		
Fasting lipid panel, fasting glucose	Identify hyperlipidemia, identify metabolic abnormalities	Overweight patients with BP at 90th-94th percentile; all patients with BP ≥95th percentile; family history of hypertension or cardiovascular disease; child with chronic renal disease
Drug screen	Identify substances that might cause hypertension	History suggestive of possible contribution by substances or drugs.
Polysomnography	Identify sleep disorder in association with hypertension	History of loud, frequent snoring
EVALUATION FOR TARGET-ORGAN DAMAGE		
Echocardiogram	Identify left ventricular hypertrophy and other indications of cardiac involvement	Patients with comorbid risk factors* and BP 90th-94th percentile; all patients with BP ≥95th percentile
Retinal exam	Identify retinal vascular changes	Patients with comorbid risk factors and BP 90th-94th percentile; all patients with BP ≥95th percentile
ADDITIONAL EVALUATION AS INDICATED		
Ambulatory blood pressure monitoring	Identify white coat hypertension, abnormal diurnal BP pattern, BP load	Patients in whom white coat hypertension is suspected, and when other information on BP pattern is needed
Plasma renin determination	Identify low renin, suggesting mineralocorticoid-related disease	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension
Renovascular imaging Isotopic scintigraphy (renal scan) Magnetic resonance angiography Duplex Doppler flow studies 3-Dimensional CT Arteriography: digital subtraction arteriography or classic	Identify renovascular disease	Positive family history of severe hypertension Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension
Plasma and urine steroid levels	Identify steroid-mediated hypertension	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension
Plasma and urine catecholamines	Identify catecholamine-mediated hypertension	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension

R/O, rule out.

*Comorbid risk factors also include diabetes mellitus and kidney disease.

From National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, Pediatrics 114(2 Suppl 4th Report):562, 2004.

Table 445-6 Causes of Renovascular Hypertension in Children	
Fibromuscular dysplasia Syndromic <ul style="list-style-type: none"> • Neurofibromatosis type 1 • Tuberous sclerosis • Williams syndrome • Marfan syndrome • Other syndromes Vasculitis <ul style="list-style-type: none"> • Takayasu disease • Polyarteritis nodosa • Kawasaki disease • Other systemic vasculitides 	Extrinsic compression <ul style="list-style-type: none"> • Neuroblastoma • Wilms tumor • Other tumors Other causes <ul style="list-style-type: none"> • Radiation • Umbilical artery catheterization • Trauma • Congenital rubella syndrome • Transplant renal artery stenosis

From Tullus K, Brennan E, Hamilton G, et al: Renovascular hypertension in children, Lancet 371:1453-1463, 2008, p. 1454, Panel 1.

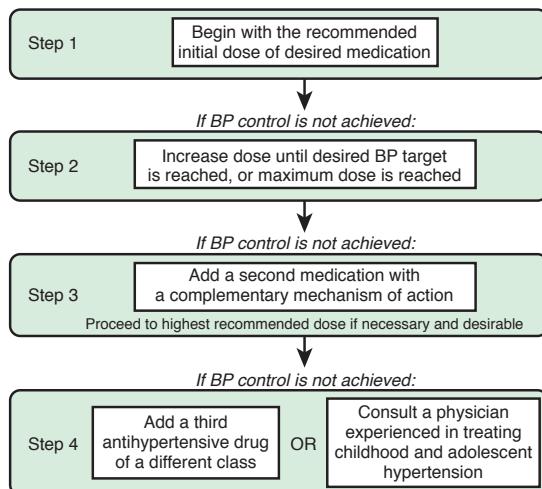


Figure 445-5 Stepped-care approach to antihypertensive therapy in children and adolescents. BP, blood pressure. (From Flynn JT, Daniels SR: Pharmacologic treatment of hypertension in children and adolescents, *J Pediatr* 149:746–754, 2006, p. 751, Fig. 2.)

Recommended Doses for Selected Antihypertensive Agents for Use in Hypertensive Children and Adolescents				
CLASS	DRUG	STARTING DOSE	INTERVAL	MAXIMUM DOSE*
Aldosterone receptor antagonist	Eplerenone Spironolactone [†]	25 mg/day 1 mg·kg ⁻¹ ·day ⁻¹	qd-bid qd-bid	100 mg/day 3.3 mg·kg ⁻¹ ·day ⁻¹ up to 100 mg/day
Angiotensin-converting enzyme inhibitors	Benazepril [†] Captopril [†] Enalapril [†] Fosinopril Lisinopril [†] Quinapril	0.2 mg·kg ⁻¹ ·day ⁻¹ up to 10 mg/day 0.3-0.5 mg/kg/dose 0.08 mg·kg ⁻¹ ·day ⁻¹ 0.1 mg·kg ⁻¹ ·day ⁻¹ up to 10 mg/day 0.07 mg·kg ⁻¹ ·day ⁻¹ up to 5 mg/day 5-10 mg/day	qd bid-tid qd qd qd qd	0.6 mg·kg ⁻¹ ·day ⁻¹ up to 40 mg/day 6 mg·kg ⁻¹ ·day ⁻¹ up to 450 mg/day 0.6 mg·kg ⁻¹ ·day ⁻¹ up to 40 mg/day 0.6 mg/kg/day up to 40 mg/day 0.6 mg/kg/day up to 40 mg/day 80 mg/day
Angiotensin receptor blockers	Candesartan Losartan [†] Olmesartan Valsartan [†]	1-6 yr, 0.2 mg·kg ⁻¹ ·day ⁻¹ 6-17 yr, <50 kg 4-8 mg once daily >50 kg 8-16 mg qd 0.75 mg·kg ⁻¹ ·day ⁻¹ up to 50 mg/day 20 to <35 kg 10 mg qd; ≥35 kg 20 mg qd 6-17 yr, 1.3 mg/kg/day up to 40 mg/day; <6 yr: 5-10 mg/day	qd qd qd qd	1-6 yr, 0.4 mg/kg; 6-17 yr, <50 kg 16 mg qd; >50 kg 32 mg qd 1.4 mg·kg ⁻¹ ·day ⁻¹ up to 100 mg/day 20 to <35 kg 20 mg qd ≥35 kg 40 mg qd 6-17 yr, 2.7 mg·kg ⁻¹ ·day ⁻¹ up to 160 mg/day; <6 yr: 80 mg/day
α- and β-Adrenergic antagonists	Labetalol [†] Carvedilol	2-3 mg·kg ⁻¹ ·day ⁻¹ 0.1 mg/kg/dose up to 12.5 mg bid	bid bid	10-12 mg·kg ⁻¹ ·day ⁻¹ up to 1.2 g/day 0.5 mg/kg/dose up to 25 mg bid
β-adrenergic antagonists	Atenolol [†] Bisoprolol/HCTZ Metoprolol Propranolol	0.5-1 mg·kg ⁻¹ ·day ⁻¹ 0.04 mg·kg ⁻¹ ·day ⁻¹ up to 2.5/6.25 mg/day 1-2 mg·kg ⁻¹ ·day ⁻¹ 1 mg·kg ⁻¹ ·day ⁻¹	qd-bid qd bid bid-tid	2 mg·kg ⁻¹ ·day ⁻¹ up to 100 mg/day 10/6.25 mg/day 6 mg·kg ⁻¹ ·day ⁻¹ up to 200 mg/day 16 mg·kg ⁻¹ ·day ⁻¹ up to 640 mg/day
Calcium channel blockers	Amlodipine [†] Felodipine Isradipine [†] Extended-release nifedipine	0.06 mg·kg ⁻¹ ·day ⁻¹ 2.5 mg/day 0.05-0.15 mg/kg/dose 0.25-0.5 mg·kg ⁻¹ ·day ⁻¹	qd qd tid-qid qd-bid	0.3 mg·kg ⁻¹ ·day ⁻¹ up to 10 mg/day 10 mg/day 0.8 mg·kg ⁻¹ ·day ⁻¹ up to 20 mg/day 3 mg·kg ⁻¹ ·day ⁻¹ up to 120 mg/day
Central α-agonist	Clonidine [†]	5-10 µg/kg/day	bid-tid	25 µg/kg/day up to 0.9 mg/day
Diuretics	Amiloride Chlorthalidone Furosemide HCTZ	5-10 mg/day 0.3 mg·kg ⁻¹ ·day ⁻¹ 0.5-2.0 mg/kg/dose 0.5-1 mg·kg ⁻¹ ·day ⁻¹	qd qd qd-bid qd	20 mg/day 2 mg·kg ⁻¹ ·day ⁻¹ up to 50 mg/day 6 mg·kg ⁻¹ ·day ⁻¹ 3 mg·kg ⁻¹ ·day ⁻¹ up to 50 mg/day
Vasodilators	Hydralazine Minoxidil	0.25 mg/kg/dose 0.1-0.2 mg·kg ⁻¹ ·day ⁻¹	tid-qid bid-tid	7.5 mg·kg ⁻¹ ·day ⁻¹ up to 200 mg/day 1 mg·kg ⁻¹ ·day ⁻¹ up to 50 mg/day

bid, Twice-daily; HCTZ, hydrochlorothiazide; qd, once daily; qid, 4 times daily; tid, 3 times daily.

*The maximum recommended adult dose should never be exceeded.

[†]Information on preparation of a stable extemporaneous suspension is available for these agents.

From Flynn JT. Management of hypertension in the young: role of antihypertensive medications. *J Cardiovasc Pharmacol* 2011;58(2):111-120.

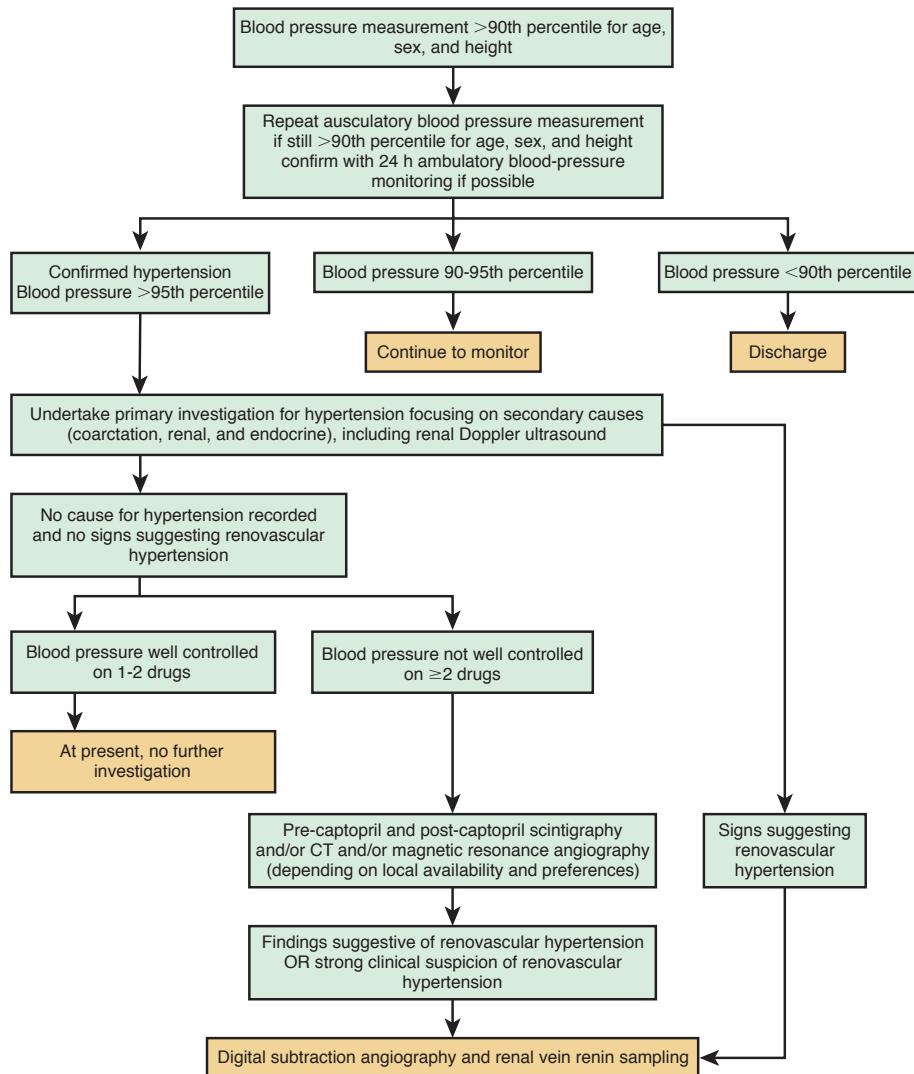


Figure 445-6 Diagnostic pathway for renovascular hypertension. (From Tullus K, Brennan E, Hamilton G, et al: Renovascular hypertension in children, Lancet 371:1453–1463, 2008, p. 1458, Fig. 6.)

Table 445-8

Antihypertensive Drugs for Management of Severe Hypertension in Children 1–17 Yr

DRUG	CLASS	DOSE	ROUTE	COMMENTS
USEFUL FOR SEVERELY HYPERTENSIVE PATIENTS WITH LIFE-THREATENING SYMPTOMS				
Esmolol	β-Adrenergic blocker	100-500 µg/kg/min	IV infusion	Very short acting—constant infusion preferred. May cause profound bradycardia
Hydralazine	Direct vasodilator	0.2-0.6 mg/kg/dose bolus: 0.20-1.0 mg/kg/dose, up to 40 mg/dose infusion: 0.25-3.0 mg/kg/hr	IV, IM IV bolus or infusion	Should be given q4h when given IV bolus Asthma and overt heart failure are relative contraindications
Labetalol	α- and β-adrenergic blocker	Bolus: 30 mcg/kg up to 2 mg/dose Infusion: 0.5-4 µg/kg/min	IV bolus or infusion	May cause reflex tachycardia
Nicardipine	Calcium channel blocker	Bolus: 30 mcg/kg up to 2 mg/dose Infusion: 0.5-4 µg/kg/min	IV bolus or infusion	Monitor cyanide levels with prolonged (>72 hr) use or in renal failure; or coadminister with sodium thiosulfate
Sodium nitroprusside	Direct vasodilator	0.5-10 µg/kg/min	IV infusion	
USEFUL FOR SEVERELY HYPERTENSIVE PATIENTS WITH LESS-SIGNIFICANT SYMPTOMS				
Clonidine	Central α-agonist	0.05-0.1 mg/dose, may be repeated up to 0.8 mg total dose	PO	Side effects include dry mouth and drowsiness
Enalaprilat	ACE inhibitor	5-10 µg/kg/dose up to 1.25 mg/dose	IV bolus	May cause prolonged hypotension and acute renal failure, especially in neonates
Fenoldopam	Dopamine receptor agonist	0.2-0.8 µg/kg/min	IV infusion	Produced modest reductions in BP in a pediatric clinical trial in patients up to 12 yr
Hydralazine	Direct vasodilator	0.25 mg/kg/dose up to 25 mg/dose	PO	Extemporaneous suspension stable for only 1 wk
Isradipine	Calcium channel blocker	0.05-0.1 mg/kg/dose up to 5 mg/dose	PO	Stable suspension can be compounded
Minoxidil	Direct vasodilator	0.1-0.2 mg/kg/dose up to 10 mg/dose	PO	Most potent oral vasodilator; long acting

ACE, angiotensin-converting enzyme; IM, intramuscular; IV, intravenous; PO, oral.

From Flynn JT: Correction to severe hypertension in children and adolescents: pathophysiology and treatment, *Pediatr Nephrol* 27(3):503–504, 2012.**Table 446-1**

Characteristics of Hematopoietic Growth Factors

GROWTH FACTOR	MOLECULAR MASS (kDa)	CHROMOSOMAL LOCATION	PRINCIPAL TARGET CELL
ERYTHROPOIETIN	30-39	7q11-12	CFU-E, fetal BFU-E, endothelial cells, neurons, astrocytes, oligodendrocytes
COLONY-STIMULATING FACTORS			
G-CSF	18-22	17q11.2-21	CFU-G, CFU-MIX, mature neutrophils
GM-CSF	18-30	5q23-31	CFU-MIX, CFU-GM, BFU-E, monocytes, mature neutrophils
M-CSF	45-70 (Dimer of 2 subunits)	5q33.1	CFU-M, macrophages
SCF	36	12q21.32	CFU-MIX, BFU-E, CFU-GM, mast cells
TGF-β	25 Homodimeric protein	19q13.2	BL-CFC
CSF-1	192 Amino acid protein	1p13.3	Monocytes, macrophages, dendritic cells, Langerhans cells
INTERLEUKINS			
IL-1	17	Alpha 2q13 Beta 2q13-21	Hepatocytes, macrophages, lymphocytes
IL-2	15-20	4q26-27	T cells, cytotoxic lymphocytes
IL-3	14-30	5q23-31	CFU-MIX, CFU-Meg, CFU-GM, BFU-E, macrophage
IL-4	16-20	5q23-31	T cells, B cells, dendritic cells
IL-5	46 (Dimer of 2 subunits)	5q23-31	CFU-Eo, B cells
IL-6	19-26	7p21-24	CFU-MIX, CFU-GM, BFU-E, monocytes, B cells, T cells, cytotoxic lymphocytes
IL-7	35	8q12-13	B cells
IL-8	8-10	4q13.3	Neutrophils, endothelial cells, T cells
IL-9	16	5q31-32	BFU-E, CFU-MIX
IL-10	18.7	1q32.1	Macrophages, lymphocytes
IL-11	23	19q13	CFU-Meg, B cells, keratinocytes
IL-12	70-75 (Dimer of 2 subunits)	p35/p40	3 (p35) and 11 (p40) T cells, NK cells, macrophages
IL-13	9	5q23-31	Pre-B lymphocytes, macrophages
IL-14	53	5q31	B cells
IL-15	14-15	4q25-35	B cells, T cells
IL-16	12-14	15q23-26	T cells
IL-17	20-30	2q31	Marrow stromal cells
IL-18	24	9p13	CD4+ T cells, NK cells
IL-21		4q26-q27	T cells
IL-23	Dimer of subunits	p19/IL-12p40	CD4+ T cells
IL-25		14q11.2	T cells, monocytes, marrow stromal cells
IL-31	4-Helix bundle	12q24.31	T cells, hematopoietic progenitors
IL-34	222 Amino acid protein	16q22.1	Monocytes, macrophages
THROMBOPOIETIN	35-38	3q27-28	Megakaryocyte progenitors, megakaryocytes

BFU-E, burst-forming units—erythroid; BL-CFU, blast colony-forming cell; CFU-E, colony-forming units—erythroid; CFU-Eo, colony-forming units—eosinophil; CFU-G, colony-forming units—granulocyte; CFU-GM, colony-forming units—granulocyte macrophage; CFU-M, colony-forming units—macrophage; CFU-Meg, colony-forming units—megakaryocyte; CFU-MIX, colony-forming units—mixed; CSF-1, colony-stimulating factor-1; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; M-CSF, macrophage colony-stimulating factor; NK, natural killer; SCF, stem cell factor; TGF-β, transforming growth factor-beta.

Diseases of the Blood

2310 Part XXI ♦ Diseases of the Blood

Table 447-1 Normal Mean and Lower Limits of Normal for Hemoglobin, Hematocrit, and Mean Corpuscular Volume

Age (yr)	HEMOGLOBIN (g/dL)		HEMATOCRIT (%)		MEAN CORPUSCULAR VOLUME (μM^3)	
	Mean	Lower Limit	Mean	Lower Limit	Mean	Lower Limit
0.5-1.9	12.5	11.0	37	33	77	70
2-4	12.5	11.0	38	34	79	73
5-7	13.0	11.5	39	35	81	75
8-11	13.5	12.0	40	36	83	76
12-14 female	13.5	12.0	41	36	85	78
12-14 male	14.0	12.5	43	37	84	77
15-17 female	14.0	12.0	41	36	87	79
15-17 male	15.0	13.0	46	38	86	78
18-49 female	14.0	12.0	42	37	90	80
18-49 male	16.0	14.0	47	40	90	80

From Brugnara C, Oski FJ, Nathan DG: Nathan and Oski's hematology of infancy and childhood, ed 7, Philadelphia, 2009, WB Saunders, p. 456.

Table 447-2 NHANES III Hemoglobin Values for Non-Hispanic Whites and African-Americans Ages 2-18 Yr

Age (yr)	WHITE NON-HISPANIC		AFRICAN- AMERICAN	
	Mean	-2 SD	Mean	-2 SD
2-5	12.21	10.8	11.95	10.37
6-10	12.87	11.31	12.40	10.74
11-15 male	13.76	11.76	13.06	10.88
11-15 female	13.32	11.5	12.61	10.85
16-18 male	15.00	13.24	14.18	12.42
16-18 female	13.39	11.61	12.37	10.37

Sample size is 5,142 (white, 2,264; African-American, 2,878).

Modified from Robbins EB, Blum S: Hematologic reference values for African American children and adolescents, Am J Hematol 82:611-614, 2007.

Table 450-1 Comparison of Diamond-Blackfan Anemia and Transient Erythroblastopenia of Childhood

FEATURE	DBA	TEC
Male:female	1.1	1.3
AGE AT DIAGNOSIS, MALE (MO)		
Mean	10	26
Median	2	23
Range	0-408	1-120
AGE AT DIAGNOSIS, FEMALE (MO)		
Mean	14	26
Median	3	23
Range	0-768	1-192
Boys >1 yr	9%	82%
Girls >1 yr	12%	80%
Etiology	Genetic	Acquired
Antecedent history	None	Viral illness
Physical examination abnormal (congenital anomalies present)	25%	0%
LABORATORY		
Hemoglobin (g/dL)	12-14.8	2.2-12.5
WBCs <5,000/ μL	15%	20%
Platelets >400,000/ μL	20%	45%
Adenosine deaminase	Increased	Normal
MCV increased at diagnosis	80%	5%
MCV increased during recovery	100%	90%
MCV increased in remission	100%	0%
HbF increased at diagnosis	100%	20%
HbF increased during recovery	100%	100%
HbF increased in remission	85%	0%
i Antigen increased	100%	20%
i Antigen increased during recovery	100%	60%
i Antigen increased in remission	90%	0%

DBA, Diamond-Blackfan anemia; HbF, fetal hemoglobin; MCV, mean cell volume; TEC, transient erythroblastopenia of childhood; WBC, white blood cell.

From Nathan DG, Orkin SH, Ginsburg D, et al, editors: Nathan and Oski's hematology of infancy and childhood, ed 6, vol 1, Philadelphia, 2003, WB Saunders, p. 329. Adapted from Alter BP: The bone marrow failure syndromes. In Nathan DG, Oski FA, editors: Hematology of infancy and childhood, ed 3, Philadelphia, 1987, WB Saunders, p. 159; and Link MP, Alter BP: Fetal erythropoiesis during recovery from transient erythroblastopenia of childhood (TEC), Pediatr Res 15:1036-1039, 1981.

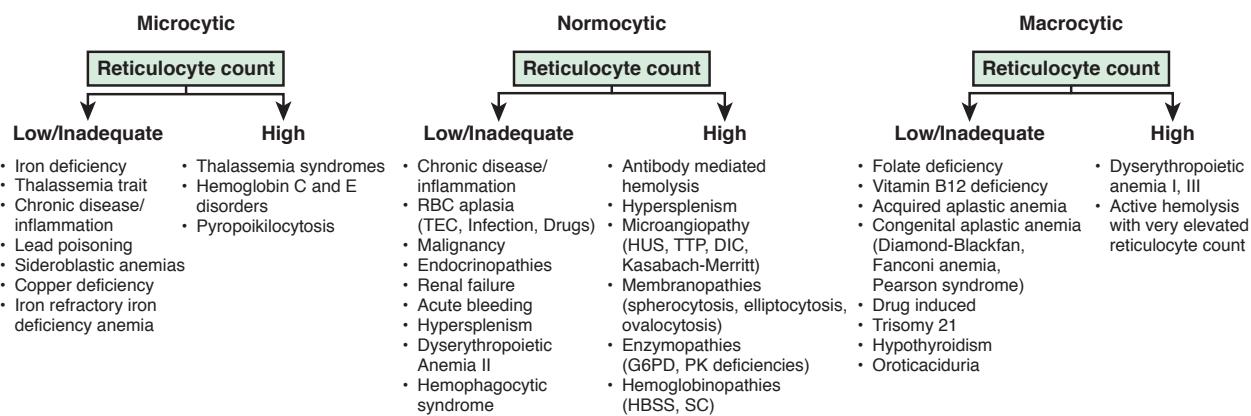


Figure 447-3 Use of the mean corpuscular volume (MCV) and reticulocyte count in the diagnosis of anemia. (Adapted from Brunetti M, Cohen J: The Harriet Lane handbook, ed 17, Philadelphia, 2005, Elsevier Mosby, p 338.)

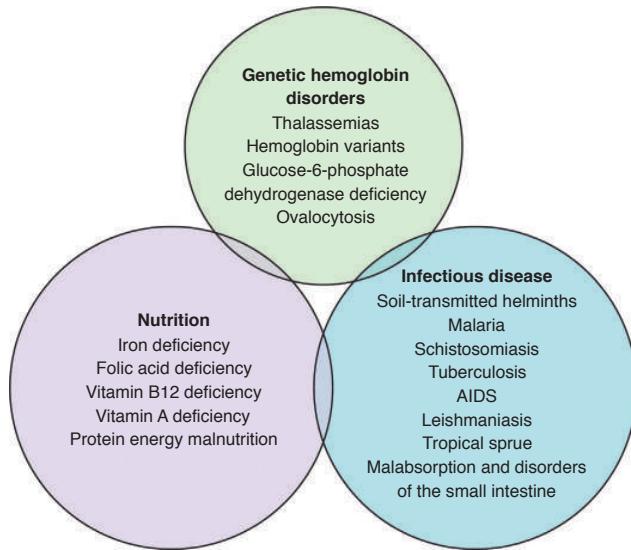


Figure 447-2 Causes of anaemia in countries with low or middle incomes. (From Balarajan Y, Ramakrishnan U, Özaltın E, et al: Anaemia in low-income and middle-income countries. Lancet 378:2123–2134, 2011, Fig. 3.)

Table 448-1 Range of Congenital Anomalies Observed in Diamond-Blackfan Anemia	
Craniofacial	Hypertelorism Broad, flat nasal bridge Cleft palate High arched palate Microcephaly Micrognathia Microtia Low-set ears Low hair line Epicantus Ptosis
Ophthalmologic	Congenital glaucoma Strabismus Congenital cataract
Neck	Short neck Webbed neck Sprengel deformity Klippel-Feil deformity
Thumbs	Triphalangeal Duplex or bifid Hypoplastic Flat thenar eminence Absent radial artery
Urogenital	Absent kidney Horseshoe kidney Hypospadias
Cardiac	Ventricular septal defect Atrial septal defect Coarctation of the aorta Complex cardiac anomalies
Other musculoskeletal	Growth retardation Syndactyly
Neuromotor	Learning difficulties

The list includes the anomalies that are most characteristic of DBA but is not exhaustive. Multiple anomalies, most commonly including craniofacial, are present in up to 25% of affected individuals.

2324 Part XXI ◆ Diseases of the Blood

Table 455-1 Indicators of Iron-Deficiency Anemia

INDICATOR	SELECTED CUTOFF VALUES TO DEFINE IRON DEFICIENCY	COMMENTS
Hemoglobin (g/dL)	<11.0 for non-Hispanic whites ages 0.5-4 yr	When used alone, it has low specificity and sensitivity. Use appropriate age specific normal values found in Table 447-1. Normal values for African-Americans are found in Table 447-2.
Mean corpuscular volume (MCV) (μm^3)	<70 from 6-24 months	A reliable, but late indicator of iron deficiency (ID). Low values can also be a result of thalassemia and other causes of microcytosis. Normal values are found in Table 447-1.
Serum ferritin (SF) ($\mu\text{g/L}$)	≤ 5 yr <12 Children >5 yr <15 In all age groups in the presence of infection <30	It is probably the most useful laboratory measure of iron stores and helps identify ID; a low value of SF is diagnostic of iron-deficiency anemia (IDA) in a patient with anemia. SF is an acute phase reactant that increases in many acute or chronic inflammatory conditions independent of iron status. Combining SF with a measurement of C-reactive protein (CRP) helps to identify these false-negative SF results.
Reticulocyte hemoglobin content (CHR) (pg)	In infants and young children <27.5 In adults ≤ 28.0	A sensitive indicator that falls within days of onset of iron-deficient erythropoiesis and is unaffected by inflammation. It is an excellent tool to recognize ID as well as IDA. False normal values can occur when MCV is increased and in thalassemia. It is not yet widely available on hematology analyzers.
Serum transferrin receptor (sTfR)	Cutoff varies with assay and with patient's age and ethnic origin	This soluble receptor is upregulated in ID and is found in increased amounts in serum. It also increased during enhanced erythropoiesis. sTfR is not substantially affected by the acute-phase response, but it might be affected by malaria, age, and ethnicity. Its application is limited by high cost of commercial assays and lack of an international standard, but it has great promise as an indicator of ID.
Transferrin saturation	<16%	It is inexpensive, but its use is limited by diurnal variation in serum iron and by many clinical disorders that affect transferrin concentrations including in inflammatory conditions.
Erythrocyte zinc protoporphyrin (ZPP) ($\mu\text{mol/mol heme}$)	≤ 5 yr >70 Children >5 yr >80 Children >5 yr on washed red cells >40	It can be measured directly on a drop of blood with a portable hematofluorometer. A useful screening test in field surveys, particularly in children, in whom uncomplicated ID is the primary cause of anemia. Lead poisoning can increase values, particularly in urban and industrial settings.
Hepcidin	To be defined; usually ≤ 10 ng/mL	Extremely elevated in anemia of inflammation and suppressed in iron deficiency anemia

Modified from Zimmermann MB, Hurrell RF: Nutritional iron deficiency, Lancet 370:511-520, 2007.

Table 455-2 Laboratory Studies Differentiating the Most Common Microcytic Anemias

STUDY	IRON-DEFICIENCY ANEMIA	α - OR β -THALASSEMIA	ANEMIA OF CHRONIC DISEASE
Hemoglobin	Decreased	Decreased	Decreased
MCV	Decreased	Decreased	Normal-decreased
RDW	Increased	Normal or minimally increased	Normal-increased
RBC	Decreased	Normal-increased	Normal-decreased
Serum ferritin	Decreased	Normal	Increased
Total Fe binding capacity	Increased	Normal	Decreased
Transferrin saturation	Decreased	Normal	Decreased
FEP	Increased	Normal	Increased
Transferrin receptor	Increased	Normal	Increased
Reticulocyte hemoglobin concentration	Decreased	Normal	Normal-decreased

FEP, free erythrocyte protoporphyrin; MCV, mean corpuscular volume; RBC, red blood cell count; RDW, red cell distribution width.

Modified from Zimmermann MB, Hurrell RF: Nutritional iron deficiency, Lancet 370:511-520, 2007.

Table 462-2	Clinical Factors Associated with Increased Risk of Bacteremia Requiring Admission in Febrile Children with Sickle Cell Disease
Seriously ill appearance	
Hypotension: systolic blood pressure <70 mm Hg at 1 yr of age or <70 mm Hg + 2 × the age in yr for older children	
Poor perfusion: capillary-refill time >4 sec	
Temperature >40.0°C (104°F)	
A corrected white-cell count >30,000/mm ³ or <5000/mm ³	
Platelet count <100,000/mm ³	
History of pneumococcal sepsis	
Severe pain	
Dehydration: poor skin turgor, dry mucous membranes, history of poor fluid intake, or decreased output of urine	
Infiltration of a segment or a larger portion of the lung	
Hemoglobin level <5.0 g/dL	

Table 467-1	Differential Diagnosis of Polycythemia
CLONAL (PRIMARY)	
Polycythemia vera	
NONCLONAL	
Congenital	
High-oxygen affinity hemoglobinopathy (e.g., hemoglobin Chesapeake, Malmö, San Diego)	
Erythropoietin receptor mutations (primary familial and congenital polycythemia [PFCP])	
Methemoglobin reductase deficiency	
Hemoglobin M disease	
2,3-Diphosphoglycerate deficiency	
Acquired	
Hormonal	
Adrenal disease	
Virilizing hyperplasia, Cushing syndrome	
Anabolic steroid therapy	
Malignant tumors	
Adrenal, cerebellar, hepatic, other	
Renal disease	
Cysts, hydronephrosis, renal artery stenosis	
Hypoxia	
Altitude	
Cardiac disease	
Lung disease	
Central hypoventilation	
Chronic carbon monoxide exposure	
Neonatal	
Delayed cord clamping (placental-fetal transfusion)	
Normal intrauterine environment	
Placental insufficiency (preeclampsia, maternal chronic hypertension, placental abruption)	
Twin-twin or maternal-fetal hemorrhage	
Perinatal asphyxia	
Infants of diabetic mothers	
Intrauterine growth retardation	
Trisomy 13, 18, or 21	
Adrenal hyperplasia	
Thyrotoxicosis	
Spurious	
Plasma volume decrease	

Table 455-3 Differential Diagnosis of Microcytic Anemia That Fails to Respond to Oral Iron

Poor compliance (true intolerance of Fe is uncommon)
Incorrect dose or medication
Malabsorption of administered iron
Ongoing blood loss, including gastrointestinal, menstrual, and pulmonary
Concurrent infection or inflammatory disorder inhibiting the response to iron
Concurrent vitamin B₁₂ or folate deficiency
Diagnosis other than iron deficiency
 Thalassemias
 Hemoglobins C and E disorders
 Anemia of chronic disease
 Lead poisoning
 Sickle thalassemias, hemoglobin SC disease
 Iron refractory iron deficiency anemia (IRIDA)
Rare microcytic anemias (see Chapter 456)

Table 455-4 Responses to Iron Therapy in Iron-Deficiency Anemia

TIME AFTER IRON ADMINISTRATION	RESPONSE
12-24 hr	Replacement of intracellular iron enzymes; subjective improvement; decreased irritability; increased appetite
36-48 hr	Initial bone marrow response; erythroid hyperplasia
48-72 hr	Reticulocytosis, peaking at 5-7 days
4-30 days	Increase in hemoglobin level
1-3 mo	Repletion of stores

Table 462-6 Known Etiologies of Acquired Methemoglobinemia

MEDICATIONS
Benzocaine
Chloroquine
Dapsone
EMLA (eutectic mixture of local anesthetics) topical anesthetic (lidocaine 2.5% and prilocaine 2.5%)
Flutamide
Lidocaine
Metoclopramide
Nitrates
Nitric oxide
Nitroglycerin
Nitroprusside
Nitrous oxide
Phenazopyridine
Prilocaine
Primaquine
Riluzole
Silver nitrate
Sodium nitrate
Sulfonamides
MEDICAL CONDITIONS
Pediatric gastrointestinal infection, sepsis
Recreational drug overdose with amyl nitrate ("poppers")
Sickle cell disease-related painful episode
MISCELLANEOUS
Aniline dyes
Fume inhalation (automobile exhaust, burning of wood and plastics)
Herbicides
Industrial chemicals: nitrobenzene, nitroethane (found in nail polish, resins, rubber adhesives)
Pesticides
Gasoline octane booster

2328 Part XXI ♦ Diseases of the Blood

Table 457-1 Hemolytic Anemias and Their Treatment			
DIAGNOSIS	DEFECT	LABORATORY TESTS	TREATMENT
CELLULAR DEFECTS			
Membrane Defects			
Hereditary spherocytosis	Cytoskeletal protein defects Often involve vertical interactions of spectrin, ankyrin, protein 3	Spherocytes on blood film Negative Coombs test eliminates immune hemolysis Increased incubated osmotic fragility Abnormal cytoskeletal protein analysis	If Hb >10 g/dL and reticulocyte count <10%: none If severe anemia, poor growth, aplastic crises, and age <2 yr: transfusion Folic acid, 1 mg qd Splenectomy (see text)
Hereditary elliptocytosis	Cytoskeletal protein defects Often involve horizontal interactions of spectrin, protein 4.1, and glycophorin c	Elliptocytes on blood film RBCs mildly heat-sensitive Abnormal cytoskeletal protein analysis	Mild types: no treatment Chronic hemolysis: transfusion and splenectomy as recommended for spherocytosis (see above) Folic acid, 1 mg qd
Hereditary pyropoikilocytosis	Cytoskeletal protein defects Homozygous or double heterozygous abnormality in horizontal interactions of α -spectrin	Extreme variation in RBC size and shape on blood film Thermal sensitivity-fragmentation at 45°C (113°F) for 15 min	Transfusion and splenectomy as recommended for spherocytosis (see above) Folic acid, 1 mg qd
Hereditary stomatocytosis	Cytoskeletal protein defects Decreased protein 7.2b (1 subset) Abnormal RBC cation and water content	Stomatocytes on blood film	Splenectomy should be avoided (see text) Folic acid, 1 mg qd
Paroxysmal nocturnal hemoglobinuria	Primary acquired marrow disorder RBCs unusually sensitive to complement-mediated lysis	Decreased WBC CD55 and CD59 or decreased RBC CD59 by flow cytometry Marrow aspirate and biopsy to assess cellularity Decreased decay-accelerating factor	Folic acid, 1 mg qd Mild cytopenias: no treatment Chronic hemolysis and other cytopenias: prednisone, qd initially, and then qod for maintenance therapy Iron for secondary iron deficiency Eculizumab (inhibits C5) Anticoagulation Marrow transplant for pancytopenia
Enzyme Deficiencies			
Pyruvate kinase deficiency	Decreased or abnormal enzyme	Pyruvate kinase assay: decreased V_{max} or, rarely, high K_m variant	In severe anemia with symptoms, poor growth and age <2 yr: transfusion Splenectomy age >6 yr, but earlier if necessary Folic acid, 1 mg qd
G6PD deficiency	A- type: age-labile enzyme Mediterranean type: no enzyme activity in circulating RBCs	G6PD assay	Avoid oxidant stress to RBCs Transfusion if acute anemia is symptomatic
Hemoglobin Abnormalities			
For discussion of hemoglobinopathies, see sections on these topics.			

Table 458-2 Hereditary Spherocytosis Disease Classification				
	TRAIT	MIILD	MODERATE	SEVERE
Hemoglobin (g/dL)	Normal	11-15	8-12	<6-8
Reticulocytes (%)	Normal (<3)	3-6	>6	>10
Bilirubin	<17	17-34	>34	>51
Transfusions	0	0	0-2	Regular
Typical heredity	AD	AD	AD or de novo mutation	AR
Splenectomy	Not indicated	Not indicated	May be indicated*	Indicated

*Splenectomy indicated if patient requires frequent transfusions for hypoplastic crises or shows poor growth or cardiomegaly.
AD, autodominant; AR, autorecessive.

Table 464-2 Selected Drugs That Cause Immune-Mediated Hemolysis			
MECHANISM	DRUG ADSORPTION (HAPten)	TERNARY (IMMUNE) COMPLEX	AUTOANTIBODY INDUCTION
Direct antiglobulin test	Positive (anti-IgG)	Positive (anti-C3)	Positive (anti-IgG)
Site of hemolysis	Extravascular	Intravascular	Extravascular
Medications	Penicillins Cephalosporins 6-mercaptopurine Tetracycline Oxaliplatin Hydrocortisone	Cephalosporins Quinidine Amphotericin B Hydrocortisone Rifampin (Rifadin) Metformin Quinine Probenecid Chlorpromazine Oxaliplatin	α -Methyldopa Cephalosporins Oxaliplatin L-Dopa Procainamide Ibuprofen Diclofenac (Voltaren) Interferon alfa

Table 457-1

Hemolytic Anemias and Their Treatment—cont'd

DIAGNOSIS	DEFECT	LABORATORY TESTS	TREATMENT
EXTRACELLULAR DEFECTS			
<i>Autoimmune</i>			
"Warm" antibody	Alteration in membrane surface antigen (Rh) or abnormal response of B lymphocytes, causing autoantibody formation "Molecular mimicry" to viral antigen	Spherocytes on blood film Positive direct antiglobulin (Coombs) test to IgG "warm" antibody or anti-C3d directed against RBCs Positive indirect Coombs test and antibody detectable in plasma Thermal amplitude 35-40°C (95-104°F) Some complement (C3b) may be detected on RBCs Tests for underlying disease Agglutination or rouleaux on blood film Positive direct Coombs test to complement (C3b) Tests for underlying disease Serology for infectious mononucleosis; anti-i present Serology for <i>Mycoplasma pneumoniae</i> ; anti-l present	If Hb >10 g/dL and reticulocyte count <10%—none Severe anemia may require transfusion; prednisone, 2 mg/kg/24 hr IVIG Rituximab Splenectomy Immunosuppressives Folic acid, 1 mg/24 hr if chronic
"Cold" antibody	"Cold" or IgM autoantibody directed against I/i antigen system		If Hb >10 g/dL and reticulocyte count <10%: none Severe anemia might require transfusion Avoid exposure to cold If severe: Rituximab Immunosuppressives and plasmapheresis Prednisone is less effective Splenectomy is not useful Folic acid, 1 mg/24 hr if chronic
<i>Fragmentation Hemolysis</i>			
DIC, TTP, HUS, aHUS, pneumococcal-induced HUS See Table 465-1	Direct damage to RBC membrane	Fragments on blood film	Treat underlying condition Transfusion, but transfused cells also will have shortened life span
Extracorporeal membrane oxygenation	Direct damage to RBC membrane	Fragments on blood film	Supportive Transfusion until ECMO is discontinued
Prosthetic heart valve	Direct damage to RBC membrane	Fragments on blood film	Folic acid, 1 mg/24 hr Iron for secondary iron deficiency
Burns, thermal injury	Direct damage to RBC membrane	Spherocytes on blood film	Supportive Transfusion
Hypersplenism	Effects of sequestration, ↓ pH, lipases and other enzymes, and macrophages on RBCs	Thrombocytopenia and neutropenia	Treat underlying condition: cytopenias all usually mild Splenectomy if complicating other anemia (e.g., thalassemia major) Folic acid, 1 mg/24 hr
<i>Plasma Factors</i>			
Liver disease	Alteration in plasma cholesterol and phospholipids	Target cells or spiculated RBCs on blood film Abnormal liver function tests	Treat underlying condition Transfusion, but transfused cells also will have shortened life span
Abetalipoproteinemia	Absence of apolipoprotein β Vitamin E deficiency and heightened sensitivity to oxidative damage	Acanthocytes on blood film Absent chylomicrons, VLDL, and LDL	Folic acid, 1 mg/24 hr Vitamin E (A, K, and D) Folic acid, 1 mg/24 hr Dietary restriction of triglycerides
Infections	Toxic effects on RBCs	Associated symptoms and signs Cultures	Antibiotics Supportive
Wilson disease	Effect of copper on RBC membrane, usually self-limited	Spherocytes on blood film Copper, ceruloplasmin Kaiser Fleischer rings Penicillamine challenge and urine copper excretion Liver biopsy for Cu content Gene analysis for mutation of ATP7B	Penicillamine Supportive Transfusion if acute anemia is symptomatic

aHUS, atypical hemolytic uremic syndrome; Cu, copper; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; G6PD, glucose-6-phosphate dehydrogenase; Hb, hemoglobin; HUS, hemolytic uremic syndrome; Ig, immunoglobulin; IVIG, intravenous immunoglobulin; LDL, low-density lipoprotein; K_m , Michaelis constant; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura; VLDL, very-low-density lipoprotein; V_{max} , maximal velocity; WBC, white blood cell.

Modified from Asselin BL, Segel GB: In Rakel R, editor: Conn's current therapy, Philadelphia, 1994, Saunders, pp 338-339.

Table 462-4 Overall Strategies for the Management of Acute Chest Syndrome

PREVENTION	
Incentive spirometry and periodic ambulation in patients admitted for sickle cell pain, surgery, or febrile episodes	
Watchful waiting in any hospitalized child or adult with sickle cell disease (pulse oximetry monitoring and frequent respiratory assessments)	
Cautious use of intravenous fluids	
Intense education and optimum care of patients who have sickle cell anemia and asthma	
DIAGNOSTIC TESTING AND LABORATORY MONITORING	
Blood cultures	
Nasopharyngeal samples for viral culture (respiratory syncytial virus, influenza)	
Blood counts every day and appropriate chemistries	
Continuous pulse oximetry	
Chest radiographs	
TREATMENT	
Blood transfusion (simple or exchange)	
Supplemental O ₂ for drop in pulse oximetry by 4% over baseline, or values <90%	
Empirical antibiotics (third-generation cephalosporin and macrolide)	
Continued respiratory therapy (incentive spirometry and chest physiotherapy as necessary)	
Bronchodilators and steroids for patients with asthma	
Optimum pain control and fluid management	

Table 462-5 Complications Associated with Sickle Cell Trait

DEFINITE ASSOCIATIONS	
Renal medullary cancer	
Hematuria	
Renal papillary necrosis	
Hyposthenuria	
Splenic infarction	
Exertional rhabdomyolysis	
Exercise-related sudden death	
Protection against severe falciparum malaria	
Microalbuminuria (adults)	

Table 462-3 Summary of the Chronology of Pain in Children with Sickle Cell Disease

PHASE	PAIN CHARACTERISTICS	SUGGESTED COMFORT MEASURES USED
1 (Baseline)	No vasoocclusive pain; pain of complications may be present, such as that connected with avascular necrosis of the hip	No comfort measures used
2 (Prepain)	No vasoocclusive pain; pain of complications may be present; prodromal signs of impending vasoocclusive episode may appear, e.g., "yellow eyes" and/or fatigue	No comfort measures used; caregivers may encourage child to increase fluids to prevent pain event from occurring
3 (Pain start point)	First signs of vasoocclusive pain appear, usually in mild form	Mild oral analgesic often given; fluids increased; child usually maintains normal activities
4 (Pain acceleration)	Intensive of pain increases from mild to moderate Some children skip this level or move quickly from phase 3 to phase 5	Stronger oral analgesic are given; rubbing, heat, or other activities are often used; child usually stays in school until the pain becomes more severe, then stays home and limits activities; is usually in bed; family searches for ways to control the pain
5 (Peak pain experience)	Pain accelerates to high moderate or severe levels and plateaus; pain can remain elevated for extended period Child's appearance, behavior, and mood are significantly different from normal	Oral analgesics are given around the clock at home; combination of comfort measures is used; family might avoid going to the hospital; if pain is very distressing to the child, parent takes the child to the emergency department After child enters the hospital, families often turn over comforting activities to healthcare providers and wait to see if the analgesics work Family caregivers are often exhausted from caring for the child for several days with little or no rest
6 (Pain decrease start point)	Pain finally begins to decrease in intensity from the peak pain level	Family caregivers again become active in comforting the child but not as intensely as during phases 4 and 5
7 (Steady pain decline)	Pain decreases more rapidly, become more tolerable for the child Child and family are more relaxed	Healthcare providers begin to wean the child from the IV analgesic; oral opioids given; discharge planning is started Children may be discharged before they are pain free
8 (Pain resolution)	Pain intensity is at a tolerable level, and discharge is imminent Child looks and acts like "normal" self; mood improves	May receive oral analgesics

Adapted from Beyer JE, Simmons LE, Woods GM, et al: A chronology of pain and comfort in children with sickle cell disease, Arch Pediatr Adolesc Med 153:913-920, 1999.

Table 462-7 The Thalassemias

THALASSEMIA	GLOBIN GENOTYPE	FEATURES	EXPRESSION	HEMOGLOBIN ANALYSIS
α-THALASSEMIA				
1 Gene allele deletion	- $\alpha/\alpha, \alpha$	Normal	Normal	Newborn: Bart 1-2%
2 Gene allele deletion trait	- $\alpha/-\alpha, -/\alpha, \alpha$	Microcytosis, mild hypochromasia	Normal, mild anemia	Newborn: Bart: 5-10%
3 Gene allele deletion hemoglobin H	-,-, α	Microcytosis, hypochromic	Mild anemia, transfusions not required	Newborn: Bart: 20-30%
2 Gene allele deletion + Constant Spring	-,- $\alpha, \alpha^{\text{Constant Spring}}$	Microcytosis, hypochromic	Moderate to severe anemia, transfusion, splenectomy.	2-3% Constant Spring, 10-15% HbH
4 Gene allele deletion	-,-,-	Anisocytosis, poikilocytosis	Hydrops fetalis	Newborn: 89-90% Bart with Gower 1 and 2 and Portland 1-2% variant hemoglobin
Nondeletional	$\alpha/\alpha, \alpha^{\text{variant}}$	Microcytosis, mild anemia	Normal	
β-THALASSEMIA				
β^0 or β^+ heterozygote: trait	$\beta^0/A, \beta^+/A$	Variable microcytosis	Normal	Elevated A ₂ , variable elevation of F
β^0 -Thalassemia	$\beta^0/\beta^0, \beta^+/\beta^0, E/\beta^0$	Microcytosis, nucleated RBC	Transfusion dependent	F 98% and A ₂ 2%, E 30-40%
β^+ -Thalassemia severe	β^+/β^+	Microcytosis nucleated RBC	Transfusion dependent/ thalassemia intermedia	F 70-95%, A ₂ 2%, trace A
Silent β^+/β^+	β^+/A	Microcytosis	Normal with only microcytosis	A ₂ 3.3-3.5%
Dominant (rare)	Hypochromic, microcytosis β^0/A	Mild to moderate anemia	β^0/A 2-5%, F 10-30%	
δ -Thalassemia	A/A	Normal	Moderately severe anemia, splenomegaly	Elevated F and A ₂
$(\delta\beta)^0$ -Thalassemia	$(\delta\beta)^0/A$	Hypochromic	Normal	A ₂ absent
$(\delta\beta)^+$ -Thalassemia Lepore Lepore	β^{Lepore}/A	Microcytosis	Mild anemia	F 5-20%
$\gamma\delta\beta$ -Thalassemia	$\beta^{\text{Lepore}}/\beta^{\text{Lepore}}$	Microcytic, hypochromic	Mild anemia	Lepore 8-20%
	$(\gamma^+\delta\beta)^0/A$	Microcytosis, microcytic, hypochromic	Thalassemia intermedia	F 80%, Lepore 20%
γ -Thalassemia	$(\gamma^+\gamma^0)/A$	Microcytosis	Moderate anemia, splenomegaly, homozygote: thalassemia intermedia	Decreased F and A ₂ compared with $\delta\beta$ -thalassemia
HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN				
Deletional	A/A	Microcytic	Mild anemia	F 100% homozygotes
Nondeletional	A/A	Normal	Normal	F 20-40%

Table 463-1 Agents Precipitating Hemolysis in Glucose-6-Phosphate Dehydrogenase Deficiency

MEDICATIONS	Others
Antibacterials	Acetanilide
Sulfonamides	Vitamin K analogs
Dapsone	Methylene blue
Trimethoprim-sulfamethoxazole	Toluidine blue
Nalidixic acid	Probenecid
Chloramphenicol	Dimercaprol
Nitrofurantoin	Acetylsalicylic acid
Antimalarials	Phenazopyridine
Primaquine	Rasburicase
Pamaquine	
Chloroquine	CHEMICALS
Quinacrine	Phenylhydrazine
Antihelminths	Benzene
β -Naphthol	Naphthalene (moth balls)
Stibophen	2,4,6-Trinitrotoluene
Niridazole	
	ILLNESS
	Diabetic acidosis
	Hepatitis
	Sepsis

Table 464-1 Diseases Characterized by Immune-Mediated Red Blood Cell Destruction

AUTOIMMUNE HEMOLYTIC ANEMIA CAUSED BY WARM REACTIVE AUTOANTIBODIES	
Primary (idiopathic)	
Secondary	Lymphoproliferative disorders
	Connective tissue disorders (especially systemic lupus erythematosus)
	Nonlymphoid neoplasms (e.g., ovarian tumors)
	Chronic inflammatory diseases (e.g., ulcerative colitis)
	Immunodeficiency disorders

AUTOIMMUNE HEMOLYTIC ANEMIA CAUSED BY COLD REACTIVE AUTOANTIBODIES (CRYOPATHIC HEMOLYTIC SYNDROMES)	
Primary (idiopathic) cold agglutinin disease	
Secondary cold agglutinin disease	Lymphoproliferative disorders
	Infections (<i>Mycoplasma pneumoniae</i> , Epstein-Barr virus)
	Paroxysmal cold hemoglobinuria
	Primary (idiopathic) viral syndromes (most common)
	Congenital or tertiary syphilis

DRUG-INDUCED IMMUNE HEMOLYTIC ANEMIA (see Table 464-2)	
Hapten/drug adsorption (e.g., penicillin)	
Ternary (immune) complex (e.g., quinine or quinidine)	
True autoantibody induction (e.g., methyldopa)	

Table 466-1 WHO Diagnostic Criteria for Polycythemia Vera**MAJOR CRITERIA**

1. Hb >18.5 g/dL (men) or Hb >16.5 g/dL (women)
- or
- Hb or Hct >99th percentile of reference range for age, sex, or altitude of residence
- or
- Hb >17 g/dL (men) or Hb >15 g/dL (women) if associated with a sustained increase of ≥2 g/dL from baseline that cannot be attributed to correction of iron deficiency
- or
- elevated red cell mass >25% above mean normal predicted value
2. Presence of JAK2 or similar mutation

MINOR CRITERIA

1. Bone marrow trilineage myeloproliferation
2. Subnormal serum erythropoietin level
3. Endogenous erythroid colony growth

DIAGNOSIS

Both major criteria and one minor criteria or first major criteria and 2 minor criteria.

Hb, hemoglobin; Hct, hematocrit.

From Tefferi A, Vardiman JW: Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. Leukemia 22:14–22, 2008.

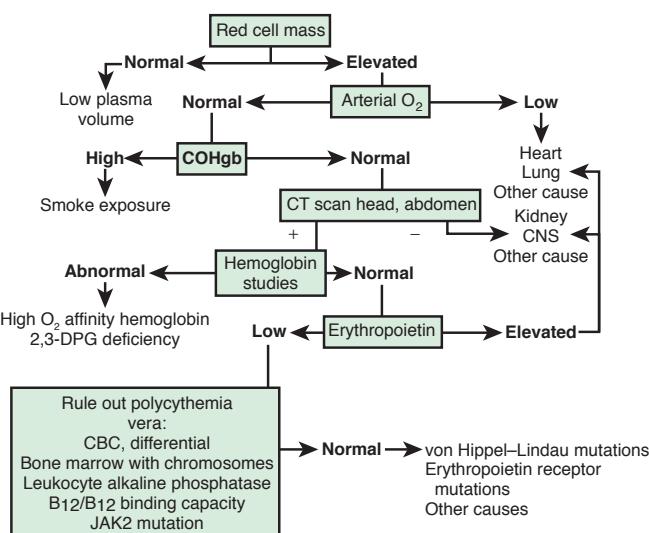


Figure 466-1 Sequential studies to evaluate polycythemia. CBC, complete blood count; CNS, central nervous system; COHgb, carboxy-hemoglobin; 2,3-DPG, 2,3-diphosphoglycerate.

Table 472-1 Guidelines for Pediatric Granulocyte Transfusions***CHILDREN AND ADOLESCENTS**

1. Severe neutropenia (blood neutrophil count <0.5 × 10⁹/L) and infection (bacterial, yeast, or fungal) unresponsive or progressive despite appropriate antimicrobial therapy
2. Qualitative neutrophil defect, neutropenia not required, and infection (bacterial or fungal) unresponsive or progressive to appropriate antimicrobial therapy

INFANTS ≤4 MO OLD[†]

Blood neutrophil count <3.0 × 10⁹/L in 1st wk of life or <1.0 × 10⁹/L thereafter and fulminant bacterial infection.

*Words in *italics* must be defined for local transfusion guidelines.

[†]No longer commonly used.

Table 473-1 Guidelines for Pediatric Plasma Transfusions*

1. Severe clotting factor deficiency AND bleeding
2. Severe clotting factor deficiency AND an invasive procedure
3. *Emergency reversal of warfarin effects*
4. Dilutional coagulopathy and bleeding (e.g., massive transfusion)
5. Anticoagulant protein (antithrombin III, proteins C and S) replacement
6. Plasma exchange replacement fluid for thrombotic thrombocytopenic purpura or for disorders with overt bleeding or in which there is risk of bleeding because of clotting protein abnormalities (e.g., liver failure)

*Words in *italics* must be defined for local transfusion guidelines.

Table 465-1 Thrombotic Microangiopathies

DISEASE*	PATHOPHYSIOLOGY	LAB FINDINGS	MANAGEMENT
TTP	Ab to AdamTS13	AdamTS13 <10% [†] Ab to AdamTS13	PLEX with plasma
HUS	<i>E. coli</i> 0157, Shiga toxin	<i>E. coli</i> 0157, Shiga toxin	Supportive ? value of PLEX
aHUS	Complement-mediated alternative pathway	AdamTS13 >10% Decreased factors H and I (inhibitors of complement) [‡]	Eculizumab (ab to C5) PLEX not indicated
Pneumococcal-induced HUS	Neuraminidase-induced RBC, platelet, and kidney damage Exposure of T-antigen on RBC and kidney	Pneumococcal infection AdamTS13 >10%	PLEX with albumin for neuraminidase and endogenous T ab removal
DIC	Sepsis, shock, endotoxin	Decreased fibrinogen, increased fibrin split products, decreased clotting factors and platelets	Treat underlying condition; replace factors and platelets if bleeding

*All show fragmentation hemolytic anemia, thrombocytopenia and potential renal and other organ damage. An elevated lactate dehydrogenase and reduced haptoglobin usually are present secondary to hemolysis.

[†]Rarely a congenital defect in AdamTS13.

[‡]May be related to inherited defect in factor H or I.

Ab/ab, antibody; aHUS, atypical hemolytic uremic syndrome; DIC, disseminated intravascular coagulation; *E. coli*, *Escherichia coli*; HUS, hemolytic uremic syndrome; PLEX, plasmapheresis; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura

Table 468-1 Inherited Pancytopenia Syndromes

Fanconi anemia
Shwachman-Diamond syndrome
Dyskeratosis congenita
Congenital amegakaryocytic thrombocytopenia
Reticular dysgenesis
Unclassified inherited bone marrow failure syndromes
Other genetic syndromes
Down syndrome
Dubowitz syndrome
Seckel syndrome
Schimke immunoosseous dysplasia
Cartilage-hair hypoplasia
Noonan syndrome

Table 468-3 Characteristic Physical Anomalies in Fanconi Anemia

ANOMALY	APPROXIMATE FREQUENCY (% OF PATIENTS)
Skin pigment changes ± café-au-lait spots	55
Short stature	51
Upper limb abnormalities (thumbs, hands, radii, ulnas)	43
Hypogonadal and genital changes (mostly male)	35
Other skeletal findings (head/face, neck, spine)	30
Eye/lid/epicanthal fold anomalies	23
Renal malformations	21
Gastrointestinal/cardiopulmonary malformations	11
Hip, leg, foot, toe abnormalities	10
Ear anomalies (external and internal), deafness	9

Table 468-2 Distinguishing Clinical Features of the Inherited Bone Marrow Failure Syndromes That May Be Initially Diagnosed in Adulthood

DISTINGUISHING FEATURES	DISEASES		
	FANCONI ANEMIA	DYSKERATOSIS CONGENITA	SCHWACHMAN-DIAMOND ANEMIA
History	Skeletal and renal malformations, low birthweight, pancytopenia, family member with bone marrow failure, MDS, acute myelogenous leukemia (AML), or squamous cell carcinoma at an early age; family member with Fanconi anemia	Intrauterine growth retardation, developmental delay, and short stature. Family history of MDS, AML, marrow failure, abnormal fingernails or toenails, leukoplakia, head and neck cancer, or pulmonary fibrosis	Pancreatic insufficiency, low birth weight, metaphyseal dysostosis, initial neutropenia, delayed development
Physical findings	Thumb and radial malformations, hyperpigmented skin lesions (café-au-lait spots), short stature, MDS, AML, squamous cell carcinoma at young age, renal and cardiac malformations, microcephaly, hypogonadism	Lacy reticular pigmentation of skin, dystrophic fingernails and toenails, premature graying of hair, hair loss, short stature, oral leukoplakia, squamous cell cancer of head and neck, pulmonary fibrosis, osteopenia, hypogonadism	Short stature, abnormal thorax
Genes inactivated	FANCA, FANCB, FANCC, FANCD1 (aka BRCA2), FANCD2, FANCE, FANCF, FANCG (aka XRCC9), FANCI, FANCJ (aka BACH1 and BRIP1), FANCL (aka PHF9 and POG), FANCM (aka Hef), and FANCN (aka PALB2). These genes encode proteins known to protect the genome from excessive damage induced by chemical crosslinking agents. These genes account for most cases of Fanconi anemia	DKC1, TERC, TERT, TINF2, NOLA2, and NOLA3 These genes encode proteins known to participate in maintenance of telomeres. They account for only half of dyskeratosis cases, so there are additional genes to be discovered	SBDS autosomal recessive marrow clonal expansion in ~15%
Screening and diagnostic tests	1. Chromosomal breakage test (in response to mitomycin C or diepoxybutane) 2. Complementation analysis (flow cytometric analysis of G ₂ arrest in melphalan-exposed cells after transduction with retroviral vectors expressing normal Fanconi anemia genes) 3. Gene sequencing	1. Quantitative analysis of telomere length ("flow FISH") 2. Gene sequencing	CT demonstrates fatty infiltration of pancreas Gene testing May evolve to myelodysplasia or leukemia Absence of pancreatic lipomatosis, fecal fat, or dysostosis does not rule out diagnosis

ADA, adenosine deaminase; FISH, fluorescent in situ hybridization.

Modified from Bagby GC: Aplastic anemia and related bone marrow failure states. In Goldman L, Schafer AI, editors, Goldman's Cecil medicine, ed 24, Philadelphia, 2012, WB Saunders, Table 168-3, p. 1086.

Table 468-4 Canadian Inherited Marrow Failure Registry Criteria for Unclassified Inherited Bone Marrow Failure Syndromes

FULFILLS CRITERIA 1 AND 2:

1. Does not fulfill criteria for any categorized inherited bone marrow failure syndrome*
2. Fulfils both of the following

FULFILLS AT LEAST 2 OF THE FOLLOWING:

- a. Chronic cytopenia(s) detected on at least 2 occasions over at least 3 mo[†]
- b. Reduced marrow progenitors or reduced clonogenic potential of hematopoietic progenitor cells or evidence of ineffective hematopoiesis[‡]
- c. High fetal hemoglobin for age[‡]
- d. Red blood cell macrocytosis (not caused by hemolysis or a nutritional deficiency)

FULFILLS AT LEAST 1 OF THE FOLLOWING:

- a. Family history of bone marrow failure
- b. Presentation at age <1 yr
- c. Anomalies involving multiple systems to suggest an inherited syndrome

*The Canadian Inherited Marrow Failure Registry diagnostic guidelines for selected syndromes were adapted from the literature and are available at <http://www.sickkids.ca/cimfr>.

[†]Cytopenia was defined as follows: neutropenia, neutrophil count of $<1.5 \times 10^9/L$; thrombocytopenia, platelet count of $<150 \times 10^9/L$; anemia, hemoglobin concentration of <2 standard deviations below mean, adjusted for age.

[‡]Hemoglobinopathies with ineffective erythropoiesis and high hemoglobin F should be excluded by clinical or laboratory testing.

Table 471-1 Guidelines for Pediatric Platelet Transfusion*

CHILDREN AND ADOLESCENTS

1. Maintain PLT count $>50 \times 10^9/L$ with bleeding
2. Maintain PLT count $>50 \times 10^9/L$ with *major invasive procedure*; $>25 \times 10^9/L$ with minor
3. Maintain PLT count $>20 \times 10^9/L$ and *marrow failure* WITH hemorrhagic risk factors
4. Maintain PLT count $>10 \times 10^9/L$ and *marrow failure* WITHOUT hemorrhagic risk factors
5. Maintain PLT count at any level with PLT dysfunction PLUS bleeding or invasive procedure

INFANTS ≤4 MO OLD

1. Maintain PLT count $>100 \times 10^9/L$ with bleeding or during extracorporeal membrane oxygenation
2. Maintain PLT count $>50 \times 10^9/L$ and an invasive procedure
3. Maintain PLT count $>20 \times 10^9/L$ and *clinically stable*
4. Maintain PLT count $>50 \times 10^9/L$ and *clinically unstable* and/or bleeding or not when on *indomethacin, nitric oxide, antibiotics, etc. affecting PLT function*
5. Maintain PLT count at any level with PLT dysfunction PLUS bleeding invasive procedure

*Words in *italics* must be defined for local transfusion guidelines.
PLT, platelet.

Table 469-1 Etiology of Acquired Aplastic Anemia

Radiation, drugs, and chemicals:

Predictable: chemotherapy, benzene
Idiosyncratic: chloramphenicol, antiepileptics, gold; 3,4-met hylendioxymethamphetamine

Viruses:

Cytomegalovirus
Epstein-Barr
Hepatitis B
Hepatitis C
Hepatitis non-A, non-B, non-C (seronegative hepatitis)
HIV

Immune diseases:

Eosinophilic fasciitis
Hyperimmunoglobulinemia
Thymoma

Pregnancy

Paroxysmal nocturnal hemoglobinuria

Marrow replacement:

Leukemia
Myelodysplasia
Myelofibrosis

Autoimmune

Other:
Cryptic dyskeratosis congenita (no physical stigmata)
Telomerase reverse transcriptase haploinsufficiency

Table 470-1 Guidelines for Pediatric Red Blood Cell Transfusions*

CHILDREN AND ADOLESCENTS

1. Maintain stable status with acute loss of $>25\%$ of circulating blood volume
2. Maintain hemoglobin $>7.0 \text{ g/dL}^{\dagger}$ in the perioperative period
3. Maintain hemoglobin $>12.0 \text{ g/dL}$ with severe cardiopulmonary disease
4. Maintain hemoglobin $>12.0 \text{ g/dL}$ during extracorporeal membrane oxygenation
5. Maintain hemoglobin $>7.0 \text{ g/dL}$ and *symptomatic chronic anemia*
6. Maintain hemoglobin $>7.0 \text{ g/dL}$ and *marrow failure*

INFANTS ≤4 MO OLD

1. Maintain hemoglobin $>12.0 \text{ g/dL}$ and *severe pulmonary disease*
2. Maintain hemoglobin $>12.0 \text{ g/dL}$ during extracorporeal membrane oxygenation
3. Maintain hemoglobin $>10.0 \text{ g/dL}$ and *moderate pulmonary disease*
4. Maintain hemoglobin $>12.0 \text{ g/dL}$ and *severe cardiac disease*
5. Maintain hemoglobin $>10.0 \text{ g/dL}$ preoperatively and during *major surgery*
6. Maintain hemoglobin $>7.0 \text{ g/dL}$ postoperatively
7. Maintain hemoglobin $>7.0 \text{ g/dL}$ and *symptomatic anemia*

*Words in *italics* must be defined for local transfusion guidelines.

[†]Pretransfusion blood hemoglobin level (convert to hematocrit values if preferred by multiplying hemoglobin values by 3) "triggering" an RBC transfusion. Hemoglobin values to maintain vary among published reports, and the guideline values to maintain should be determined locally to fit the practices judged to be optimal by local MDs.

Table 475-1 Coagulation Factors

CLOTTING FACTOR	SYNONYM	DISORDER
I	Fibrinogen	Congenital deficiency (afibrinogenemia) or dysfunction (dysfibrinogenemia)
II	Prothrombin	Congenital deficiency or dysfunction
V	Labile factor, proaccelerin	Congenital deficiency (parahemophilia)
VII	Stable factor or proconvertin	Congenital deficiency
VIII	Antihemophilic factor	Congenital deficiency is hemophilia A (classic hemophilia)
IX	Christmas factor	Congenital deficiency is hemophilia B (sometimes referred to as Christmas disease)
X	Stuart-Prower factor	Congenital deficiency
XI	Plasma thromboplastin antecedent	Congenital deficiency (sometimes referred to as hemophilia C)
XII	Hageman factor	Congenital deficiency is not associated with clinical symptoms
XIII	Fibrin-stabilizing factor	Congenital deficiency

Table 475-1 Coagulation Factors

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X	Stuart-Prower factor	Congenital deficiency
XI	Plasma thromboplastin antecedent	Congenital deficiency (sometimes referred to as hemophilia C)
XII	Hageman factor	Congenital deficiency is not associated with clinical symptoms
XIII	Fibrin-stabilizing factor	Congenital deficiency

Table 475-2 Reference Values for Coagulation Tests in Healthy Children*

TEST	28-31 Wk GESTATION	30-36 Wk GESTATION	FULL TERM	1-5 Yr	6-10 Yr	11-18 Yr	ADULT
SCREENING TESTS							
Prothrombin time (sec)	15.4 (14.6-16.9)	13.0 (10.6-16.2)	13.0 (10.1-15.9)	11 (10.6-11.4)	11.1 (10.1-12.0)	11.2 (10.2-12.0)	12 (11.0-14.0)
Activated partial thromboplastin time (sec)	108 (80-168)	53.6 (27.5-79.4) ^{†\$}	42.9 (31.3-54.3) [‡]	30 (24-36)	31 (26-36)	32 (26-37)	33 (27-40)
Bleeding time (min)				6 (2.5-10) [‡]	7 (2.5-13) [‡]	5 (3-8) [‡]	4 (1-7)
PROCOAGULANTS							
Fibrinogen	256 (160-550)	243 (150-373) ^{†\$}	283 (167-399)	276 (170-405)	279 (157-400)	300 (154-448)	278 (156-40)
Factor II	31 (19-54)	45 (20-77) [‡]	48 (26-70) [‡]	94 (71-116) [‡]	88 (67-107) [‡]	83 (61-104) [‡]	108 (70-146)
Factor V	65 (43-80)	88 (41-144) ^{\$}	72 (34-108) [‡]	103 (79-127)	90 (63-116) [‡]	77 (55-99) [‡]	106 (62-150)
Factor VII	37 (24-76)	67 (21-113) [‡]	66 (28-104) [‡]	82 (55-116) [‡]	86 (52-120) [‡]	83 (58-115) [‡]	105 (67-143)
Factor VIII procoagulant	79 (37-126)	111 (5-213)	100 (50-178)	90 (59-142)	95 (58-132)	92 (53-131)	99 (50-149)
von Willebrand factor	141 (83-223)	136 (78-210)	153 (50-287)	82 (60-120)	95 (44-144)	100 (46-153)	92 (50-158)
Factor IX	18 (17-20)	35 (19-65) ^{†\$}	53 (15-91) [‡]	73 (47-104) [‡]	75 (63-89) [‡]	82 (59-122) [‡]	109 (55-163)
Factor X	36 (25-64)	41 (11-71) [‡]	40 (12-68) [‡]	88 (58-116) [‡]	75 (55-101) [‡]	79 (50-117)	106 (70-152)
Factor XI	23 (11-33)	30 (8-52) ^{†\$}	38 (40-66) [‡]	30 (8-52) [‡]	38 (10-66)	74 (50-97) [‡]	97 (56-150)
Factor XII	25 (5-35)	38 (10-66) ^{†\$}	53 (13-93) [‡]	93 (64-129)	92 (60-140)	81 (34-137) [‡]	108 (52-164)
Prekallikrein	26 (15-32)	33 (9-89) [‡]	37 (18-69) [‡]	95 (65-130)	99 (66-131)	99 (53-145)	112 (62-162)
High-molecular-weight kininogen	32 (19-52)	49 (9-89) [‡]	54 (6-102) [‡]	98 (64-132)	93 (60-130)	91 (63-119)	92 (50-136)
Factor XIIIa [‡]		70 (32-108) [‡]	79 (27-131) [‡]	108 (72-143)	109 (65-151)	99 (57-140)	105 (55-155)
Factor XIIIb [‡]		81 (35-127) [‡]	76 (30-122) [‡]	113 (69-156) [‡]	116 (77-154) [‡]	102 (60-143)	98 (57-137)
ANTICOAGULANTS							
Antithrombin-III	28 (20-38)	38 (14-62) ^{†\$}	63 (39-87) [‡]	111 (82-139)	111 (90-131)	106 (77-132)	100 (74-126)
Protein C		28 (12-44) ^{†\$}	35 (17-53) [‡]	66 (40-92) [‡]	69 (45-93) [‡]	83 (55-111) [‡]	96 (64-128)
Protein S:							
Total (units/mL)		26 (14-38) ^{†\$}	36 (12-60) [‡]	86 (54-118)	78 (41-114)	72 (52-92)	81 (61-113)
Free (units/mL)				45 (21-69)	42 (22-62)	38 (26-55)	45 (27-61)
Plasminogen (units/mL)		170 (112-248)	195 (125-265)	98 (78-118)	92 (75-108)	86 (68-103)	99 (77-122)
Tissue-type plasminogen activator (ng/mL)		8.48 (3.00-16.70)	9.6 (5.0-18.9)	2.15 (1.0-4.5) [‡]	2.42 (1.0-5.0) [‡]	2.16 (1.0-4.0) [‡]	1.02 (0.68-1.36)
Antiplasmin (units/mL)		78 (40-116)	85 (55-115)	105 (93-117)	99 (89-110)	98 (78-118)	102 (68-136)
Plasminogen activator inhibitor-I		5.4 (0.0-12.2) [‡]	6.4 (2.0-15.1)	5.42 (1.0-10.0)	6.79 (2.0-12.0) [‡]	6.07 (2.0-10.0) [‡]	3.60 (0.0-11.0)

*All factors except fibrinogen are expressed as units/mL (fibrinogen in mg/mL), in which pooled normal plasma contains 1 unit/mL. All data are expressed as the mean, followed by the upper and lower boundaries encompassing 95% of the normal population (shown in parentheses). Normal ranges above vary based on the reagents and instruments used.

[†]Levels for 19-27 wk and 28-31 wk gestation are from multiple sources and cannot be analyzed statistically.

[‡]Values are significantly different from those of adults.

[§]Values are significantly different from those of full-term infants.

[¶]Value given as CTA (Committee on Thrombolytic Agents) units/mL. Normal ranges above vary based on the reagents and instruments used.

Data from Andrew M, Paes B, Johnston M: Development of the hemostatic system in the neonate and young infant, Am J Pediatr Hematol Oncol 12:95, 1990; and Andrew M, Vegh P, Johnston M, et al: Maturation of the hemostatic system during childhood, Blood 80:1998, 1992.

Table 476-1 Treatment of Hemophilia

TYPE OF HEMORRHAGE	HEMOPHILIA A	HEMOPHILIA B
Hemarthrosis*	50-60 IU/kg factor VIII concentrate ^t on day 1; then 20-30 IU/kg on days 2, 3, 5 until joint function is normal or back to baseline. Consider additional treatment every other day for 7-10 days. Consider prophylaxis.	80-100 IU/kg on day 1; then 40 IU/kg on days 2, 4. Consider additional treatment every other day for 7-10 days. Consider prophylaxis.
Muscle or significant subcutaneous hematoma	50 IU/kg factor VIII concentrate; 20 IU/kg every-other-day treatment may be needed until resolved	80 IU/kg factor IX concentrate ^t ; treatment every 2-3 days may be needed until resolved
Mouth, deciduous tooth, or tooth extraction	20 IU/kg factor VIII concentrate; antifibrinolytic therapy; remove loose deciduous tooth	40 IU/kg factor IX concentrate ^t ; antifibrinolytic therapy ^s ; remove loose deciduous tooth
Epistaxis	Apply pressure for 15-20 min; pack with petrolatum gauze; give antifibrinolytic therapy; 20 IU/kg factor VIII concentrate if this treatment fails ^l	Apply pressure for 15-20 min; pack with petrolatum gauze; antifibrinolytic therapy; 30 IU/kg factor IX concentrate ^t if this treatment fails
Major surgery, life-threatening hemorrhage	50-75 IU/kg factor VIII concentrate, then initiate 25 IU/kg q8-12h to maintain trough level >50 IU/dL for 5-7 days, then 50 IU/kg q24h to maintain trough >25 IU/dL for 7 days	120 IU/kg factor IX concentrate ^t , then 50-60 IU/kg every 12-24 hr to maintain factor IX at >40 IU/dL for 5-7 days, and then at >30 IU/dL for 7 days
Iliopsoas hemorrhage	50 IU/kg factor VIII concentrate, then 25 IU/kg every 12 hr until asymptomatic, then 20 IU/kg every other day for a total of 10-14 days**	120 IU/kg factor IX concentrate ^t ; then 50-60 IU/kg every 12-24 hr to maintain factor IX at >40 IU/dL until patient is asymptomatic; then 40-50 IU every other day for a total of 10-14 days**††
Hematuria	Bed rest; 1.5x maintenance fluids; if not controlled in 1-2 days, 20 IU/kg factor VIII concentrate; if not controlled, give prednisone (unless patient is HIV-infected)	Bed rest; 1.5x maintenance fluids; if not controlled in 1-2 days, 40 IU/kg factor IX concentrate ^t ; if not controlled, give prednisone (unless patient is HIV-infected)
Prophylaxis	20-40 IU/kg factor VIII concentrate every other day to achieve a trough level $\geq 1\%$	30-50 IU/kg factor IX concentrate ^t every 2-3 days to achieve a trough level $\geq 1\%$

*For hip hemarthrosis, orthopedic evaluation for possible aspiration is advisable to prevent avascular necrosis of the femoral head.

^tFor mild or moderate hemophilia, desmopressin, 0.3 µg/kg, should be used instead of factor VIII concentrate, if the patient is known to respond with a hemostatic level of factor VIII; if repeated doses are given, monitor factor VIII levels for tachyphylaxis.

^sStated doses apply for recombinant factor IX concentrate; for plasma-derived factor IX concentrate, use 70% of the stated dose.

^lDo not give antifibrinolytic therapy until 4-6 hr after a dose of prothrombin complex concentrate.

^{**}Nonprescription coagulation-promoting products may be helpful.

^{**††}Repeat radiologic assessment should be performed before discontinuation of therapy.

^{††}If repeated doses of factor IX concentrate are required, use highly purified, specific factor IX concentrate.

Adapted from Montgomery RR, Gill JC, Scott JP: Hemophilia and von Willebrand disease. In Nathan DG, Orkin SH, editors: Nathan and Oski's hematology of

Table 477-2 VWD Classification

	TYPE 1	TYPE 3	TYPE 2A	TYPE 2B*	TYPE 2M	TYPE 2N
VWF:Ag	↓	Absent	↓	↓	↓	Normal or ↓
VWF:RCo	↓	Absent	↓↓	↓↓	↓↓	Normal or ↓
FVIII	Normal	↓↓	Normal or ↓	Normal or ↓	Normal or ↓	↓↓
Multimer distribution	Normal	Absent	Loss of HMWM	Loss of HMWM	Normal	Normal

*Platelet count is also usually decreased in type 2B VWD.

FVIII, factor VIII; HMWM, high-molecular-weight multimers; VWF:Ag, VWF antigen; VWF:RCo, VWF ristocetin cofactor activity.

Table 477-3 VWD Treatment

TREATMENT	VWD TYPES	ADMINISTRATION	DOSING
Desmopressin*	Type 1 VWD Some type 2 VWD (use with caution)	IV or IN	0.3 µg/kg IV ^t 1 spray IN (<50 kg) 2 sprays IN (>50 kg)
von Willebrand factor concentrates ^t	Type 3 VWD Type 2 VWD Severe type 1 VWD (or type 1 clearance defects)	IV	40-60 ristocetin cofactor activity units/kg (adjust dose depending on baseline VWF level and desired peak VWF level)
Antifibrinolytics	Mucosal bleeding, all types of VWD	PO or IV	Aminocaproic acid: 100 mg/kg PO loading dose followed by 50 mg/kg q 6 hours ^s Tranexamic acid: 1300 mg PO tid × 5 days

*Recommended treatment with Stimate brand nasal spray, as this form is concentrated to give 150 µg/spray. Other forms are much more dilute and will not result in desired increase in VWF.

^tMaximum recommended dose is 20-30 µg/day.

^sCurrently both Humate-P and Wilate are approved for treatment of VWD. A recombinant VWF preparation is currently undergoing clinical trials.

[§]Maximum recommended dose is 24 g/day.

IN, intranasal; IV, intravenous; PO, oral administration.

Table 478-1 Common Inherited Thrombophilias and Accompanying Diagnostic Laboratory Studies

THROMBOPHILIA	PREVALENCE IN WHITE POPULATION %	ODDS RATIO FOR FIRST EPISODE VTE IN CHILDHOOD*	LABORATORY STUDIES
Factor V Leiden mutation			DNA-based PCR assay (or screen with activated protein C resistance)
Heterozygote	3-7	3.8	
Homozygote	0.06-0.25	80-100	
Prothrombin 20210 mutation			DNA-based PCR assay
Heterozygote	1-3	2.6	
Homozygote	—	—	
Antithrombin deficiency	0.02-0.04	9.4	Antithrombin activity via chromogenic or clotting assay
Protein S deficiency	0.03-0.13	5.8	Protein S activity via assay or immunologic assay of free and total protein S antigen
Protein C deficiency	0.2	7.7	Protein C activity via chromogenic or clotting assay
Hyperhomocystinemia	—	—	Fasting homocysteine
Elevated VIII	—	—	Factor VIII activity via one-stage clotting or chromogenic assay

*Data from Young G, Albisetti M, Bonduel M, et al: Impact of inherited thrombophilia on venous thromboembolism in children. *Circulation* 118:1373-1382, 2008.
PCR, polymerase chain reaction; VTE, venous thromboembolism.

Table 479-1 Risk Factors for Thrombosis

General	Indwelling catheter including PICC (peripherally inserted central venous catheter) lines Infection Trauma Surgery Cancer Immobility Cardiac disease/prosthetic valve Systemic lupus Rheumatoid arthritis Inflammatory bowel disease Polycythemia/dehydration Nephrotic syndrome Diabetes Pregnancy Obesity Prematurity Paroxysmal nocturnal hemoglobinuria Antiphospholipid antibody syndrome Thrombotic thrombocytopenic purpura
Inherited thrombophilia	Factor V Leiden mutation Prothrombin mutation Antithrombin deficiency Protein C deficiency Protein S deficiency Homocystinuria Elevated factor VIII Dysfibrinogenemia
Anatomic	Thoracic outlet obstruction (Paget-Schroetter syndrome) May-Thurner syndrome Absence of the inferior vena cava
Medications	Estrogen-containing contraceptives Asparaginase Heparin (heparin-induced thrombocytopenia) Corticosteroids

Table 474-1 Estimated Risks in Transfusion Per Unit Transfused in the United States

ADVERSE EFFECT	ESTIMATED RISK
Febrile reaction	1/300
Urticaria or other cutaneous reaction	1/50-100
Red blood cell alloimmunization	1/100
Mistransfusion	1/14,000-19,000
Hemolytic reaction	1/6,000
Fatal hemolysis	1/1,000,000
Transfusion-related acute lung injury (TRALI)	1/5,000
HIV1 and HIV2	1/2,000,000-3,000,000
Hepatitis B	1/100,000-200,000
Hepatitis C	1/1,000,000-2,000,000
Human T-cell lymphotropic virus (HTLV) I and II	1/641,000
Bacterial contamination (usually platelets)	1/5,000,000
Malaria	1/4,000,000
Anaphylaxis	1/20,000-50,000
Graft-versus-host disease	Uncommon
Immunomodulation	Unknown
Hepatitis A	Unknown
Parvovirus	Unknown
Dengue fever	Unknown
Babesiosis	Unknown
West Nile virus	Unknown
<i>Trypanosoma cruzi</i>	Unknown
<i>Leishmania</i> spp.	Unknown
Variant Creutzfeldt-Jakob prion disease	Unknown

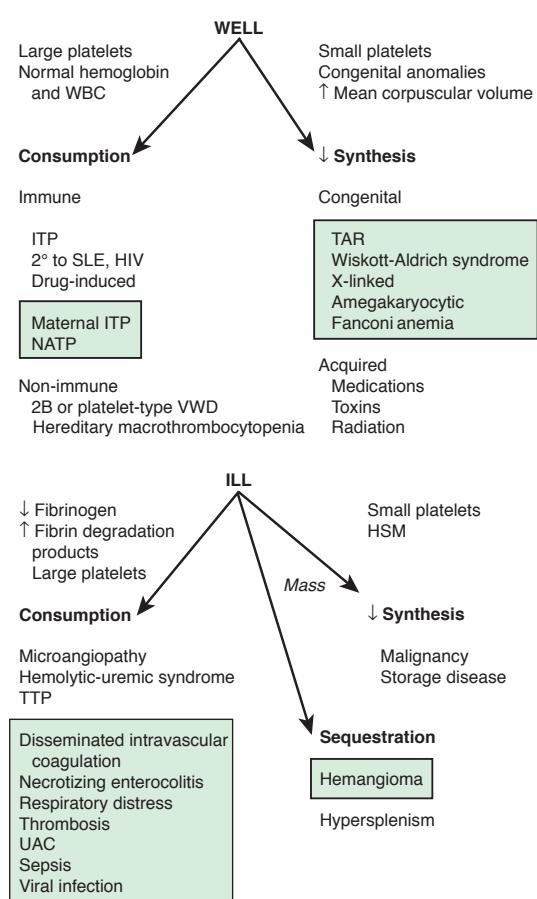


Table 487-1 Diseases Associated with Hyposplenism or Splenic Atrophy

CONGENITAL FORMS	AUTOIMMUNE DISORDERS
Normal and premature neonates	Systematic lupus erythematosus
Isolated congenital hypoplasia	Rheumatoid arthritis
Ivemark syndrome	Glomerulonephritis
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome	Wegener granulomatosis
Hypoparathyroidism syndrome	Goodpasture syndrome
Stormorken syndrome	Sjögren syndrome
Heterotaxia syndromes	Nodous polyarteritis
	Thyroiditis
	Sarcoidosis
GASTROINTESTINAL DISORDERS	INFECTIOUS DISEASES
Coeliac disease	HIV/AIDS
Inflammatory bowel disease	Pneumococcal meningitis
Whipple disease	Malaria
Dermatitis herpetiformis	
Intestinal lymphangiectasia	
Idiopathic chronic ulcerative enteritis	
HEPATIC DISORDERS	IATROGENIC FORMS
Active chronic hepatitis	Exposure to methyldopa
Primary biliary cirrhosis	High-dose steroids
Hepatic cirrhosis and portal hypertension	Total parenteral nutrition
Alcoholism and alcoholic hepatopathy	Splenic irradiation
ONCOHEMATOLOGIC DISORDERS	ALTERATION IN SPLENIC CIRCULATION
Hemoglobin S diseases	Thrombosis of splenic artery
Bone marrow transplantation	Thrombosis of splenic vein
Chronic graft-versus-host disease	Thrombosis of coeliac artery
Acute leukemia	
Chronic myeloproliferative disorders	
Fanconi syndrome	MISCELLANEOUS
Splenic tumors	Amyloidosis
Mastocytosis	

Table 483-1 Causes of Disseminated Intravascular Coagulation

INFECTIOUS
Meningococcemia (purpura fulminans)
Bacterial sepsis (staphylococcal, streptococcal, <i>Escherichia coli</i> , <i>Salmonella</i>)
Rickettsia (Rocky Mountain spotted fever)
Virus (cytomegalovirus, herpes simplex, hemorrhagic fevers)
Malaria
Fungus
TISSUE INJURY
Central nervous system trauma (massive head injury)
Multiple fractures with fat emboli
Crush injury
Profound shock or asphyxia
Hypothermia or hyperthermia
Massive burns
MALIGNANCY
Acute promyelocytic leukemia
Acute monoblastic or promyelocytic leukemia
Widespread malignancies (neuroblastoma)
VENOM OR TOXIN
Snake bites
Insect bites
MICROANGIOPATHIC DISORDERS
"Severe" thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome
Giant hemangioma (Kasabach-Merritt syndrome)
GASTROINTESTINAL DISORDERS
Fulminant hepatitis
Ischemic bowel
Pancreatitis
HEREDITARY THROMBOTIC DISORDERS
Antithrombin III deficiency
Homozygous protein C deficiency
NEWBORN
Maternal toxemia
Bacterial or viral sepsis (group B streptococcus, herpes simplex)
Abruptio placenta
Severe respiratory distress syndrome
Necrotizing enterocolitis
Erythroblastosis fetalis
Fetal demise of a twin
MISCELLANEOUS
Severe acute graft rejection
Acute hemolytic transfusion reaction
Severe collagen-vascular disease
Kawasaki disease
Heparin-induced thrombosis
Infusion of "activated" prothrombin complex concentrates
Hyperpyrexia/encephalopathy, hemorrhagic shock syndrome

Table 490-1 Differential Diagnosis of Systemic Generalized Lymphadenopathy

INFANT	CHILD	ADOLESCENT
COMMON CAUSES		
Syphilis	Viral infection	Viral infection
Toxoplasmosis	EBV	EBV
CMV	CMV	CMV
HIV	Toxoplasmosis	HIV
		Toxoplasmosis
		Syphilis
RARE CAUSES		
Chagas disease (congenital)	Serum sickness	Serum sickness
Leukemia	SLE, JIA	SLE, JIA
Tuberculosis	Leukemia/lymphoma	Leukemia/lymphoma/Hodgkin disease
Reticuloendotheliosis	Tuberculosis	Lymphoproliferative disease
Lymphoproliferative disease	Measles	Tuberculosis
Metabolic storage disease	Sarcoidosis	Histoplasmosis
Histiocytic disorders	Fungal infection	Sarcoidosis
	Plague	Fungal infection
	Langerhans cell histiocytosis	Plague
	Chronic granulomatous disease	Drug reaction
	Sinus histiocytosis	Castleman disease
	Drug reaction	

Table 484-1 Differential Diagnosis of Thrombocytopenia in Children and Adolescents

DESTRUCTIVE THROMBOCYTOPENIAS	
Primary Platelet Consumption Syndromes	
<i>Immune thrombocytopenias</i>	Platelets in contact with foreign material Congenital heart disease Drug-induced via direct platelet effects (ristocetin, protamine) Type 2B VWD or platelet-type VWD
Acute and chronic ITP	
Autoimmune diseases with chronic ITP as a manifestation	
Cyclic thrombocytopenia	
Autoimmune lymphoproliferative syndrome and its variants	
Systemic lupus erythematosus	
Evans syndrome	
Antiphospholipid antibody syndrome	
Neoplasia-associated immune thrombocytopenia	
Thrombocytopenia associated with HIV	
Neonatal immune thrombocytopenia	
Alloimmune	
Autoimmune (e.g., maternal ITP)	
Drug-induced immune thrombocytopenia (including heparin-induced thrombocytopenia)	
Posttransfusion purpura	
Allergy and anaphylaxis	
Posttransplant thrombocytopenia	
<i>Nonimmune thrombocytopenias</i>	
Thrombocytopenia of infection	
Bacteremia or fungemia	
Viral infection	
Protozoan	
Thrombotic microangiopathic disorders	
Hemolytic-uremic syndrome	
Eclampsia, HELLP syndrome	
Thrombotic thrombocytopenic purpura	
Bone marrow transplantation-associated microangiopathy	
Drug-induced	

HELLP, hemolysis, elevated liver enzymes, and low platelets; HIV, human immunodeficiency virus; ITP, immune thrombocytopenic purpura; VWD, von Willebrand disease.

From Wilson DB: Acquired platelet defects. In Orkin SH, Nathan DG, Ginsburg D, et al, editors: Nathan and Oski's hematology of infancy and childhood, ed 7, Philadelphia, 2009, WB Saunders, p. 1555, Box 33-1.

Table 484-2 Classification of Fetal and Neonatal Thrombocytopenias*

CONDITION		CONDITION
Fetal	Alloimmune thrombocytopenia Congenital infection (e.g., CMV, toxoplasma, rubella, HIV) Aneuploidy (e.g., trisomy 18, 13, or 21, or triploidy) Autoimmune condition (e.g., ITP, SLE) Severe Rh hemolytic disease Congenital/inherited (e.g., Wiskott-Aldrich syndrome)	Thrombosis (e.g., aortic, renal vein) Bone marrow replacement (e.g., congenital leukemia) Kasabach-Merritt syndrome Metabolic disease (e.g., propionic and methylmalonic acidemia) Congenital/inherited (e.g., TAR, CAMT)
Early-onset neonatal (<72 hr)	Placental insufficiency (e.g., PET, IUGR, diabetes) Perinatal asphyxia Perinatal infection (e.g., <i>Escherichia coli</i> , GBS, herpes simplex) DIC Alloimmune thrombocytopenia Autoimmune condition (e.g., ITP, SLE) Congenital infection (e.g., CMV, toxoplasma, rubella, HIV)	Late-onset neonatal (>72 hr) Late-onset sepsis NEC Congenital infection (e.g., CMV, toxoplasma, rubella, HIV) Autoimmune Kasabach-Merritt syndrome Metabolic disease (e.g., propionic and methylmalonic acidemia) Congenital/inherited (e.g., TAR, CAMT)

*The most common conditions are shown in bold.

CAMT, congenital amegakaryocytic thrombocytopenia; CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; GBS, group B streptococcus; ITP, idiopathic thrombocytopenic purpura; IUGR, intrauterine growth restriction; NEC, necrotizing enterocolitis; PET, preeclampsia; SLE, systemic lupus erythematosus; TAR, thrombocytopenia with absent radii.

Table 487-2 Diagnostic Techniques for and Features of Spleen Dysfunction

DESCRIPTION		COMMENTS
Immunoglobulin M memory B cells	Cells dependent on spleen for survival. Produced in marginal zone	Special tests required
Technetium-99m-labeled sulphur colloidal scintiscan	Quantitation of splenic uptake of colloidal sulphur particles enables a fairly accurate static assessment of spleen function	Hypertrophy of the left hepatic lobe might be a limiting factor (this technique does not clearly show whether the mass originated in the liver or the spleen in the presence of an overlapping hypertrophic left hepatic lobe)
Technetium-99m-labeled or rubidium-81-labeled heat-damaged autologous erythrocyte clearance	Measurement of clearance time allows a dynamic evaluation of spleen function	Preexisting erythrocyte defects, difficult erythrocyte incorporation of the radioisotope, false-positive or false-negative results in relation to excessive or insufficient heat damage make the test not suitable for clinical practice
Detection of Howell-Jolly bodies by staining	Erythrocytes with nuclear remnants Flow cytometry	No need for special equipment; inaccurate in the quantitation of splenic hypofunction
Detection of pitted erythrocytes by phase-interference microscopy	Erythrocytes with membrane indentations (4% upper limit of the normal range)	Need for phase-interference microscopy; counts enable a wide range of measurements and correlate with radioisotopic methods

Table 486-1 Differential Diagnosis of Splenomegaly by Pathophysiology

ANATOMIC LESIONS	Parasitic
Cysts, pseudocysts	Malaria
Hamartomas	Toxoplasmosis, especially congenital
Polysplenia syndrome	<i>Toxocara canis</i> , <i>Toxocara cati</i> (visceral larva migrans)
Hemangiomas and lymphangiomas	Leishmaniasis (kala-azar)
Hematoma or rupture (traumatic)	Schistosomiasis (hepatic-portal involvement)
Peliosis	Trypanosomiasis
HYPERPLASIA CAUSED BY HEMATOLOGIC DISORDERS	Fascioliasis
Acute and Chronic Hemolysis*	Babesiosis
Hemoglobinopathies (sickle cell disease in infancy with or without sequestration crisis and sickle variants, thalassemia major, unstable hemoglobins)	IMMUNOLOGIC AND INFLAMMATORY PROCESSES*
Erythrocyte membrane disorders (hereditary spherocytosis, elliptocytosis, pyropoikilocytosis)	Systemic lupus erythematosus
Erythrocyte enzyme deficiencies (severe G6PD deficiency, pyruvate kinase deficiency)	Rheumatoid arthritis
Immune hemolysis (autoimmune and isoimmune hemolysis)	Mixed connective tissue disease
Paroxysmal nocturnal hemoglobinuria	Systemic vasculitis
Chronic Iron Deficiency	Serum sickness
Extramedullary Hematopoiesis	Drug hypersensitivity, especially to phenytoin
Myeloproliferative diseases: CML, juvenile CML, myelofibrosis with myeloid metaplasia, polycythemia vera	Graft-versus-host disease
Osteopetrosis	Sjögren syndrome
Patients receiving granulocyte and granulocyte-macrophage colony-stimulating factors	Cryoglobulinemia
INFECTIONS†	Amyloidosis
Bacterial	Sarcoidosis
Acute sepsis: <i>Salmonella typhi</i> , <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> type b, <i>Staphylococcus aureus</i>	Autoimmune lymphoproliferative syndrome
Chronic infections: infective endocarditis, chronic meningococcemia, brucellosis, tularemia, cat-scratch disease	Posttransplant lymphoproliferative disease
Local infections: splenic abscess (<i>S. aureus</i> , streptococci, less often <i>Salmonella</i> species, polymicrobial infection), pyogenic liver abscess (anaerobic bacteria, Gram-negative enteric bacteria), cholangitis	Large granular lymphocytosis and neutropenia
Viral*	Histiocytosis syndromes
Acute viral infections, especially in children	Hemophagocytic syndromes (nonviral, familial)
Congenital CMV, herpes simplex, rubella	
Hepatitis A, B, and C; CMV	
EBV	
Viral hemophagocytic syndromes: CMV, EBV, HHV-6	
HIV	
Spirochetal	
Syphilis, especially congenital syphilis	
Leptospirosis	
Rickettsial	
Rocky Mountain spotted fever	
Q fever	
Typhus	
Fungal/Mycobacterial	
Miliary tuberculosis	
Disseminated histoplasmosis	
South American blastomycosis	
Systemic candidiasis (in immunosuppressed patients)	
MALIGNANCIES	
Primary: leukemia (acute, chronic), lymphoma, angiosarcoma, Hodgkin disease, mastocytosis	
Metastatic	
STORAGE DISEASES	
Lipidosis (Gaucher disease, Niemann-Pick disease, infantile GM1 gangliosidosis)	
Mucopolysaccharidoses (Hurler, Hunter-type)	
Mucolipidosis (I-cell disease, sialidosis, multiple sulfatase deficiency, fucosidosis)	
Defects in carbohydrate metabolism: galactosemia, fructose intolerance, glycogen storage disease IV	
Sea-blue histiocyte syndrome	
Tangier disease	
Wolman disease	
Hyperchylomicronemia type I, IV	
CONGESTIVE*	
Heart failure	
Intrahepatic cirrhosis or fibrosis	
Extrahepatic portal (thrombosis), splenic, and hepatic vein obstruction (thrombosis, Budd-Chiari syndrome)	

*Common.

†Chronic or recurrent infection suggests underlying immunodeficiency.

CML, chronic myelogenous leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; G6PD, glucose-6-phosphate dehydrogenase; HHV-6, human herpesvirus 6; HIV, human immunodeficiency virus.

Table 479-2 Comparison of Antithrombotic Agents

	rTPA	UNFRACTIONATED HEPARIN*	WARFARIN	LMW HEPARIN (ENOXAPARIN)
Indication	Recent onset of life- or limb-threatening thrombus	Acute or chronic thrombus, prophylaxis	Subacute or chronic thrombosis, thromboprophylaxis for cardiac valves	Acute or chronic thrombus, prophylaxis
Administration	IV, Continuous infusion	IV, Continuous infusion	PO, once daily	SC injection, twice daily
Monitoring	"Lytic state": FDP or D-dimer	PTT	INR	Anti-Xa activity
Other	Higher risk of bleeding	Difficult to titrate, requires frequent dose adjustments	Heavily influenced by drug and diet	More stable and easy to titrate; concern of osteopenia with long-term use

FDP, fibrin degradation product; INR, international normalized ratio; LMW, low-molecular-weight; PTT, partial thromboplastin time; rTPA, recombinant tissue-type plasminogen activator.

*Higher dose is required in newborns.

2414 Part XXI ◆ Diseases of the Blood

Table 490-2 Sites of Local Lymphadenopathy and Associated Diseases	
CERVICAL	
Oropharyngeal infection (viral or group A streptococcal, staphylococcal)	
Scalp infection/infestation (head lice)	
Mycobacterial lymphadenitis (tuberculosis and nontuberculous mycobacteria)	
Viral infection (EBV, CMV, HHV-6)	
Cat-scratch disease	
Toxoplasmosis	
Kawasaki disease	
Thyroid disease	
Kikuchi disease	
Sinus histiocytosis (Rosai-Dorfman disease)	
Autoimmune lymphoproliferative disease	
Periodic fever, aphthous stomatitis, pharyngitis, cervical adenopathy (PFAPA) syndrome	
ANTERIOR AURICULAR	
Conjunctivitis	
Other eye infection	
Oculoglandular tularemia	
Facial cellulitis	
Otitis media	
Viral infection (especially rubella, parvovirus)	
SUPRACLAVICULAR	
Malignancy or infection in the mediastinum (right)	
Metastatic malignancy from the abdomen (left)	
Lymphoma	
Tuberculosis	
EPISTROCLEAR	
Hand infection, arm infection*	
Lymphoma [†]	
Sarcoid	
Syphilis	
INGUINAL	
Urinary tract infection	
Venereal disease (especially syphilis or lymphogranuloma venereum)	
Other perineal infections	
Lower extremity suppurative infection	
Plague	
HILAR (NOT PALPABLE, FOUND ON CHEST RADIOGRAPH OR CT)	
Tuberculosis [†]	
Histoplasmosis [†]	
Blastomycosis [†]	
Coccidioidomycosis [†]	
Leukemia/lymphoma [†]	
Hodgkin disease [†]	
Metastatic malignancy*	
Sarcoidosis [†]	
Castleman disease	
AXILLARY	
Cat-scratch disease	
Arm or chest wall infection	
Malignancy of chest wall	
Leukemia/lymphoma	
Brucellosis	
ABDOMINAL	
Malignancies	
Mesenteric adenitis (measles, tuberculosis, <i>Yersinia</i> , group A streptococcus)	

*Unilateral.

[†]Bilateral.

CMV, cytomegalovirus; CT, computed tomography; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6.

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, ed 2, Philadelphia, 2004, Elsevier, p. 864.

Table 495-1 Factors Predisposing to Childhood Leukemia**GENETIC CONDITIONS**

- Down syndrome
- Fanconi anemia
- Bloom syndrome
- Diamond-Blackfan anemia
- Shwachman-Diamond syndrome
- Kostmann syndrome
- Neurofibromatosis type 1
- Ataxia-telangiectasia
- Severe combined immune deficiency
- Paroxysmal nocturnal hemoglobinuria
- Li-Fraumeni syndrome

ENVIRONMENTAL FACTORS

- Ionizing radiation
- Drugs
- Alkylating agents
- Epipodophyllotoxin
- Benzene exposure

Cancer and Benign Tumors

2418 Part XXII ◆ Cancer and Benign Tumors

Table 491-2 Known Risk Factors for Selected Childhood Cancers

CANCER TYPE	RISK FACTOR	COMMENTS
Acute lymphoid leukemia	Ionizing radiation	Although primarily of historical significance, prenatal diagnostic x-ray exposure increases risk.
	Race Genetic factors*	Therapeutic irradiation for cancer treatment also increases risk. White children have a 2-fold higher rate than black children in the United States. Down syndrome is associated with an estimated 10-20-fold increased risk. NF1, Bloom syndrome, ataxia-telangiectasia, and Langerhans cell histiocytosis, among others, are associated with an elevated risk.
Acute myeloid leukemias	Chemotherapeutic agents Genetic factors*	Alkylating agents and epipodophyllotoxins increase risk. Down syndrome and NF1 are strongly associated. Familial monosomy 7 and several other genetic syndromes are also associated with increased risk.
Brain cancers	Therapeutic ionizing radiation to the head Genetic factors*	With the exception of cancer radiation therapy, higher risk from radiation treatment is essentially of historical importance. NF1 is strongly associated with optic gliomas, and, to a lesser extent, with other central nervous system tumors. Tuberous sclerosis and several other genetic syndromes are associated with increased risk.
Hodgkin disease	Family history Infections	Monozygotic twins and siblings are at increased risk. EBV is associated with increased risk.
Non-Hodgkin lymphoma	Immunodeficiency Infections	Acquired and congenital immunodeficiency disorders and immunosuppressive therapy increase risk. EBV is associated with Burkitt lymphoma in Africa.
Osteosarcoma	Ionizing radiation Chemotherapy Genetic factors*	Cancer radiation therapy and high radium exposure increase risk. Alkylating agents increase risk. Increased risk is apparent with Li-Fraumeni syndrome and hereditary retinoblastoma.
Ewing sarcoma	Race	White children have about a 9-fold higher incidence rate than black children in the United States.
Neuroblastoma		Neurocristopathies.
Retinoblastoma	Genetic factors*	No established other risk factors.
Wilms tumor	Congenital anomalies	Aniridia, Beckwith-Wiedemann syndrome, and other congenital and genetic conditions are associated with increased risk.
	Race	Asian children reportedly have about half the rates of white and black children.
Renal medullary carcinoma	Sickle cell trait	Etiology unknown.
Rhabdomyosarcoma	Congenital anomalies and genetic conditions	Li-Fraumeni syndrome and NF1 are believed to be associated with increased risk. There is some concordance with major birth defects.
Hepatoblastoma	Genetic factors*	Beckwith-Wiedemann syndrome, hemihypertrophy, Gardner syndrome, and family history of adenomatous polyposis are associated with increased risk.
Leiomyosarcoma	Immunosuppression and EBV infection	EBV is associated with leiomyosarcoma for all forms of congenital and acquired immunosuppression but not leiomyosarcoma among immunocompetent persons.
Malignant germ cell tumors	Cryptorchidism	Cryptorchidism is a risk factor for testicular germ cell tumors.

*See Chapter 492, Table 492-2.

EBV, Epstein-Barr virus; NF1, neurofibromatosis type 1.

Scheurer ME, Bondy ML, Gurney JG: Epidemiology of childhood cancer. In Pizzo PA, Poplack DG, editors: Principles and practice of pediatric oncology, ed 6, Philadelphia, 2011, Lippincott Williams & Wilkins, p. 15.

Table 492-2 Familial or Genetic Susceptibility to Malignancy

DISORDER	TUMOR/CANCER	COMMENT
CHROMOSOMAL SYNDROMES		
Chromosome 11p deletion syndrome with sporadic aniridia	Wilms tumor	Associated with genitourinary anomalies, mental retardation, <i>WT1</i> gene
Chromosome 13q deletion syndrome	Retinoblastoma, sarcoma	Associated with intellectual disability, skeletal malformations; autosomal dominant (bilateral) or sporadic new mutations, <i>RB1</i> gene
Trisomy 21	Lymphocytic or nonlymphocytic leukemia, especially megakaryocytic leukemia; transient leukemoid reaction	Risk of ALL is increased 20%; risk of AML is increased 400%; patients have an increased sensitivity to chemotherapy
Klinefelter syndrome (47,XXY)	Breast cancer, extragonadal germ cell tumors	
Trisomy 8	Preleukemia	
Noonan syndrome	JMML	Autosomal dominant; mutations in <i>PTPN11</i> gene
Monosomy 5 or 7	Myelodysplastic syndrome	Recurrent infections may precede neoplasia
CHROMOSOMAL INSTABILITY		
Xeroderma pigmentosum	Basal cell and squamous cell carcinomas; melanoma	Autosomal recessive; failure to repair UV-damaged DNA. Mutations in <i>XP</i> gene on chromosome 3p25
Fanconi anemia	Leukemia, myelodysplastic syndrome, liver neoplasias, rare head and neck tumors, GI and GU cancers	Autosomal recessive; chromosome fragility; positive diethoxybutane test result. Mutations in <i>FANCM</i> gene family
Bloom syndrome	Leukemia, lymphoma, and solid tumors	Autosomal recessive; increase sister chromatid exchange; mutations in <i>BLM</i> gene; member of the RecQ helicase gene
Ataxia-telangiectasia	Lymphoma, leukemia, less commonly central nervous system and nonneural solid tumors	Autosomal recessive; sensitive to X-irradiation, radiomimetic drugs; mutation in <i>ATM</i> tumor-suppressor gene
Dysplastic nevus syndrome	Melanoma	Autosomal dominant; some cases associated with mutations in <i>CDKN2A</i> gene
Rothmund-Thompson syndrome	Osteosarcoma; skin cancers	Autosomal recessive; mutation in RecQ helicase gene family
Werner syndrome (premature aging)	Soft tissue sarcomas	Autosomal recessive; mutation in the <i>WRN</i> gene; member of the RecQ helicase gene family
IMMUNODEFICIENCY SYNDROMES		
Wiskott-Aldrich syndrome	Lymphoma, leukemia	X-linked recessive; <i>WAS</i> gene mutation (Xp11.22-23); WASP protein functions in signal transduction associated with cytoskeletal actin filament rearrangement
X-linked immunodeficiency (Duncan syndrome)	Lymphoproliferative disorder	X-linked; Epstein-Barr viral infection can result in fatal outcome; mutation in <i>SH2D1A</i> gene locus
X-linked agammaglobulinemia (Bruton disease)	Lymphoma, leukemia	X-linked; mutation in <i>BTK</i> gene resulting in absence of mature B cells
Severe combined immunodeficiency	Leukemia, lymphoma	X-linked; mutations in <i>ADA</i> gene

Table 492-2 Familial or Genetic Susceptibility to Malignancy—cont'd

DISORDER	TUMOR/CANCER	COMMENT
OTHERS		
Neurofibromatosis 1	Neurofibroma, optic glioma, acoustic neuroma, astrocytoma, meningioma, pheochromocytoma, sarcoma	Autosomal dominant; mutation in tumor-suppressor gene, <i>NF1</i>
Neurofibromatosis 2	Bilateral acoustic neuromas, meningiomas	Autosomal dominant; mutation in tumor-suppressor gene, <i>NF2</i>
Tuberous sclerosis	Fibroangiomatous nevi, myocardial rhabdomyoma	Autosomal dominant
Gorlin-Goltz syndrome (nevus basal cell carcinoma syndrome)	Multiple basal cell carcinomas; medulloblastoma	Autosomal dominant; mutation in <i>PTCH</i> gene
Li-Fraumeni syndrome	Bone, soft tissue sarcoma, breast	Mutation of <i>P53</i> tumor-suppressor gene, autosomal dominant
Retinoblastoma	Sarcoma	Autosomal recessive; increased risk of secondary malignancy 10–20 yr later; mutation in <i>RB</i> tumor-suppressor gene
Hemihypertrophy ± Beckwith syndrome	Wilms tumor, hepatoblastoma, adrenal carcinoma	<i>WT1</i> gene; 25% develop tumor, most in 1st 5 yr of life
von Hippel-Landau disease	Hemangioblastoma of the cerebellum and retina, pheochromocytoma, renal cancer	Autosomal dominant; mutation of tumor-suppressor gene, <i>VHL</i> gene
Multiple endocrine neoplasia syndrome, type 1 (Wermer syndrome)	Parathyroid, pancreatic islet, and pituitary tumors	Autosomal dominant; mutation in <i>PYGM</i> tumor-suppressor gene
Multiple endocrine neoplasia syndrome, type 2A (Sipple syndrome)	Medullary carcinoma of the thyroid, hyperparathyroidism, pheochromocytoma	Autosomal dominant; mutations in CYS-rich regions of the <i>RET</i> gene activate this protooncogene; <i>RET</i> codes for a tyrosine kinase; monitor calcitonin and calcium levels
Multiple endocrine neoplasia type 2B (multiple mucosal neuroma syndrome)	Mucosal neuroma, pheochromocytoma, medullary thyroid carcinoma, Marfan habitus; neuropathy	Autosomal dominant; mutation in catalytic site (codon 883 or 914) activates protooncogene; <i>RET</i> codes for a tyrosine kinase
Familial adenomatous polyposis	Colorectal, thyroid carcinoma, duodenal and periampullar carcinomas; pediatric hepatoblastoma	Autosomal dominant; mutation in <i>APC</i> gene
Familial juvenile polyposis	Colorectal carcinoma	Autosomal dominant; mutation in <i>SMAD4</i> gene
Hereditary nonpolyposis colon cancer (Lynch syndrome, NHPCC)	Colon cancer	Autosomal dominant; mutation in mismatch repair genes; <i>hMSH2</i> , <i>hMLH1</i> , <i>PMS1</i> , <i>PMS2</i> , <i>hMSH6</i> , <i>hMSG3</i>
Turcot syndrome	Pediatric brain tumors and increased risk of colon carcinoma and polyps	Mutation in <i>APC</i> gene
Familial adenomatous polyposis coli	Adenocarcinoma of colon	Autosomal dominant, <i>APC</i> gene
Gardner syndrome	Adenocarcinoma of colon, skull and soft tissue tumors	Autosomal dominant, <i>APC</i> gene
Peutz-Jeghers syndrome	Gastrointestinal carcinoma, ovarian neoplasia	Autosomal dominant, <i>LKB1</i> gene codes for a Ser/Thr kinase that regulates cell cycle, metabolism, cell polarity
Hemochromatosis	Hepatocellular carcinoma	Autosomal dominant; malignancy associated with cirrhotic liver
Glycogen storage disease 1 (von Gierke disease)	Hepatocellular carcinoma	Autosomal recessive; malignancy associated with cirrhotic liver
Tyrosinemia, galactosemia	Hepatocellular carcinoma	Mutation in glucose-6-phosphatase or glucose-6-phosphatase translocase genes
<i>BRCA1</i> and <i>BRCA2</i>	Breast, ovarian	Autosomal recessive; tumor associated with cirrhotic liver
Diamond-Blackfan anemia	AML, myelodysplastic syndrome, osteogenic sarcoma	DNA repair defect
Shwachman-Diamond syndrome	AML, myelodysplasia	Autosomal dominant; family 9 genes encoding ribosomal proteins
Hereditary diffuse gastric cancer	Gastric cancer	Autosomal recessive; <i>SBDS</i> gene; chromosome 7q11.21
Pleuropulmonary blastoma family tumor and dysplasia syndrome (DICER1)	Pulmonary blastoma	Autosomal dominant; <i>CDH1</i> gene
Hereditary neuroblastoma	Neuroblastoma	Encoded protein is a ribonuclease required for microRNA processing
Hereditary paraganglioma–pheochromocytoma syndrome	Paraganglioma	Two genes have been identified:
Congenital or cyclic neutropenia	Pheochromocytomas	<ul style="list-style-type: none"> • Anaplastic lymphoma kinase (<i>ALK</i>) at chromosome 2p23 • Paired-like homeobox 2b (<i>PHOX2B</i>) at chromosome 4q12
	Myelodysplastic syndrome	Mutation in the mitochondrial enzyme succinate dehydrogenase protein (SDH)
	AML	<i>ELANE</i> mutation at 19p13.3; elastase; neutrophil expressed

ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; GI, gastrointestinal; GU, genitourinary; JMML, juvenile myelomonocytic leukemia; NHPCC, nonhereditary polyposis colon cancer.

Table 493-1 Common Manifestations of Childhood Malignancies

	SIGNS AND SYMPTOMS	POTENTIAL ETIOLOGY	POSSIBLE ONCOLOGIC DIAGNOSIS
Constitutional/Systemic	Fever, persistent or recurrent infection, neutropenia	Bone marrow infiltration	Leukemia, neuroblastoma
	Fever of unknown origin, weight loss, night sweats	Lymphoma	Hodgkin and non-Hodgkin lymphoma
	Painless lymphadenopathy	Lymphoma, metastatic solid tumor	Leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, thyroid carcinoma
	Hypertension	Renal or adrenal tumor	Neuroblastoma, pheochromocytoma, Wilms tumor
	Soft tissue mass	Local or metastatic tumor	Ewing sarcoma, osteosarcoma, neuroblastoma, thyroid carcinoma, rhabdomyosarcoma, Langerhans cell histiocytosis
Neurologic/Ophthalmologic	Headache with emesis, visual disturbances, ataxia, papilledema, cranial nerve palsies	Increased intracranial pressure	Primary brain tumor; metastasis
	Leukokoria (white pupil)	Retinal mass	Retinoblastoma
	Periorbital ecchymosis	Metastasis	Neuroblastoma
	Miosis, ptosis, heterochromia	Horner syndrome: compression of cervical sympathetic nerves	Neuroblastoma
	Opsoclonus myoclonus, ataxia	Neurotransmitters? Autoimmunity?	Neuroblastoma
Respiratory/Thoracic	Exophthalmos, proptosis	Orbital tumor	Rhabdomyosarcoma, lymphoma, Langerhans cell histiocytosis
	Cough, stridor, pneumonia, tracheobronchial compression; superior vena cava syndrome	Anterior mediastinal mass	Germ cell tumor, non-Hodgkin lymphoma, Hodgkin lymphoma
Gastrointestinal	Vertebral or nerve root compression; dysphagia	Posterior mediastinal mass	Neuroblastoma, neuroenteric cyst
	Abdominal mass	Adrenal, renal, or lymphoid tumor	Neuroblastoma, Wilms tumor, lymphoma
Hematologic	Diarrhea	Vasoactive intestinal polypeptide	Neuroblastoma, ganglioneuroma
	Pallor, anemia	Bone marrow infiltration	Leukemia, neuroblastoma
Musculoskeletal	Petechiae, thrombocytopenia	Bone marrow infiltration	Leukemia, neuroblastoma
	Bone pain, limp, arthralgia	Primary bone tumor, metastasis to bone	Osteosarcoma, Ewing sarcoma, leukemia, neuroblastoma
Endocrine	Diabetes insipidus, galactorrhea, poor growth	Neuroendocrine involvement of hypothalamus or pituitary gland	Adenoma, craniopharyngioma, prolactinoma, Langerhans cell histiocytosis

Table 493-2 Work-up of Common Pediatric Malignancies to Assess Primary Tumor and Potential Metastases

MALIGNANCY	BONE MARROW ASPIRATE OR BIOPSY	CHEST X-RAY	CT SCAN	MRI	PET SCAN	BONE SCAN	CSF ANALYSIS	SPECIFIC MARKERS	OTHER TESTS
Leukemia	Yes (includes flow cytometry, cytogenetics, molecular studies)	Yes	—	—	—	—	Yes	—	—
Non-Hodgkin lymphoma	Yes (includes flow cytometry, cytogenetics, molecular studies)	Yes	Yes	—	Yes	Yes (selected cases)	Yes	—	—
Hodgkin lymphoma	Yes (in advanced stage)	Yes	Yes	—	Yes	Yes (selected cases)	—	—	—
CNS tumors	—	—	—	Yes	—	—	Yes (selected tumors)	—	—
Neuroblastoma	Yes (includes cytogenetics, molecular studies)	—	Yes	—	—	Yes	—	VMA, HVA	MIBG scan; bone x-rays
Wilms tumor	—	Yes	Yes	—	—	—	—	—	—

Continued

Table 493-2 Work-up of Common Pediatric Malignancies to Assess Primary Tumor and Potential Metastases—cont'd

MALIGNANCY	BONE MARROW ASPIRATE OR BIOPSY	CHEST X-RAY	CT SCAN	MRI	PET SCAN	BONE SCAN	CSF ANALYSIS	SPECIFIC MARKERS	OTHER TESTS
Rhabdomyosarcoma	Yes	Yes	Yes	Yes (selected sites)	—	Yes	Yes (for parameningeal tumors only)	—	—
Osteosarcoma	—	Yes	Yes (of chest)	Yes (for primary tumors)	—	Yes	—	—	—
Ewing sarcoma	Yes	Yes	Yes (of chest)	Yes (for primary tumors)	—	Yes	—	—	—
Germ cell tumors	—	Yes	Yes	Consider MRI of brain	—	—	—	AFP, HCG	—
Liver tumors	—	Yes	Yes	—	—	—	—	AFP	—
Retinoblastoma	Selected cases	—	Yes	Yes (includes brain)	—	Selected cases	Selected cases	—	—

AFP, α -Fetoprotein; CNS, central nervous system; CSF, cerebrospinal fluid; HCG, human chorionic gonadotropin; HVA, homovanillic acid; MIBG, metaiodobenzylguanidine; PET, positron emission tomography; VMA, vanillylmandelic acid.

Table 494-2 Common Chemotherapeutic Agents Used in Children

DRUG	MECHANISM OF ACTION OR CLASSIFICATION	INDICATION(S)	ADVERSE REACTIONS (PARTIAL LIST)	COMMENTS
Methotrexate	Folic acid antagonist; inhibits dihydrofolate reductase	ALL, non-Hodgkin lymphoma, osteosarcoma, Hodgkin lymphoma, medulloblastoma	Myelosuppression, mucositis, stomatitis, dermatitis, hepatitis With long-term administration; osteopenia and bone fractures With high-dose administration; renal and CNS toxicity With intrathecal administration; arachnoiditis, leukoencephalopathy, leukomyelopathy	Systemic administration may be PO, IM, or IV; also may be administered intrathecally Plasma methotrexate levels must be monitored with high-dose therapy and when low doses are administered to patients with renal dysfunction, and leucovorin rescue applied accordingly
6-Mercaptopurine (Purinethol)	Purine analog; inhibits purine synthesis	ALL	Myelosuppression, hepatic necrosis, mucositis; allopurinol increases toxicity	Allopurinol inhibits metabolism
Cytarabine (cytosine arabinoside; Ara-C)	Pyrimidine analog; inhibits DNA polymerase	ALL, AML, non-Hodgkin lymphoma, Hodgkin lymphoma	Nausea, vomiting, myelosuppression, conjunctivitis, mucositis, CNS dysfunction With intrathecal administration; arachnoiditis, leukoencephalopathy, leukomyelopathy	Systemic administration may be PO, IM, or IV; may also be administered intrathecally
Cyclophosphamide (Cytoxan)	Alkylates guanine; inhibits DNA synthesis	ALL, non-Hodgkin lymphoma, Hodgkin lymphoma, soft tissue sarcoma, Ewing sarcoma, Wilms tumor, neuroblastoma	Nausea, vomiting, myelosuppression, hemorrhagic cystitis, pulmonary fibrosis, inappropriate ADH secretion, bladder cancer, anaphylaxis	Requires hepatic activation and thus is less effective in presence of liver dysfunction. Mesna prevents hemorrhagic cystitis
Ifosfamide (Ifex)	Alkylates guanine; inhibits DNA synthesis	Non-Hodgkin lymphoma, Wilms tumor, soft tissue sarcoma	Nausea, vomiting, myelosuppression, hemorrhagic cystitis, pulmonary fibrosis, inappropriate ADH secretion, CNS dysfunction, cardiac toxicity, anaphylaxis	Mesna prevents hemorrhagic cystitis

Continued

Table 494-2 Common Chemotherapeutic Agents Used in Children—cont'd

DRUG	MECHANISM OF ACTION OR CLASSIFICATION	INDICATION(S)	ADVERSE REACTIONS (PARTIAL LIST)	COMMENTS
Doxorubicin (Adriamycin), daunorubicin (Cerubidine), and idarubicin (Idamycin)	Binds to DNA, intercalation	ALL, AML, osteosarcoma, Ewing sarcoma, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma	Nausea, vomiting, cardiomyopathy, red urine, tissue necrosis on extravasation, myelosuppression, conjunctivitis, radiation dermatitis, arrhythmia	Dexrazoxane reduces risk of cardiotoxicity
Dactinomycin	Binds to DNA, inhibits transcription	Wilms tumor, rhabdomyosarcoma, Ewing sarcoma	Nausea, vomiting tissue necrosis on extravasation, myelosuppression, radiosensitizer, mucosal ulceration	
Bleomycin (Blenoxane)	Binds to DNA, cleaves DNA strands	Hodgkin disease, non-Hodgkin lymphoma, germ cell tumors	Nausea, vomiting, pneumonitis, stomatitis, Raynaud phenomenon, pulmonary fibrosis, dermatitis	
Vincristine (Oncovin)	Inhibits microtubule formation	ALL, non-Hodgkin lymphoma, Hodgkin disease, Wilms tumor, Ewing sarcoma, neuroblastoma, rhabdomyosarcoma	Local cellulitis, peripheral neuropathy, constipation, ileus, jaw pain, inappropriate ADH secretion, seizures, ptosis, minimal myelosuppression	IV administration only; must not be allowed to extravasate
Vinblastine (Velban)	Inhibits microtubule formation	Hodgkin lymphoma, non-Hodgkin lymphoma, Langerhans cell histiocytosis, CNS tumors	Local cellulitis, leukopenia	IV administration only; must not be allowed to extravasate
L-Asparaginase	Depletion of L-asparagine	ALL; AML, when used in combination with cytarabine	Allergic reaction pancreatitis, hyperglycemia, platelet dysfunction and coagulopathy, encephalopathy	PEG-asparaginase now preferred to L-asparaginase
Pegasparagase (Oncaspar)	Polyethylene glycol conjugate of L-asparagine	ALL	Indicated for prolonged asparagine depletion and for patients with allergy to L-asparaginase	
Prednisone and dexamethasone (Decadron)	Lymphatic cell lysis	ALL; Hodgkin lymphoma, non-Hodgkin lymphoma	Cushing syndrome, cataracts, diabetes, hypertension, myopathy, osteoporosis, avascular necrosis, infection, peptic ulceration, psychosis	
Carmustine (BiCNU)	Carbamylation of DNA; inhibits DNA synthesis	CNS tumors, non-Hodgkin lymphoma, Hodgkin lymphoma	Nausea, vomiting, delayed myelosuppression (4-6 wk); pulmonary fibrosis, carcinogenic stomatitis	Phenobarbital increases metabolism, decreases activity
Carboplatin and cisplatin (Platinol)	Inhibits DNA synthesis	Osteosarcoma, neuroblastoma, CNS tumors, germ cell tumors	Nausea, vomiting, renal dysfunction, myelosuppression, ototoxicity, tetany, neurotoxicity, hemolytic-uremic syndrome, anaphylaxis	Aminoglycosides may increase nephrotoxicity
Etoposide (VePesid)	Topoisomerase inhibitor	ALL, non-Hodgkin lymphoma, germ cell tumor, Ewing sarcoma	Nausea, vomiting, myelosuppression, secondary leukemia	
Tretinoin (all <i>trans</i> -retinoic acid); and isotretinoin (<i>cis</i> -retinoic acid); Accutane)	Enhances normal differentiation	Acute promyelocytic leukemia; neuroblastoma	Dry mouth, hair loss, pseudotumor cerebri, premature epiphyseal closure, birth defects	

ADH, antidiuretic hormone; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CNS, central nervous system; PEG, polyethylene glycol.

Table 494-3 Infectious Complications of Malignancy

PREDISPOSING FACTOR	ETOLOGY	SITE OF INFECTION	INFECTIOUS AGENTS
Neutropenia	Chemotherapy, bone marrow infiltration	Sepsis, shock, pneumonia, soft tissue, proctitis, mucositis	<i>Streptococcus viridans</i> , <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Candida</i> , <i>Aspergillus</i> , anaerobic oral and rectal bacteria
Immunosuppression, lymphopenia, lymphocyte-monocyte dysfunction	Chemotherapy, corticosteroid	Pneumonia, meningitis, disseminated viral infection	<i>Pneumocystis jiroveci</i> , <i>Cryptococcus neoformans</i> , <i>Mycobacterium</i> , <i>Nocardia</i> , <i>Listeria monocytogenes</i> , <i>Candida</i> , <i>Aspergillus</i> , <i>Strongyloides</i> , <i>Toxoplasma</i> , varicella-zoster virus, cytomegalovirus, herpes simplex
Indwelling central venous catheter	Nutrition, administration of chemotherapy	Line sepsis, tract of tunnel, exit site	<i>S. epidermidis</i> , <i>S. aureus</i> , <i>Candida albicans</i> , <i>P. aeruginosa</i> , <i>Aspergillus</i> , <i>Corynebacterium</i> , <i>Streptococcus faecalis</i> , <i>Mycobacterium fortuitum</i> , <i>Propionibacterium acnes</i>

Table 494-4 Oncologic Emergencies

CONDITION	MANIFESTATIONS	ETOLOGY	MALIGNANCY	TREATMENT
METABOLIC				
Hyperuricemia	Uric acid nephropathy	Tumor lysis syndrome	Lymphoma, leukemia	Allopurinol, alkalinize urine; hydration and diuresis, rasburicase
Hyperkalemia	Arrhythmias, cardiac arrest	Tumor lysis syndrome	Lymphoma, leukemia	Kayexalate, sodium bicarbonate, glucose, and insulin; check for pseudohyperkalemia from leukemic cell lysis in test tube
Hyperphosphatemia	Hypocalcemic tetany; metastatic calcification, photophobia, pruritus	Tumor lysis syndrome	Lymphoma, leukemia	Hydration, forced diuresis; stop alkalinization; oral aluminum hydroxide to bind phosphate
Hyponatremia	Seizure, lethargy (may also be asymptomatic)	SIADH; fluid, sodium losses in vomiting	Leukemia, CNS tumor	Restrict free water for SIADH; replace sodium if depleted
Hypercalcemia	Anorexia, nausea, polyuria, pancreatitis, gastric ulcers; prolonged PR, shortened QT interval	Bone resorption; ectopic parathormone, vitamin D, or prostaglandins	Metastasis to bone, rhabdomyosarcoma, leukemia	Hydration and furosemide diuresis; corticosteroids; calcitonin, bisphosphonates
HEMATOLOGIC				
Anemia	Pallor, weakness, heart failure	Bone marrow suppression or infiltration; blood loss	Any with chemotherapy	Packed red blood cell transfusion
Thrombocytopenia	Petechiae, hemorrhage	Bone marrow suppression or infiltration	Any with chemotherapy	Platelet transfusion
Disseminated intravascular coagulation	Shock, hemorrhage	Sepsis, hypotension, tumor factors	Promyelocytic leukemia, others	Fresh-frozen plasma; platelets, cryoprecipitate, treat underlying disorder
Neutropenia	Infection	Bone marrow suppression or infiltration	Any with chemotherapy	If febrile, administer broad-spectrum antibiotics, and filgrastim (G-CSF) if appropriate
Hyperleukocytosis ($>100,000/\text{mm}^3$)	Hemorrhage, thrombosis; pulmonary infiltrates, hypoxia; tumor lysis syndrome	Leukostasis; vascular occlusion	Leukemia	Leukapheresis; chemotherapy; hydroxyurea
Graft-versus-host disease	Dermatitis, diarrhea, hepatitis	Immunosuppression and nonirradiated blood products; bone marrow transplantation	Any with immunosuppression	Corticosteroids; cyclosporine; tacrolimus; antithymocyte globulin
SPACE-OCCUPYING LESIONS				
Spinal cord compression	Back pain \pm radicular Cord above T10: symmetric weakness, increased deep tendon reflex; sensory level present; toes up Conus medullaris (T10-L2): symmetric weakness, increased knee reflexes; decreased ankle reflexes; saddle sensory loss; toes up or down Cauda equina (below L2): asymmetric weakness; loss of deep tendon reflex and sensory deficit; toes down	Metastasis to vertebra and extramedullary space	Neuroblastoma; medulloblastoma	MRI or myelography for diagnosis; corticosteroids; radiotherapy; laminectomy; chemotherapy
Increased intracranial pressure	Confusion, coma, emesis, headache, hypertension, bradycardia, seizures, papilledema, hydrocephalus; cranial nerves III and VI palsies	Primary or metastatic brain tumor	Neuroblastoma, astrocytoma; glioma	CT or MRI for diagnosis; corticosteroids; phenytoin; ventriculostomy tube; radiotherapy; chemotherapy
Superior vena cava syndrome	Distended neck veins; plethora, edema of head and neck, cyanosis, proptosis, Horner syndrome	Superior mediastinal mass	Lymphoma	Chemotherapy; radiotherapy
Tracheal compression	Respiratory distress	Mediastinal mass compressing trachea	Lymphoma	Radiation, corticosteroids

CNS, Central nervous system; G-CSF, granulocyte colony-stimulating factor; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Modified from Kliegman RM, Marcdante KJ, Jenson HB, et al, editors: Nelson essentials of pediatrics, ed 6, Philadelphia, 2011, WB Saunders, p. 590.

2434 Part XXII ◆ Cancer and Benign Tumors

Table 494-5 Late Effects and High-Risk Features of Childhood Cancer and Its Treatment

LATE EFFECTS	EXPOSURE	SELECTED HIGH-RISK FACTORS	AT-RISK DIAGNOSTIC GROUPS
NEUROCOGNITIVE Neurocognitive deficits Functional deficits in: <ul style="list-style-type: none">• Executive function• Sustained attention• Memory• Processing speed• Visual-motor integration Learning deficits Diminished IQ Behavioral change	Chemotherapy: <ul style="list-style-type: none">• Methotrexate Radiation affecting brain: <ul style="list-style-type: none">• Cranial• Ear/infratemporal• Total-body irradiation (TBI)	Age <3 yr at time of treatment Female sex Supratentorial tumor Premorbid or family history of learning or attention problems Radiation doses >24 Gy Whole-brain irradiation	Acute lymphoblastic leukemia Brain tumor Sarcoma (head and neck or osteosarcoma)
NEUROSENSORY Hearing loss, sensorineural Hearing loss, conductive Tympanosclerosis Otosclerosis Eustachian tube dysfunction Visual impairment Cataracts Lacrimal duct atrophy Xerophthalmia Retinopathy Glaucoma Peripheral neuropathy, sensory	Chemotherapy: <ul style="list-style-type: none">• Cisplatin• Carboplatin Radiation affecting hearing: <ul style="list-style-type: none">• Cranial• Infratemporal• Nasopharyngeal Radiation affecting hearing: <ul style="list-style-type: none">• Cranial• Infratemporal• Nasopharyngeal Chemotherapy: <ul style="list-style-type: none">• Busulfan• Glucocorticoids Radiation affecting eye: <ul style="list-style-type: none">• Cranial• Orbital/eye• TBI Chemotherapy: <ul style="list-style-type: none">• Vincristine• Vinblastine• Cisplatin• Carboplatin	Higher cisplatin dose (360 mg/m^2) Higher radiation dose impacting ear (>30 Gy) Concurrent radiation and cisplatin Higher radiation dose affecting ear (>30 Gy) Higher radiation dose impacting eye ($\geq 15 \text{ Gy}$ for cataracts; >45 Gy for retinopathy and visual impairment) Higher cisplatin dose ($\geq 300 \text{ mg/m}^2$)	Brain tumor Germ cell tumor Sarcoma (head and neck) Neuroblastoma Hepatoblastoma Brain tumor Sarcoma (head and neck) Brain tumor Acute lymphoblastic leukemia Retinoblastoma Rhabdomyosarcoma (orbital) Allogeneic HSCT Acute lymphoblastic leukemia Brain tumor Hodgkin lymphoma Germ cell tumor Non-Hodgkin lymphoma Sarcoma Neuroblastoma Wilms tumor Carcinoma
NEUROMOTOR Peripheral neuropathy, motor	Chemotherapy: <ul style="list-style-type: none">• Vincristine• Vinblastine		Acute lymphoblastic leukemia Hodgkin lymphoma Non-Hodgkin lymphoma Sarcoma Brain tumor Neuroblastoma Wilms tumor
ENDOCRINE GH deficiency Precocious puberty Obesity Hypothyroidism, central Gonadotropin deficiency Adrenal insufficiency, central Hypothyroidism, primary	Radiation affecting HPA: <ul style="list-style-type: none">• Cranial• Orbital/eye Ear/infratemporal Nasopharyngeal TBI Neck, mantle irradiation	Female sex Radiation dose to HPA >18 Gy Female sex Younger age (<4 yr) Radiation dose to HPA >18 Gy Radiation dose to thyroid >20 Gy	Acute lymphoblastic leukemia Sarcoma (facial) Carcinoma (nasopharyngeal) Acute lymphoblastic leukemia Brain tumor Sarcoma (facial) Carcinoma (nasopharyngeal) Hodgkin lymphoma

Table 494-5 Late Effects and High-Risk Features of Childhood Cancer and Its Treatment—cont'd

LATE EFFECTS	EXPOSURE	SELECTED HIGH-RISK FACTORS	AT-RISK DIAGNOSTIC GROUPS
REPRODUCTIVE Gonadal dysfunction Delayed or arrested puberty Premature menopause Germ cell dysfunction or failure Infertility	Chemotherapy, alkylating: <ul style="list-style-type: none">• Busulfan• Carmustine (BCNU)• Chlorambucil• Cyclophosphamide• Ifosfamide• Lomustine (CCNU)• Mechlorethamine• Melphalan• Procarbazine Radiation affecting reproductive system: <ul style="list-style-type: none">• Whole abdomen (girls)• Pelvic• Lumbar/sacral spine (girls)• Testicular (boys)• TBI	Higher alkylating agent dose Alkylating agent conditioning for HSCT Radiation dose ≥ 15 Gy in prepubertal girls Radiation dose ≥ 10 Gy in pubertal girls For germ cell failure in boys, any pelvic irradiation For androgen insufficiency, gonadal irradiation, $\geq 20-30$ Gy in boys	Acute lymphoblastic leukemia, high risk Brain tumor Hodgkin lymphoma, advanced or unfavorable Non-Hodgkin lymphoma, advanced or unfavorable Sarcoma Neuroblastoma Wilms tumor, advanced Autologous or allogeneic HSCT
CARDIAC Cardiomyopathy Arrhythmias	Chemotherapy: <ul style="list-style-type: none">• Daunorubicin• Doxorubicin• Idarubicin	Female sex Age < 5 yr at time of treatment Higher doses of chemotherapy (≥ 300 mg/m ²) Higher doses of cardiac radiation (≥ 30 Gy) Combined-modality therapy with cardiotoxic chemotherapy and irradiation	Hodgkin lymphoma Leukemia Non-Hodgkin lymphoma Sarcoma Wilms tumor Neuroblastoma
Cardiomyopathy Arrhythmias Pericardial fibrosis Valvular disease Myocardial infarction Atherosclerotic heart disease	Radiation affecting heart: <ul style="list-style-type: none">• Chest• Mantle• Mediastinum• Axilla• Spine• Upper abdomen		
PULMONARY Pulmonary fibrosis Interstitial pneumonitis Restrictive lung disease Obstructive lung disease	Chemotherapy: <ul style="list-style-type: none">• Bleomycin• Busulfan• Carmustine (BCNU)• Lomustine (CCNU) Radiation impacting lungs: <ul style="list-style-type: none">• Mantle• Mediastinum• Whole lung• TBI	Higher doses of chemotherapy Combined modality therapy with pulmonary toxic chemotherapy and irradiation	Brain tumor Germ cell tumor Hodgkin lymphoma Sarcoma (chest wall or intrathoracic) Autologous or allogeneic HSCT
GASTROINTESTINAL Chronic enterocolitis Strictures Bowel obstruction	Radiation affecting gastrointestinal tract (≥ 30 Gy) Abdominal surgery	Higher radiation dose to bowel (≥ 45 Gy) Combined modality therapy with abdominal irradiation and radiomimetic chemotherapy (dactinomycin or anthracyclines) Combined modality therapy with abdominal surgery and irradiation	Sarcoma (retroperitoneal or pelvic primary)
HEPATIC Hepatic fibrosis Cirrhosis	Radiation affecting liver	Higher radiation dose or treatment volume (20-30 Gy to entire liver or ≥ 40 Gy to at least one third of liver)	Sarcoma Neuroblastoma
RENAL Renal insufficiency Hypertension Glomerular injury Tubular injury	Chemotherapy: <ul style="list-style-type: none">• Ifosfamide• Cisplatin• Carboplatin Radiation affecting kidneys: <ul style="list-style-type: none">• Whole abdomen• Upper abdominal fields• TBI		

GH, Growth hormone; HPA, hypothalamic–pituitary–adrenal axis; HSCT, hematopoietic stem cell transplantation; TBI, total-body irradiation.
From Kurt BA, Armstrong GT, Cash DK, et al: Primary care management of the childhood cancer survivor, J Pediatr 152:458–466, 2008.

2442 Part XXII ◆ Cancer and Benign Tumors

Table 496-3 Chemotherapy Regimens Commonly Used for Children, Adolescents, and Young Adults with Hodgkin Lymphoma

CHEMOTHERAPY REGIMEN	CORRESPONDING AGENTS
ABVD	Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine
ABVD-Rituxan	Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine, rituximab
ABVD	Doxorubicin (Adriamycin), brentuximab, vinblastine, dacarbazine
ABVE (DBVE)	Doxorubicin (Adriamycin), bleomycin, vincristine, etoposide
VAMP	Vincristine, doxorubicin (Adriamycin), methotrexate, prednisone
OPPA ± COPP (females)	Vincristine (Oncovin), prednisone, procarbazine, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
OEPA ± COPP (males)	Vincristine (Oncovin), etoposide, prednisone, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
COPP/ABV	Cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine, doxorubicin (Adriamycin), bleomycin, vinblastine
BEACOPP (advanced stage)	Bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
COPP	Cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
CHOP	Cyclophosphamide, doxorubicin (Adriamycin), vincristine (Oncovin), prednisone
ABVE-PC (DBVE-PC)	Doxorubicin (Adriamycin), bleomycin, vincristine, etoposide, prednisone, cyclophosphamide
ICE ± (Brentuximab)	Ifosfamide, carboplatin, etoposide ± brentuximab
Ifos/Vino ± (Brentuximab)	Ifosfamide, vinorelbine ± brentuximab

Table 496-1 New World Health Organization/Revised European-American Classification of Lymphoid Neoplasms Classification System for Hodgkin Lymphoma

Nodular lymphocyte predominance
Classical Hodgkin lymphoma
Lymphocyte rich
Mixed cellularity
Nodular sclerosis
Lymphocyte depletion

Table 495-3 WHO Classification of Acute Myeloid Neoplasms

- Acute myeloid leukemia with recurrent genetic abnormalities
- AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
 - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
 - APL with t(15;17)(q22;q12); PML-RARA
 - AML with t(9;11)(p22;q23); MLL3-MLL
 - AML with t(6;9)(p23;q34); DEK-NUP214
 - AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
 - AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
 - Provisional entity: AML with mutated NPM1
 - Provisional entity: AML with mutated CEBPA
- Acute myeloid leukemia with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- Acute myeloid leukemia, not otherwise specified
- AML with minimal differentiation
 - AML without maturation
 - AML with maturation
 - Acute myelomonocytic leukemia
 - Acute monoblastic/monocytic leukemia
 - Acute erythroid leukemia
 - Pure erythroid leukemia
 - Erythroleukemia, erythroid/myeloid
 - Acute megakaryoblastic leukemia
 - Acute basophilic leukemia
 - Acute panmyelosis with myelofibrosis
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
- Transient abnormal myelopoiesis
 - Myeloid leukemia associated with Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm

AML, acute myelogenous leukemia; APL, acute promyelocytic leukemia.

Table 496-2 Ann Arbor Staging Classification for Hodgkin Lymphoma*

STAGE	DEFINITION
I	Involvement of a single lymph node (I) or of a single extralymphatic organ or site (IE)
II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and 1 or more lymph node regions on the same side of the diaphragm (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by involvement of the spleen (IIIS) or by localized involvement of an extralymphatic organ or site (IIIE) or both (IIISE)
IV	Diffuse or disseminated involvement of 1 or more extralymphatic organs or tissues with or without associated lymph node involvement

Table 496-4 Treatment Regimens and Outcome by Disease Staging

		LOCALIZED/LOW STAGE	INTERMEDIATE	ADVANCED
Hodgkin lymphoma	Treatment	POG study 9426/GPOH-HD 95: ABVD-type therapy ± IFRT (risk adapted based on early response to chemotherapy)	Stanford/DAL-HD-90: COPP-based or dose-intense multiagent chemotherapy + low-dose RT POG 9426/CCG 5942: ABVD-type therapy ± IFRT (risk adapted)	POG 8725/DAL-HD-90: Dose-intense multiagent chemotherapy + low-dose RT HD9/HD12/CCG 59704: Dose-intense BEACOPP ± IFRT
	Prognosis	5 yr EFS: 85-90% 5 yr OS: 95%	Stanford/DAL-HD-90: 5 yr EFS: 89-92% POG 9426/CCG 5942: 5 yr EFS: 84% 5 yr OS: 91%	POG 8725: 5-yr EFS: 72-89% (age based) DAL-HD-90: 5 yr EFS: 86% 5 yr OS: 85-90% HD9/HD12/CCG 59704: 5 yr EFS/OS: 88-93/~100%

Table 496-4 Treatment Regimens and Outcome by Disease Staging—cont'd

		LOCALIZED/LOW STAGE	INTERMEDIATE	ADVANCED
Burkitt lymphoma and diffuse large B-cell lymphoma	Treatment	FAB/LMB 96 Group A therapy: Complete surgical resection followed by 2 cycles of chemotherapy	FAB/LMB 96 Group B therapy with reduced cyclophosphamide and no maintenance therapy; COG ANHL01P1: FAB/LMB Group B therapy + rituximab	FAB/LMB 96: standard-intensity Group C therapy: Reduction, induction, intensification, and maintenance therapy COG ANHL01P1: FAB/LMB Group C therapy + rituximab
	Prognosis	4 yr EFS: 98% (CI ₉₅ 94-99.5%) 4 yr OS: 99% (CI ₉₅ 96-99.9%)	FAB/LMB96: 4 yr EFS: 92% (CI ₉₅ 90-94%) 4 yr OS: 95% (CI ₉₅ 93-96%) *PMB DLBCL has worse prognosis (EFS/OS: 66/73%) COG ANHL01P1: 3 yr EFS 93% (CI ₉₅ 79-98%) 3 yr OS 95% (CI ₉₅ 83-99%)	FAB/LMB96: 4 yr EFS: BM+/CNS-: 91% ± 3% BM-/CNS+: 85% ± 6% BM+/CNS+: 66% ± 7% COG ANHL01P1: 3 yr EFS/OS: BM+ or CNS+: 90% (CI ₉₅ 75-96%) CNS+: 93% (CI ₉₅ 61-99%)
Lymphoblastic lymphoma	Treatment	NHL-BFM86/90/95: COG A5971: ALL-type therapy × 2 yr without prophylactic cranial RT	No intermediate group; disease classified as localized (stages I/II) or advanced (stages III/IV)	NHL-BFM86/90/95: ALL-type therapy × 2 yr ± px CRT CCG 5941: Intensive chemotherapy × 1 yr + cranial RT if CNS + at diagnosis
	Prognosis	COG A5971: 5 yr EFS: 90 (CI ₉₅ 78-96%) 5 yr OS: 96 (CI ₉₅ 84-99%)	No intermediate group; see above	NHL-BFM95: 5 yr EFS: 90% ± 3% (III), 95 ± 5% (IV) CCG 5941: 5 yr EFS/OS: 78% ± 5%/85% ± 4%
Anaplastic large cell lymphoma	Treatment	EICHL ALCL 99: Short intensive chemotherapy + HD MTX Completely resected stage I disease may be treated with surgery alone	No intermediate group; disease classified as standard risk (no skin, visceral, or mediastinal involvement) or high risk (presence of skin, mediastinal, or visceral involvement)	ALCL 99, CCG 5941: Short intensive chemotherapy + HD MTX COG ANHL0131: APO (doxorubicin, prednisone, vincristine) ± vinblastine
	Prognosis	EICHL database: 5 yr PFS: 89% (CI ₉₅ 82-96%) 5 yr OS: 94% (CI ₉₅ 89-99%)	No intermediate group; see above	ALCL99: 2 yr EFS: 71% (CI ₉₅ 75-77%) 2 yr OS: 94% (CI ₉₅ 89-95%) COG5941: 5 yr EFS 68% (CI ₉₅ 57-78%) 5 yr OS: 80% (CI ₉₅ 69-87%) COH ANHL0131: 2 yr EFS 79% (CI ₉₅ 71-88%) 2 yr OS 89% (CI ₉₅ 83-95%)

ABVD, doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; BEACOPP, bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine; BM, bone marrow (involvement); CCG, Children's Cancer Group; CI₉₅, 95% confidence interval; CNS, central nervous system (involvement); COG, Children's Oncology Group; COPP, cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine; CRT, chemoradiotherapy; EFS, event-free survival; EICHL, European Intergroup for Childhood Non-Hodgkin Lymphoma; FAB, French-American-British; HD MTX, high-dose methotrexate; IFRT, involved field radiation therapy; LMB, Lymphome Malins de Burkitt; MTX, methotrexate; NHL-BFM, non-Hodgkin lymphoma Berlin-Frankfurt-Munster; OS, overall survival; PFS, progression-free survival; PMB DLBCL, primary mediastinal B-cell diffuse large B-cell lymphoma; POG, Pediatric Oncology Group; px, prophylactic; RT, radiation therapy.

Table 496-5 St. Jude Staging System for Childhood Non-Hodgkin Lymphoma

STAGE	DESCRIPTION
I	A single tumor (extranodal) or single anatomic area (nodal), with the exclusion of mediastinum or abdomen
II	A single tumor (extranodal) with regional node involvement Two or more nodal areas on the same side of the diaphragm Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm A primary gastrointestinal tract tumor, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only, which must be grossly (>90%) resected
III	Two single tumors (extranodal) on opposite sides of the diaphragm Two or more nodal areas above and below the diaphragm Any primary intrathoracic tumor (mediastinal, pleural, or thymic) Any extensive primary intraabdominal disease
IV	Any of the above, with initial involvement of central nervous system or bone marrow at time of diagnosis

Table 496-6 Risk Stratification Groups for Pediatric B-Cell NHL

Low Risk	Berlin-Frankfurt-Munster (BFM)	French-American-British (FAB)
	R1 Stage I or II, completely resected	Group A Resected stage I and abdominal completely resected stage II
	R2 Stage I or II, not resected Stage III with LDH <500 U/L	Group B All patients not in Group A or C
	R3 Stage III with LDH ≥500 to <1000 U/L or Stage IV with LDH <1000 U/L and CNS-negative	
High Risk	R4 Stage III or IV with LDH ≥1000 U/L and/or CNS-positive	Group C Bone marrow disease (≥25% L3 blasts) and/or CNS-positive

From Murphy SB: Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults, Semin Oncol 7:332-339, 1980.

2454 Part XXII ◆ Cancer and Benign Tumors

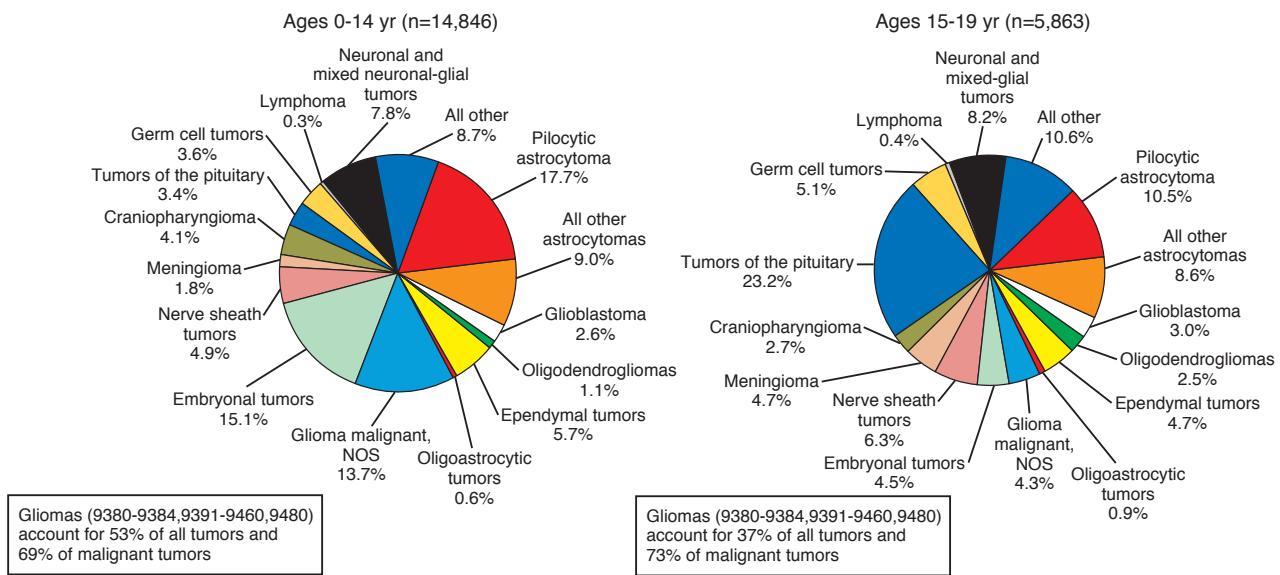


Figure 497-1 Distribution of childhood primary brain and CNS tumors by histology. (From Dolecek TA, Propp JM, Stroup NE, Kruchko C: CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009, Neuro Oncol 14:v1-v49, 2012.)

Table 497-1 Familial Syndromes Associated with Pediatric Brain Tumors				
SYNDROME	CENTRAL NERVOUS SYSTEM MANIFESTATIONS		CHROMOSOME	GENE
Neurofibromatosis type 1 (autosomal dominant)	Optic pathway gliomas, astrocytoma, malignant peripheral nerve sheath tumors, neurofibromas		17q11	NF1
Neurofibromatosis type 2 (autosomal dominant)	Vestibular schwannomas, meningiomas, spinal cord ependymoma, spinal cord astrocytoma, hamartomas		22q12	NF2
von Hippel-Lindau (autosomal dominant)	Hemangioblastoma		3p25-26	VHL
Tuberous sclerosis (autosomal dominant)	Subependymal giant cell astrocytoma, cortical tubers		9q34 16q13	TSC1 TSC2
Li-Fraumeni (autosomal dominant)	Astrocytoma, primitive neuroectodermal tumor		17q13	TP53
Cowden (autosomal dominant)	Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease)		10q23	PTEN
Turcot (autosomal dominant)	Medulloblastoma Glioblastoma		5q21 3p21 7p22	APC hMLH1 hPSM2
Nevus basal cell carcinoma Gorlin (autosomal dominant)	Medulloblastoma		9q31	PTCH1

Modified from Kleihues P, Cavenee WK: World Health Organization classification of tumors: pathology and genetics of tumors of the nervous system, Lyon, 2000, IARC Press.

Table 497-2 Posterior Fossa Tumors of Childhood				
TUMOR	RELATIVE INCIDENCE (%)	PRESENTATION	DIAGNOSIS	PROGNOSIS
Medulloblastoma	35-40	2-3 mo of headaches, vomiting, truncal ataxia	Heterogeneously or homogeneously enhancing fourth ventricular mass; may be disseminated	65-85% survival; dependent on stage/type; poorer (20-70%) in infants
Cerebellar astrocytoma	35-40	3-6 mo of limb ataxia; secondary headaches, vomiting	Cerebellar hemisphere mass, usually with cystic and solid (mural nodule) components	90-100% survival in totally resected pilocytic type
Brainstem glioma	10-15	1-4 mo of double vision, unsteadiness, weakness, and cranial nerve dysfunction, including facial weakness, swallowing dysfunction, and oculomotor abnormalities	Diffusely expanded, minimally or partially enhancing mass in 80%; 20% more focal tectal or cervicomедullary lesion	>90% mortality in diffuse tumors; better in localized
Ependymoma	10-15	2-5 mo of unsteadiness, headaches, double vision, and facial asymmetry	Usually enhancing, fourth ventricular mass with cerebellopontine predilection	>75% survival in totally resected lesions
Atypical teratoid/rhabdoid	>5 (10-15% of infantile malignant tumors)	As in medulloblastoma, but primarily in infants; often associated facial weakness and strabismus	As in medulloblastoma, but often more laterally extended	≤20% survival in infants

Modified from Packer RJ, MacDonald T, Vezina G: Central nervous system tumors, Pediatr Clin North Am 55:121-145, 2008.

2462 Part XXII ◆ Cancer and Benign Tumors

Table 498-2 Children's Oncology Group Neuroblastoma Risk Stratification

RISK GROUP	STAGE	AGE	MYCN AMPLIFICATION STATUS	PLOIDY	SHIMADA
Low risk	1	Any	Any	Any	Any
Low risk	2A/2B	Any	Not amplified	Any	Any
High risk	2A/2B	Any	Amplified	Any	Any
Intermediate risk	3	<547 days	Not amplified	Any	Any
Intermediate risk	3	≥547 days	Not amplified	Any	FH
High risk	3	Any	Amplified	Any	Any
High risk	3	≥547 days	Not amplified	Any	UH
High risk	4	<365 days	Amplified	Any	Any
Intermediate risk	4	<365 days	Not amplified	Any	Any
High risk	4	365 to <547 days	Amplified	Any	Any
High risk	4	365 to <547 days	Any	DNA index = 1	Any
High risk	4	365 to <547 days	Any	Any	UH
Intermediate risk	4	365 to <547 days	Not amplified	DNA index > 1	FH
High risk	4	≥547 days	Any	Any	Any
Low risk	4S	<365 days	Not amplified	DNA index > 1	FH
Intermediate risk	4S	<365 days	Not amplified	DNA index = 1	Any
Intermediate risk	4S	<365 days	Not amplified	Any	UH
High risk	4S	<365 days	Amplified	Any	Any

FH, Favorable histology; UH, unfavorable histology.

Courtesy of Children's Oncology Group; from Park JR, Eggert A, Caron H: Neuroblastoma: biology, prognosis, and treatment, Pediatr Clin North Am 55:97–120, 2008.

Table 498-3 International Neuroblastoma Staging System

STAGE	DEFINITION	INCIDENCE (%)	SURVIVAL AT 5 YR* (%)
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive)	5	≥90
2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically	10	70-80
2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor; enlarged contralateral lymph nodes must be negative microscopically	10	70-80
3	Unresectable unilateral tumor infiltrating across the midline, [†] with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (resectable) or by lymph node involvement	25	40-70
4	Any primary tumor with dissemination to distant lymph nodes; bone, bone marrow, liver, skin, and other organs (except as defined for stage 4S)	60	85-90 if age at diagnosis is <18 mo 30-40 if age at diagnosis is >18 mo
4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and bone marrow [‡] (limited to infants <1 yr of age)	5	>80

*Survival is influenced by other characteristics, such as MYCN amplification. Percentages are approximate.

[†]The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the other side of the vertebral column.[‡]Marrow involvement in stage 4S should be minimal (i.e., <10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate). More extensive marrow involvement would be considered stage 4. Results of the metaiodobenzylguanidine (MIBG) scan (if performed) should be negative in the marrow.

Modified from Kliegman RM, Marcdante KJ, Jenson HB, et al, editors: Nelson essentials of pediatrics, ed 5, Philadelphia, 2006, WB Saunders, p. 746; and Brodeur GM, Pritchard J, Berthold F, et al: Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment, J Clin Oncol 11:1466–1477, 1993.

symptoms because of the mass itself, including spinal cord compression, bowel obstruction, and superior vena cava syndrome.

Children with neuroblastoma can also present with neurologic signs and symptoms. Neuroblastoma originating in the superior cervical ganglion can result in **Horner syndrome**. Paraspinal neuroblastoma

tumors can invade the neural foramina, causing spinal cord and nerve root compression. Neuroblastoma can also be associated with a paraneoplastic syndrome of autoimmune origin, termed *opsoclonus-myoclonus-ataxia syndrome*, in which patients experience rapid, uncontrollable jerking eye and body movements, poor coordination,

Table 498-4 Phenotypic and Genetic Features of Neuroblastoma, Treatment, and Survival According to Prognostic Category

VARIABLE	PROGNOSTIC CATEGORY*			Tumor Stage 4S
	Low Risk	Intermediate Risk	High Risk	
Pattern of disease	Localized tumor	Localized tumor with locoregional lymph node extension; metastases to bone marrow and bone in infants	Metastases to bone marrow and bone (except in infants)	Metastases to liver and skin (with minimal bone marrow involvement) in infants
Tumor genomics	Whole-chromosome gains	Whole-chromosome gains	Segmental chromosomal aberrations	Whole-chromosome gains
Treatment	Surgery [†]	Moderate-intensity chemotherapy; surgery [†]	Dose-intensive chemotherapy, surgery, and external-beam radiotherapy to primary tumor and resistant metastatic sites; myeloablative chemotherapy with autologous hematopoietic stem cell rescue; isotretinoin with anti-ganglioside GD2 immunotherapy	Supportive care [‡]
Survival rate	>98%	90-95%	40-50%	>90%

*Patients are assigned to prognostic groups according to risk, as described by the Children's Oncology Group, with the level of risk defining the likelihood of death from disease. Stage 4S disease is considered separately here because of the unique phenotype of favorable biologic features and relentless early progression but ultimately full and complete regression of the disease.

[†]The goal of surgery is to safely debulk the tumor mass and avoid damage to surrounding normal structures while also obtaining sufficient material for molecular diagnostic studies. Some localized tumors may spontaneously regress without surgery.

[‡]Low-dose chemotherapy or radiation therapy, or both, is used in patients with life-threatening hepatic involvement, especially in infants <2 mo of age, who are at much higher risk for life-threatening complications from massive hepatomegaly.

Table 499-3 Differential Diagnosis of Abdominal and Pelvic Tumors in Children

TUMOR	PATIENT AGE	CLINICAL SIGNS	LABORATORY FINDINGS
Wilms	Preschool	Unilateral flank mass, aniridia, hemihypertrophy	Hematuria, polycythemia, thrombocytosis, elevated partial thromboplastin time value
Neuroblastoma	Preschool	Gastrointestinal/genitourinary obstruction, raccoon eyes, myoclonus opsclonus, diarrhea, skin nodules	Increased urinary vanillylmandelic acid, or homovanillic acid, or ferritin, stippled calcification in the mass
Non-Hodgkin lymphoma	>1 yr	Intussusception in patients >2 yr old	Increased lactic dehydrogenase, blood cytopenia from bone marrow involvement
Rhabdomyosarcoma	All	Gastrointestinal/genitourinary obstruction, abdominal pain, vaginal bleeding, paratesticular mass	Hypercalcemia, blood cytopenia from bone marrow involvement
Germ cell tumor/teratoma	Preschool, teenage	Girls: abdominal pain, vaginal bleeding Boys: testicular mass, new-onset hydrocele, sacrococcygeal mass/dimple	Increased human chorionic gonadotropin, increased α -fetoprotein
Hepatoblastoma	Birth-3 yr	Large firm liver	Increased α -fetoprotein
Hepatoma	School age, teenage	Large firm nodule, hepatitis B, cirrhosis	Increased α -fetoprotein

Table 499-4 Staging of Wilms Tumor

Stage I	Tumor confined to the kidney and completely resected. Renal capsule or sinus vessels not involved. Tumor not ruptured or biopsied. Regional lymph nodes examined and negative.
Stage II	Tumor extends beyond the kidney but is completely resected with negative margins and lymph nodes. At least 1 of the following has occurred: (a) penetration of renal capsule, (b) invasion of renal sinus vessels.
Stage III	Residual tumor present following surgery confined to the abdomen, including gross or microscopic tumor; spillage of tumor preoperatively or intraoperatively; biopsy prior to nephrectomy, regional lymph node metastases; tumor implants on the peritoneal surface; extension of tumor thrombus into the inferior vena cava including thoracic vena cava and heart.
Stage IV	Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region.
Stage V	Bilateral renal involvement by tumor.

2470 Part XXII ◆ Cancer and Benign Tumors

Table 500-3 Features of Most Common Types of Nonrhabdomyosarcoma Soft Tissue Sarcomas

TISSUE TYPE	TUMOR	NATURAL HISTORY AND BIOLOGY
Adipose	Liposarcoma	A very rare tumor. Usually arises in the extremities or retroperitoneum; associated with a nonrandom translocation, t(12;16)(q13;p11). Tends to be locally invasive and rarely metastasizes; wide local excision is the treatment of choice. The role of radiation therapy and chemotherapy in treating gross residual or metastatic disease is not established.
Fibrous	Fibrosarcoma	Most common soft tissue sarcoma in children younger than 1 yr. Congenital fibrosarcoma is a low-grade malignancy that commonly arises in the extremities or trunk and rarely metastasizes. Surgical excision is treatment of choice; dramatic responses to preoperative chemotherapy may occur. In children older than 4 yr, the natural history is similar to that in adults (a 5 yr survival rate of 60%); wide surgical excision and preoperative chemotherapy are commonly used. Associated with t(12;15)(p13;q25) or trisomy 11, also +8, +17, +20.
	Malignant fibrous histiocytoma	Most commonly arises in the trunk and extremities, deep in the subcutaneous layer. Histologically subdivided into storiform, giant cell, myxoid, and angiomyxoid variants. The angiomyxoid type tends to affect younger patients and is curable with surgical resection alone. Wide surgical excision is the treatment of choice. Chemotherapy has produced objective tumor regressions.
Vascular	Hemangiopericytoma	Often arises in the lower extremities or retroperitoneum; may manifest as hypoglycemia and hypophosphatemic rickets. Both benign and malignant histology. Nonrandom translocations t(12;19)(q13;q13) and t(13;22)(q22;q13.3) have been described. Complete surgical excision is the treatment of choice. Chemotherapy and radiation therapy may produce responses.
	Angiosarcoma	Rare in children; 33% arise in skin, 25% in soft tissue, and 25% in liver, breast, or bone. Associated with chronic lymphedema and exposure to vinyl chloride in adults. Survival rate is poor (12% at 5 yr) despite some responses to chemotherapy/radiation therapy.
	Hemangioendothelioma	Can occur in soft tissue, liver, and lung. Localized lesions have a favorable outcome; lesions in lung and liver often are multifocal and have a poor prognosis.
Peripheral nerves	Neurofibrosarcoma	Also known as the malignant peripheral nerve sheath tumor. Develops in up to 16% of patients with neurofibromatosis type 1 (NF1); almost 50% occur in patients with NF1. Deletions of chromosome 22q11-q13 or 17q11 and p53 mutations have been reported. Commonly arises in trunk and extremities and is usually locally invasive. Complete surgical excision is necessary for survival; response to chemotherapy is suboptimal.
Synovium	Synovial sarcoma	The most common nonrhabdomyosarcoma soft tissue sarcoma in some series. Often manifesting in the 3rd decade, but 33% of patients are younger than age 20 yr. Typically arises around the knee or thigh and is characterized by a nonrandom translocation t(X;18)(p11;q11). Wide surgical excision is necessary. Radiation therapy is effective in microscopic residual disease, and ifosfamide-based therapy is active in advanced disease.
Unknown	Alveolar soft part sarcoma	Slow-growing tumor; tends to recur or to metastasize to lung and brain years after diagnosis. Often arises in the extremities and head and neck.
Smooth muscle	Leiomyosarcoma	Often arises in the gastrointestinal tract and may be associated with a t(12;14)(q14;q23) translocation. Associated with Epstein-Barr virus in immunodeficiency syndromes (including AIDS). Complete surgical excision is the treatment of choice.

Table 501-1 Comparison of Features of Osteosarcoma and the Ewing Family of Tumors

FEATURE	OSTEOSARCOMA	EWING FAMILY OF TUMORS
Age	Second decade	Second decade
Race	All races	Primarily whites
Sex (M:F)	1.5:1	1.5:1
Cell	Spindle cell-producing osteoid	Undifferentiated small round cell, probably of neural origin
Predisposition	Retinoblastoma, Li-Fraumeni syndrome, Paget disease, radiotherapy	None known
Site	Metaphyses of long bones	Diaphyses of long bones, flat bones
Presentation	Local pain and swelling; often, history of injury	Local pain and swelling; fever
Radiographic findings	Sclerotic destruction (less commonly lytic); sunburst pattern	Primarily lytic, multilaminar periosteal reaction ("onion-skinning")
Differential diagnosis	Ewing sarcoma, osteomyelitis	Osteomyelitis, eosinophilic granuloma, lymphoma, neuroblastoma, rhabdomyosarcoma
Metastasis	Lungs, bones	Lungs, bones
Treatment	Chemotherapy Ablative surgery of primary tumor	Chemotherapy Radiotherapy and/or surgery of primary tumor
Outcome	Without metastases, 70% cured; with metastases at diagnosis, <20% survival	Without metastases, 60% cured; with metastases at diagnosis, 20-30% survival

Table 507-5 Spectrum of Diseases Characterized By Hemophagocytosis

PRIMARY HLH (see Table 507-3)
HLH WITH IMMUNODEFICIENCY, AUTOINFLAMMATORY STATES (see Table 507-3)
INFECTION-ASSOCIATED HLH (see Table 507-2)
MALIGNANCY-ASSOCIATED HLH
Lymphoma
Leukemia
MACROPHAGE ACTIVATION SYNDROME (MAS) ASSOCIATED WITH AUTOIMMUNE DISEASE
Systemic-onset juvenile idiopathic arthritis
Systemic lupus erythematosus
Enthesitis-related arthritis
Inflammatory bowel disease

Table 507-4 Diagnostic Guidelines for Hemophagocytic Lymphohistiocytosis

The diagnosis of HLH is established by fulfilling one of the following two criteria:	
1.	A molecular diagnosis consistent with HLH (e.g., PRF mutations, SAP mutations) or
2.	Having 5 of the following 8 signs or symptoms: a. Fever b. Splenomegaly c. Cytopenia (affecting ≥2 cell lineages; hemoglobin ≤9 g/dL [or ≤10 g/dL for infants <4 wk of age], platelets <100,000/µL, neutrophils <1,000/µL) d. Hypertriglyceridemia (≥265 mg/dL) and/or hypofibrinogenemia (≤150 mg/dL) e. Hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy f. Low or absent natural killer cell cytotoxicity g. Hyperferritinemia (≥500 ng/mL) h. Elevated soluble CD25 (interleukin-2R α chain; ≥2,400 U/mL)

Table 507-2 Infections Associated with Hemophagocytic Syndrome

VIRAL
Adenovirus
Cytomegalovirus
Dengue virus
Epstein-Barr virus
Enteroviruses
Herpes simplex viruses (HSV1, HSV2)
Human herpesviruses (HHV6, HHV8)
Human immunodeficiency virus
Influenza viruses
Parvovirus B19
Varicella-zoster virus
Hepatitis viruses
Measles
Parechovirus
BACTERIAL
<i>Babesia microti</i>
<i>Brucella abortus</i>
Enteric Gram-negative rods
<i>Haemophilus influenzae</i>
<i>Mycoplasma pneumoniae</i>
<i>Staphylococcus aureus</i>
<i>Streptococcus pneumoniae</i>
<i>Candida albicans</i>
<i>Cryptococcus neoformans</i>
<i>Histoplasma capsulatum</i>
<i>Fusarium</i>
MYCOBACTERIAL
<i>Mycobacterium tuberculosis</i>
RICKETTSIAL
<i>Coxiella burnetii</i>
Other rickettsial diseases
PARASITIC
<i>Leishmania donovani</i>
<i>Plasmodium</i>

DISEASE	CELLULAR CHARACTERISTICS OF LESIONS		TREATMENT
LCH	Langerhans cell histiocytosis	Langerhans-like cells (CD1a-positive, CD207-positive) with Birbeck granules (LCH cells)	Local therapy for isolated lesions; chemotherapy for disseminated disease
HLH	Familial hemophagocytic lymphohistiocytosis Infection-associated hemophagocytic syndrome [†] Associated with albinism syndromes [*] Associated with immunocompromised states Associated with autoimmune/ autoinflammatory states	Morphologically normal reactive macrophages with prominent erythrophagocytosis, and CD8-positive T cells	Chemotherapy; allogeneic bone marrow transplantation
Other	Juvenile xanthogranuloma Rosai-Dorfman disease Malignant histiocytosis	Characteristic vacuolated lesional histiocytes with foamy cytoplasm Hemophagocytic histiocytes Neoplastic proliferation of cells with characteristics of monocytes/macrophages or their precursors	None or excisional biopsy for localized disease; chemotherapy, radiotherapy for disseminated disease None if localized; surgery for bulk reduction; chemotherapy if organ systems involvement Antineoplastic chemotherapy, including anthracyclines
Other	Acute monocytic leukemia [‡]	M5 by FAB classification	Antineoplastic chemotherapy

^{*}Chediak-Higashi and Hermansky-Pudlak syndromes.[†]Also called secondary hemophagocytic lymphohistiocytosis.^{*}See Chapter 495.2.

FAB, French-American-British; LCH, Langerhans cell histiocytosis; HLH, hemophagocytic lymphohistiocytosis.

Nephrology

Table 509-1 Other Causes of Red Urine

HEME POSITIVE	Dyes (Vegetable/Fruit)
Hemoglobin	Beets
Myoglobin	Blackberries
HEME NEGATIVE	Food and candy coloring
Drugs	Rhubarb
Chloroquine	Metabolites
Deferoxamine	Homogentisic acid
Ibuprofen	Melanin
Iron sorbitol	Methemoglobin
Metronidazole	Porphyrin
Nitrofurantoin	Tyrosinosis
Phenazopyridine (Pyridium)	Urates
Phenolphthalein	
Phenothiazines	
Rifampin	
Salicylates	
Sulfasalazine	

Table 509-2 Causes of Hematuria in Children

UPPER URINARY TRACT DISEASE	
<i>Isolated renal disease</i>	
Immunoglobulin (Ig) A nephropathy (Berger disease)	
Alport syndrome (hereditary nephritis)	
Thin glomerular basement membrane nephropathy	
Postinfectious GN (poststreptococcal GN)*	
Membranous nephropathy	
Membranoproliferative GN*	
Rapidly progressive GN	
Focal segmental glomerulosclerosis	
Anti-glomerular basement membrane disease	
<i>Multisystem disease</i>	
Systemic lupus erythematosus nephritis*	
Henoch-Schönlein purpura nephritis	
Granulomatosis with polyangiitis (formerly Wegener granulomatosis)	
Polyarteritis nodosa	
Goodpasture syndrome	
Hemolytic-uremic syndrome	
Sickle cell glomerulopathy	
HIV nephropathy	
<i>Tubulointerstitial disease</i>	
Pyelonephritis	
Interstitial nephritis	
Papillary necrosis	
Acute tubular necrosis	
<i>Vascular</i>	
Arterial or venous thrombosis	
Malformations (aneurysms, hemangiomas)	
Nutcracker syndrome	
Hemoglobinopathy (sickle cell trait/disease)	
Crystalluria	
<i>Anatomic</i>	
Hydronephrosis	
Cystic-syndromic kidney disease	
Polycystic kidney disease	
Multicystic dysplasia	
Tumor (Wilms tumor, rhabdomyosarcoma, angiomyolipoma, medullary carcinoma)	
Trauma	
LOWER URINARY TRACT DISEASE	
Inflammation (infectious and noninfectious)	
Cystitis	
Urethritis	
Urolithiasis	
Trauma	
Coagulopathy	
Heavy exercise	
Bladder tumor	
Factitious syndrome, factitious syndrome by proxy [†]	

*Denotes glomerulonephritides presenting with hypocomplementemia.

[†]Formerly Munchausen syndrome and Munchausen syndrome by proxy. GN, glomerulonephritis.

Table 509-3 Common Causes of Gross Hematuria

Urinary tract infection
Meatal stenosis
Perineal irritation
Trauma
Urolithiasis
Hypercalciuria
Coagulopathy
Tumor
Glomerular
Postinfectious glomerulonephritis
Henoch-Schönlein purpura nephritis
IgA nephropathy
Alport syndrome (hereditary nephritis)
Thin glomerular basement membrane disease
Systemic lupus erythematosus nephritis

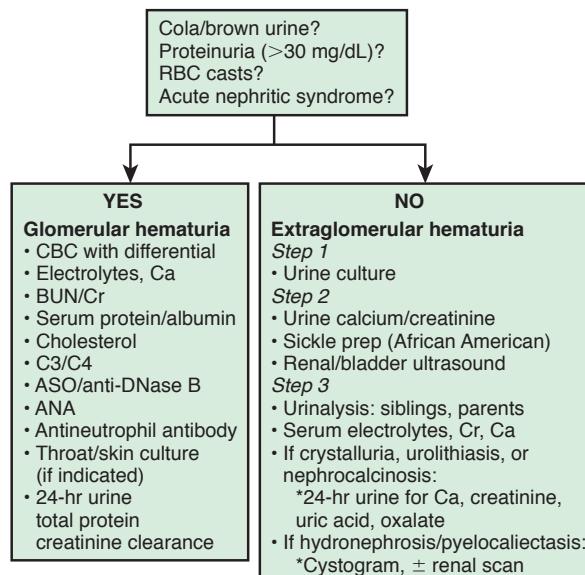


Figure 509-1 Algorithm of the general approach to the laboratory and radiologic evaluation of the patient with glomerular or extraglomerular hematuria. ANA, antinuclear antibody; ASO, antistreptolysin O; BUN, blood urea nitrogen; C3/C4, complement; CBC, complete blood cell count; Cr, creatinine; RBC, red blood cell.

DISEASES	POSTSTREPTOCOCCAL GLOMERULONEPHRITIS	IgA NEPHROPATHY	GOODPASTURE SYNDROME	IDIOPATHIC RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS
CLINICAL MANIFESTATIONS				
Age and sex	All ages, mean 7 yr, 2:1 male	10-35 yr, 2:1 male	15-30 yr, 6:1 male	Adults, 2:1 male
Acute nephritic syndrome	90%	50%	90%	90%
Asymptomatic hematuria	Occasionally	50%	Rare	Rare
Nephrotic syndrome	10-20%	Rare	Rare	10-20%
Hypertension	70%	30-50%	Rare	25%
Acute renal failure	50% (transient)	Very rare	50%	60%
Other	Latent period of 1-3 wk	Follows viral syndromes	Pulmonary hemorrhage; iron deficiency anemia	None
Laboratory findings	↑ ASO titers (70%) Positive streptozyme (95%) ↓C3-C9; normal C1, C4	↑ Serum IgA (50%) IgA in dermal capillaries	Positive anti-GBM antibody	Positive ANCA in some
Immunogenetics	HLA-B12, D "EN" (9)*	HLA-Bw 35, DR4 (4)*	HLA-DR2 (16)*	None established
RENAL PATHOLOGY				
Light microscopy	Diffuse proliferation	Focal proliferation	Focal → diffuse proliferation with crescents	Crescentic GN
Immunofluorescence	Granular IgG, C3	Diffuse mesangial IgA	Linear IgG, C3	No immune deposits
Electron microscopy	Subepithelial humps	Mesangial deposits	No deposits	No deposits
Prognosis	95% resolve spontaneously 5% RPGN or slowly progressive	Slow progression in 25-50%	75% stabilize or improve if treated early	75% stabilize or improve if treated early
Treatment	Supportive	Uncertain (options include steroids, fish oil, and ACE inhibitors)	Plasma exchange, steroids, cyclophosphamide	Steroid pulse therapy

*Relative risk.

ACE, angiotensin-converting enzyme; ANCA, antineutrophil cytoplasmic antibody; ASO, anti-streptolysin O; GBM, glomerular basement membrane; GN, glomerulonephritis; HLA, human leukocyte antigen; Ig, immunoglobulin; RPGN, idiopathic rapidly progressive glomerulonephritis.

Table 516-1 Classification of Rapidly Progressive ("Crescentic") Glomerulonephritis

PRIMARY

- Type I: Anti-glomerular basement membrane antibody disease, Goodpasture syndrome (with pulmonary disease)
- Type II: Immune complex mediated
- Type III: Pauciimmune (usually antineutrophil cytoplasmic antibody-positive)

SECONDARY

- Membranoproliferative glomerulonephritis
- Immunoglobulin A nephropathy, Henoch-Schönlein purpura
- Poststreptococcal glomerulonephritis
- Systemic lupus erythematosus
- Polyarteritis nodosa, hypersensitivity angiitis

Table 527-5 Causes of Nephrotic Syndrome in Infants Younger Than 1 Year

SECONDARY CAUSES

- Infections**
- Syphilis
- Cytomegalovirus
- Toxoplasmosis
- Rubella
- Hepatitis B
- HIV
- Malaria
- Drug reactions
- Toxins
- Mercury
- Systemic lupus erythematosus

Syndromes with associated renal disease

- Syndromes with associated renal disease
- Nail-patella syndrome
- Lowe syndrome
- Nephropathy associated with congenital brain malformation
- Denys-Drash syndrome: Wilms tumor
- Hemolytic-uremic syndrome

PRIMARY CAUSES

- Congenital nephrotic syndrome
- Diffuse mesangial sclerosis
- Minimal change disease
- Focal segmental sclerosis
- Membranous nephropathy

Table 514-1 Classification of Lupus Nephritis

CLASS	CLINICAL FEATURES
I. Minimal mesangial LN	No renal findings
II. Mesangial proliferative LN	Mild clinical renal disease; minimally active urinary sediment; mild to moderate proteinuria (never nephrotic) but may have active serology
III. Focal proliferative LN <50% glomeruli involved	More active sediment changes; often active serology; increased proteinuria (approximately 25% nephrotic); hypertension may be present; some evolve into class IV pattern; active lesions require treatment, chronic do not
A. Active	
A/C. Active and chronic	
C. Chronic	
IV. Diffuse proliferative LN (>50% glomeruli involved); all may be with segmental or global involvement (S or G)	Most severe renal involvement with active sediment, hypertension, heavy proteinuria (frequent nephrotic syndrome), often reduced glomerular filtration rate; serology very active. Active lesions require treatment
A. Active	
A/C. Active and chronic	
C. Chronic	
V. Membranous LN glomerulonephritis	Significant proteinuria (often nephrotic) with less active lupus serology
VI. Advanced sclerosing LN	More than 90% glomerulosclerosis; no treatment prevents renal failure

LN, lupus nephritis.

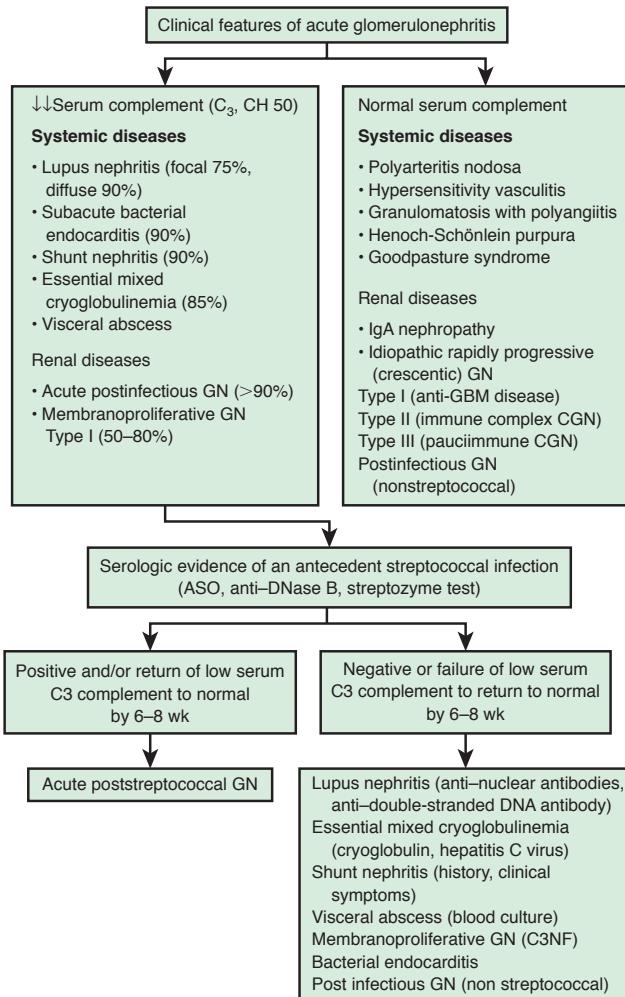


Figure 511-3 Differential diagnosis of acute glomerulonephritis (GN). ASO, anti-streptolysin O; GBM, glomerular basement membrane; NF, nuclear factor.

Table 518-1 Thrombotic Microangiopathies Overview and Classification

TMA associated with genetic or immune-mediated abnormalities of the complement system
Genetically determined factor H deficiency
Genetic membrane cofactor protein (CD46) abnormalities
Complement factor 1 deficiency
Gain-of-function mutations of complement factor B
Complement C3 mutations
Acquired anti-C3 autoantibodies
Immune-mediated factor H deficiency
TTP associated with genetic or immune-mediated ADAMTS13 abnormalities
Infectious disease-associated TMA
STEC-HUS
Neuraminidase (pneumococcal)-associated TMA
HIV infection
Systemic disease-associated TMA
Antiphospholipid syndrome
Systemic lupus erythematosus
Scleroderma
Malignant hypertension
Malignancy
Pregnancy-associated TMA
TTP
Hemolysis, elevated liver enzymes, and low platelet count syndrome
Postpartum HUS
Drug-associated TMA (>50 substances reported)
Mitomycin
Quinidine
Ticlopidine
Clopidogrel
Calcineurin inhibitors
Oral contraception
Gemcitabine
Anti-VEGF
Metabolic disease-associated TMA
Deficiency in cobalamin C metabolism HUS
Transplant-associated TMA
De novo HUS
Recurrent posttransplantation HUS

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; HIV, human immunodeficiency virus; HUS, hemolytic-uremic syndrome; STEC-HUS, Shiga toxin-producing *Escherichia coli* hemolytic-uremic syndrome; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; VEGF, vascular endothelial growth factor.

Table 521-2 Autosomal Recessive Polycystic Kidney Disease and Hepatorenal Fibrocystic Disease Phenotypes				
DISEASE	GENE(S)	RENAL DISEASE	HEPATIC DISEASE	SYSTEMIC FEATURES
ARPKD	PKHD1	Collecting duct dilation	CHF; Caroli disease	No
ADPKD	PKD1; PKD2	Cysts along entire nephron	Biliary cysts; CHF (rare)	Yes: adults
NPHP	NPHP1-NPHP16	Cysts at the corticomedullary junction	CHF	+/-
Joubert syndrome and related disorders	JBTS1-JBTS20	Cystic dysplasia; NPHP	CHF; Caroli disease	Yes
Bardet-Biedel syndrome	BBS1-BBS18	Cystic dysplasia; NPHP	CHF	Yes
Meckel-Gruber syndrome	MKS1-MKS10	Cystic dysplasia	CHF	Yes
Oral-facial-digital syndrome, type I	OFD1	Glomerular cysts	CHF (rare)	Yes
Glomerulocystic disease	PKD1; HNF1B; UMOD	Enlarged; normal or hypoplastic kidneys	CHF (with PKD1 mutations)	+/-
Jeune syndrome (asphyxiating thoracic dystrophy)	IFT80 (ATD2) DYNC2H1 (ATD3) ATD1, ATD4, ATD5	Cystic dysplasia	CHF; Caroli disease	Yes
Renal-hepatic-pancreatic dysplasia (Ivemark II)	NPHP3, NEK8	Cystic dysplasia	Intrahepatic biliary dysgenesis	Yes
Zellweger syndrome	PEX1-3;5-6;10-11;13;14;16;19;26	Renal cortical microcysts	Intrahepatic biliary dysgenesis	Yes

NPHP, Nephronophthisis. CHF, congenital hepatic fibrosis.

Modified from Guay-Woodford LM, Bissler JJ, Braun MC, et al: Consensus expert recommendations for the diagnosis and management of autosomal recessive polycystic kidney disease: Report of an international conference. J Pediatr 165:611-617, 2014.

Table 521-1 Comparison of Clinical Features of Cystic Kidney Diseases

DISEASE	INHERITANCE	FREQUENCY	GENE PRODUCT	AGE OF ONSET	CYST ORIGIN	RENOMEGLAY	CAUSE OF ESRD	OTHER MANIFESTATIONS
ADPKD	AD	400-1,000	Poly cystin 1 Poly cystin 2	20s and 30s; <2% before age 15 Occasional perinatal onset	Anywhere (including the Bowman capsule)	Yes	Yes	Liver cysts Cerebral aneurysms Hypertension Mitral valve prolapse Kidney stones UTIs
ARPKD	AR	6,000-10,000	Fibrocystin/ polyductin	First yr of life; perinatal onset	Distal nephron, CD	Yes	Yes	Hepatic fibrosis Pulmonary hypoplasia Hypertension
ACKD	No	90% of ESRD patients at 8 yr	None	Years after onset of ESRD	Proximal and distal tubules	Rarely	No	None
Simple cysts	No	50% in those older than 40 yr	None	Adulthood	Anywhere (usually cortical)	No	No	None
Nephronophthisis	AR	80,000	Nephrocystins (NPHP1-9)	Childhood or adolescence	Medullary DCT	No	Yes	Retinal degeneration; neurologic, skeletal, hepatic, cardiac malformations
MCKD	AD	Rare	Uromodulin, others	Adulthood	Medullary DCT	No	Yes	Hyperuricemia, gout
MSK	No	5,000-20,000	None	30s	Medullary CD	No	No	Kidney stones Hypercalciuria
Tuberous sclerosis	AD	10,000	Hamartin (TSC1) Tuberin (TSC2)	Childhood	Loop of Henle, DCT	Rarely	Rarely	Renal cell carcinoma Tubers, seizures Angiomyolipoma Hypertension
VHL syndrome	AD	40,000	VHL protein	20s	Cortical nephrons	Rarely	Rarely	Renal angioma, CNS hemangioblastoma, renal cell carcinoma, pheochromocytoma
Oral-facial-digital syndrome	XD	250,000	OFD1 protein	Childhood or adulthood	Renal glomeruli	Rarely	Yes	Malformation of the face, oral cavity, and digits; liver cysts; mental retardation
Bardet-Biedl syndrome	AR	65,000-160,000	BBS 14	Adulthood	Renal calyces	Rarely	Yes	Syndactyly and polydactyly, obesity, retinal dystrophy, male hypogonitalism, hypertension, mental retardation

ACKD, acquired cystic kidney disease; AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; AR, autosomal recessive; ARPKD, autosomal recessive polycystic kidney disease; CD, collecting duct; CNS, central nervous system; DCT, distal convoluted tubule; ESRD, end-stage renal disease; MCKD, medullary cystic kidney disease; MSK, medullary sponge kidney; UTI, urinary tract infection; VHL, von Hippel-Lindau; XD, X-linked dominant.

From Arnaout MA. Cystic kidney disease. In Goldman L, Schafer AI, editors: Goldman's Cecil medicine, ed 24, Philadelphia, 2012, Elsevier Saunders, Table 129-1, p. 796.

Table 523-1 Methods Available to Test for Proteinuria			
METHOD	INDICATIONS	NORMAL RANGE	COMMENTS
Dipstick testing	Routine screening for proteinuria performed in the office	Negative or trace in a concentrated urine specimen (specific gravity: ≥ 1.020)	False-positive test can occur if urine is very alkaline (pH > 8.0) or very concentrated (specific gravity: >1.025)
24 hr urine for protein and creatinine* excretion	Quantitation of proteinuria (as well as creatinine clearances)	<100 mg/m ² /24 hr or <150 mg/24 hr in a documented 24 hr collection	More accurate than spot urine analysis; inconvenient for patient; limited use in pediatric practice
Spot urine for protein/creatinine ratio—preferably on first morning urine specimen	Semiquantitative assessment of proteinuria	<0.2 mg protein/mg creatinine in children >2 yr old <0.5 mg protein/mg creatinine in those 6–24 mo old	Simplest method to quantitate proteinuria; less accurate than measuring 24 hr proteinuria
Microalbuminuria	Assess risk of progressive glomerulopathy in patients with diabetes mellitus	<30 mg urine albumin per gram of creatinine on first morning urine	Therapy should be intensified in diabetics with microalbuminuria

*Note that in a 24 hr urine specimen, the creatinine content should be measured to determine whether the specimen is truly a 24 hr collection. The amount of creatinine in a 24 hr specimen can be estimated as follows: females, 15–20 mg/kg; males, 20–25 mg/kg.

Adapted from Hogg RJ, Portman RJ, Milliner D, et al, *Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a Pediatric Nephrology Panel Established at the National Kidney Foundation Conference on Proteinuria, Albuminuria, Risk Assessment, Detection, and Elimination (PARADE)*, Pediatrics 105(6):1242–1249, 2000.

Table 527-1 Causes of Childhood Nephrotic Syndrome	
IDIOPATHIC NEPHROTIC SYNDROME	SECONDARY CAUSES OF NEPHROTIC SYNDROME
Minimal change disease	Infections
Focal segmental glomerulosclerosis	Endocarditis
Membranous nephropathy	Hepatitis B, C
Glomerulonephritis associated with nephrotic syndrome—membranoproliferative glomerulonephritis, crescentic glomerulonephritis, immunoglobulin A nephropathy	HIV-1
GENETIC DISORDERS ASSOCIATED WITH PROTEINURIA OR NEPHROTIC SYNDROME	Infectious mononucleosis
Nephrotic Syndrome (Typical)	Malaria
Finnish-type congenital nephrotic syndrome (absence of nephrin)	Syphilis (congenital and secondary)
Focal segmental glomerulosclerosis (mutations in nephrin, podocin, MYO1E, α -actinin 4, TRPC6)	Toxoplasmosis
Diffuse mesangial sclerosis (mutations in laminin β_2 chain)	Schistosomiasis
Denys-Drash syndrome (mutations in WT1 transcription factor)	Filariasis
Congenital nephrotic syndrome with lung and skin involvement (α -integrin α -3 mutation)	Drugs
Mitochondrial disorders	Captopril
Proteinuria With or Without Nephrotic Syndrome	Penicillamine
Nail-patella syndrome (mutation in LMX1B transcription factor)	Gold
Alport syndrome (mutation in collagen biosynthesis genes)	Nonsteroidal antiinflammatory drugs
Multisystem Syndromes With or Without Nephrotic Syndrome	Pamidronate
Galloway-Mowat syndrome	Interferon
Charcot-Marie-Tooth disease	Mercury
Jeune syndrome	Heroin
Cockayne syndrome	Lithium
Laurence-Moon-Biedl-Bardet syndrome	Immunologic or Allergic Disorders
Metabolic Disorders With or Without Nephrotic Syndrome	Vasculitis syndromes
Alagille syndrome	Castleman disease
α_1 -Antitrypsin deficiency	Kimura disease
Fabry disease	Beesting
Glutaric aciduria	Food allergens
Glycogen storage disease	Serum sickness
Hurler syndrome	Associated With Malignant Disease
Partial lipodystrophy	Lymphoma
Mitochondrial cytopathies	Leukemia
Sickle cell disease	Solid tumors

Adapted from Eddy AA, Symons JM: Nephrotic syndrome in childhood, Lancet 362:629–638, 2003.

Table 527-2 Summary of Primary Renal Diseases That Manifest as Idiopathic Nephrotic Syndrome

FEATURES	MINIMAL CHANGE NEPHROTIC SYNDROME	FOCAL SEGMENTAL GLOMERULOSCLEROSIS	MEMBRANOUS NEPHROPATHY	MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS	
				Type I	Type II
DEMOGRAPHICS					
Age (yr)	2-6, some adults	2-10, some adults	40-50	5-15	5-15
Sex	2:1 male	1.3:1 male	2:1 male	Male-female	Male-female
CLINICAL MANIFESTATIONS					
Nephrotic syndrome	100%	90%	80%	60%*	60%*
Asymptomatic proteinuria	0	10%	20%	40%	40%
Hematuria (microscopic or gross)	10-20%	60-80%	60%	80%	80%
Hypertension	10%	20% early	Infrequent	35%	35%
Rate of progression to renal failure	Does not progress	10 yr	50% in 10-20 yr	10-20 yr	5-15 yr
Associated conditions	Usually none	HIV, heroin use, sickle cell disease, reflux nephropathy	Renal vein thrombosis; medications; SLE; hepatitis B, C; lymphoma; tumors	None	Partial lipodystrophy
GENETICS					
	None except in congenital nephrotic syndrome (see Table 527-3)	Podocin, α -actinin 4, TRPC6 channel, INF-2, MYH-9	None	None	None
LABORATORY FINDINGS					
	Manifestations of nephrotic syndrome ↑ BUN in 15-30% Normal complement levels	Manifestations of nephrotic syndrome ↑ BUN in 20-40% Normal complement levels	Manifestations of nephrotic syndrome Normal complement levels	Low complement levels—C1, C4, C3-C9	Normal complement levels—C1, C4, low C3-C9
RENAL PATHOLOGY					
Light microscopy	Normal	Focal sclerotic lesions	Thickened GBM, spikes	Thickened GBM, proliferation	Lobulation
Immunofluorescence	Negative	IgM, C3 in lesions	Fine granular IgG, C3	Granular IgG, C3	C3 only
Electron microscopy	Foot process fusion	Foot process fusion	Subepithelial deposits	Mesangial and subendothelial deposits	Dense deposits
REMISSION ACHIEVED AFTER 8 WK OF ORAL CORTICOSTEROID THERAPY					
	90%	15-20%	Resistant	Not established/resistant	Not established/resistant

*Approximate frequency as a cause of idiopathic nephrotic syndrome. Approximately 10% of cases of adult nephrotic syndrome are a result of various diseases that usually manifest as acute glomerulonephritis.

↑, Elevated; BUN, blood urea nitrogen; C, complement; GBM, glomerular basement membrane; Ig, immunoglobulin; SLE, systemic lupus erythematosus.

Modified from Couser WG: Glomerular disorders. In Wyngaarden JB, Smith LH, Bennett JC, editors: Cecil textbook of medicine, ed 19, Philadelphia, 1992, WB Saunders, p. 560.

Table 526-1 Causes of Proteinuria

TRANSIENT PROTEINURIA	GLOMERULAR DISEASES WITH PROTEINURIA AS A PROMINENT FEATURE
Fever	Acute postinfectious glomerulonephritis (streptococcal, endocarditis, hepatitis B or C virus, HIV)
Exercise	Immunoglobulin A nephropathy
Dehydration	Henoch-Schönlein purpura nephritis
Cold exposure	Lupus nephritis
Congestive heart failure	Serum sickness
Seizure	Alport syndrome
Stress	Vasculitic disorders
ORTHOSTATIC (POSTURAL) PROTEINURIA	Reflux nephropathy
GLOMERULAR DISEASES CHARACTERIZED BY ISOLATED PROTEINURIA	TUBULAR DISEASES
Idiopathic (minimal change) nephrotic syndrome	Cystinosis
Focal segmental glomerulosclerosis	Wilson disease
Mesangial proliferative glomerulonephritis	Lowe syndrome
Membranous nephropathy	Dent disease (X-linked recessive nephrolithiasis)
Membranoproliferative glomerulonephritis	Galactosemia
Amyloidosis	Tubulointerstitial nephritis
Diabetic nephropathy	Acute tubular necrosis
Sickle cell nephropathy	Renal dysplasia

NSAID, nonsteroidal antiinflammatory drug.

Table 529-1 Common Causes of Renal Tubular Acidosis

PROXIMAL RENAL TUBULAR ACIDOSIS		
Primary		
Sporadic		
Inherited		
• Inherited renal disease (idiopathic Fanconi)		
• Sporadic (most common)		
• Autosomal dominant		
• Autosomal recessive		
• X-linked (Dent disease)		
• Inherited syndromes		
• Cystinosis		
• Tyrosinemia type 1		
• Galactosemia		
• Oculocerebral dystrophy (Lowe syndrome)		
• Wilson disease		
• Hereditary fructose intolerance		
Secondary		
Intrinsic renal disease		
• Autoimmune diseases (Sjögren syndrome)		
• Hypokalemic nephropathy		
• Renal transplant rejection		
Hematologic disease		
• Myeloma		
Drugs		
• Gentamicin		
• Cisplatin		
• Ifosfamide		
• Sodium valproate		
Heavy metals		
• Lead		
• Cadmium		
• Mercury		
Organic compounds		
• Toluene		
Nutritional		
• Kwashiorkor		
Hormonal		
• Primary hyperparathyroidism		
DISTAL RENAL TUBULAR ACIDOSIS		
Primary		
Sporadic		
Inherited		
• Inherited renal diseases		
• Autosomal dominant		
• Autosomal recessive		
• Autosomal recessive with early-onset hearing loss		
• Autosomal recessive with later-onset hearing loss		
• Inherited syndromes associated with type I renal tubular acidosis		
• Marfan syndrome		
• Wilson syndrome		
• Ehlers-Danlos syndrome		
• Familial hypercalcioria		
Secondary		
Intrinsic renal		
• Interstitial nephritis		
• Pyelonephritis		
• Transplant rejection		
• Sickle cell nephropathy		
• Lupus nephritis		
• Nephrocalcinosis		
• Medullary sponge kidney		
Urologic		
• Obstructive uropathy		
• Vesicoureteral reflux		
• Hepatic		
• Cirrhosis		
Toxins or medications		
• Amphotericin B		
• Lithium		
• Toluene		
• Cisplatin		
HYPOKALEMIC RENAL TUBULAR ACIDOSIS		
Primary		
Sporadic		
Genetic		
• Hypoaldosteronism		
• Addison disease		
• Congenital adrenal hyperplasia		
• Pseudohypoaldosteronism (type I or II)		
Secondary		
Urologic		
• Obstructive uropathy		
Intrinsic renal		
• Pyelonephritis		
• Interstitial nephritis		
Systemic		
• Diabetes mellitus		
• Sickle cell nephropathy		
Drugs		
• Trimethoprim/sulfamethoxazole		
• Angiotensin-converting enzyme inhibitors		
• Cyclosporine		
• Prolonged heparinization		
Addison disease		

Table 535-6 Standardized Terminology for Stages of Chronic Kidney Disease (NKF KDOQI Guidelines)

STAGE	DESCRIPTION	GFR (mL/min/1.73 m ²)
1	Kidney damage with normal or increased GFR	>90
2	Kidney damage with mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	5-29
5	Kidney failure	<15 or on dialysis

GFR, glomerular filtration rate; NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

Table 535-8 Merits of Peritoneal Dialysis in Pediatric Patients with End-Stage Renal Disease

ADVANTAGES
Ability to perform dialysis treatment at home
Technically easier than hemodialysis, especially in infants
Ability to live a greater distance from medical center
Freedom to attend school and after-school activities
Less-restrictive diet
Less expensive than hemodialysis
Independence (adolescents)
DISADVANTAGES
Catheter malfunction
Catheter-related infections (peritonitis, exit site)
Impaired appetite (due to full peritoneal cavity)
Negative body image
Caregiver burnout

Table 529-1 Common Causes of Renal Tubular Acidosis

PROXIMAL RENAL TUBULAR ACIDOSIS		Secondary
Primary		Intrinsic renal
Sporadic		<ul style="list-style-type: none"> • Interstitial nephritis • Pyelonephritis • Transplant rejection • Sickle cell nephropathy • Lupus nephritis • Nephrocalcinosis • Medullary sponge kidney
Inherited		Urologic
<ul style="list-style-type: none"> • Inherited renal disease (idiopathic Fanconi) <ul style="list-style-type: none"> • Sporadic (most common) • Autosomal dominant • Autosomal recessive • X-linked (Dent disease) • Inherited syndromes <ul style="list-style-type: none"> • Cystinosis • Tyrosinemia type 1 • Galactosemia • Oculocerebral dystrophy (Lowe syndrome) • Wilson disease • Hereditary fructose intolerance 		
Secondary		Toxins or medications
Intrinsic renal disease		<ul style="list-style-type: none"> • Amphotericin B • Lithium • Toluene • Cisplatin
<ul style="list-style-type: none"> • Autoimmune diseases (Sjögren syndrome) • Hypokalemic nephropathy • Renal transplant rejection 		HYPERKALEMIC RENAL TUBULAR ACIDOSIS
Hematologic disease		Primary
<ul style="list-style-type: none"> • Myeloma 		Sporadic
Drugs		Genetic
<ul style="list-style-type: none"> • Gentamicin • Cisplatin • Ifosfamide • Sodium valproate 		<ul style="list-style-type: none"> • Hypoaldosteronism • Addison disease • Congenital adrenal hyperplasia • Pseudohypoaldosteronism (type I or II)
Heavy metals		Secondary
<ul style="list-style-type: none"> • Lead • Cadmium • Mercury 		Urologic
Organic compounds		<ul style="list-style-type: none"> • Obstructive uropathy • Pyelonephritis • Interstitial nephritis
<ul style="list-style-type: none"> • Toluene 		Systemic
Nutritional		<ul style="list-style-type: none"> • Diabetes mellitus • Sickle cell nephropathy
<ul style="list-style-type: none"> • Kwashiorkor 		Drugs
Hormonal		<ul style="list-style-type: none"> • Trimethoprim/sulfamethoxazole • Angiotensin-converting enzyme inhibitors • Cyclosporine • Prolonged heparinization
<ul style="list-style-type: none"> • Primary hyperparathyroidism 		Addison disease
DISTAL RENAL TUBULAR ACIDOSIS		
Primary		
Sporadic		
Inherited		
<ul style="list-style-type: none"> • Inherited renal diseases <ul style="list-style-type: none"> • Autosomal dominant • Autosomal recessive • Autosomal recessive with early-onset hearing loss • Autosomal recessive with later-onset hearing loss • Inherited syndromes associated with type I renal tubular acidosis <ul style="list-style-type: none"> • Marfan syndrome • Wilson syndrome • Ehlers-Danlos syndrome • Familial hypercalcuria 		

Table 531-1 Bartter and Gitelman Syndromes

	TYPE I BARTTER SYNDROME	TYPE II BARTTER SYNDROME	TYPE III BARTTER SYNDROME	TYPE IV BARTTER SYNDROME	TYPE V BARTTER SYNDROME	GITELMAN SYNDROME
Inheritance	AR	AR	AR	AR	AD	AR
Affected tubular region	TAL	TAL + CCD	TAL + DCT	TAL + DCT	TAL	DCT
Gene	SLC12A2	KCNJ1	CLCBRK	BSND	CASR	SLC12A3 Few have CLCNKB
Onset	Prenatal, postnatal	Prenatal, postnatal	Variable	Prenatal, postnatal	Variable	Adolescent, adult
Urine PGE2	Very high	Very high	Slightly elevated	Elevated	Elevated	Normal
Hypokalemic metabolic alkalosis	Present	Present	Present	Present	Present	Present
Features	Polyhydramnios, prematurity, nephrocalcinosis, dehydration, hyposthenuria, polyuria, failure to thrive	Same as type I	Failure to thrive, dehydration, salt craving, low serum magnesium in 20%, mildest form	Same as type I, with sensorineural hearing loss and no nephrocalcinosis	Hypocalcemia, low parathyroid hormone levels, hypercalcuria, uncommon cause of Bartter syndrome	Hypomagnesemia in 100%, mild dehydration, occasional growth retardation, tetany

AD, autosomal dominant; AR, autosomal recessive; CCD, cortisol collecting duct; DCT, descending convoluted tubule; PGE₂, prostaglandin E₂; TAL, thick ascending loop of Henle.

2536 Part XXIII ◆ Nephrology

Table 532-1 Etiology of Interstitial Nephritis

ACUTE	CHRONIC
Drugs	Drugs and toxins
• Antimicrobials <ul style="list-style-type: none"> • Penicillin derivatives • Cephalosporins • Sulfonamides • Trimethoprim-sulfamethoxazole • Ciprofloxacin • Tetracyclines • Vancomycin • Erythromycin derivatives • Rifampin • Amphotericin B • Acyclovir 	• Analgesics <ul style="list-style-type: none"> • Cyclosporine • Lithium • Heavy metals
Infections	Infections (see Acute)
• Anticonvulsants <ul style="list-style-type: none"> • Carbamazepine • Phenobarbital • Phenytoin • Sodium valproate 	Disease-associated <ul style="list-style-type: none"> • Metabolic and hereditary • Cystinosis • Oxalosis • Fabry disease • Wilson disease • Sickle cell nephropathy • Alport syndrome • Juvenile nephronophthisis, medullary cystic disease
• Other drugs <ul style="list-style-type: none"> • Allopurinol • All-trans-retinoic acid • 5-Aminosalicylic acid • Cimetidine • Cyclosporine • Diuretics • Escitalopram • Interferon • Mesalazine • Quetiapine • Olanzapine • Nonsteroidal antiinflammatory drugs • Protease inhibitors • Proton pump inhibitors • Aristolochic acid (traditional Chinese herb) 	Immunologic <ul style="list-style-type: none"> • Systemic lupus erythematosus • Crohn disease • Chronic allograft rejection • Tubulointerstitial nephritis and uveitis (TINU) syndrome • Antitubular basement disease
• Adenovirus	Urologic <ul style="list-style-type: none"> • Posterior urethral valves • Eagle-Barrett syndrome • Ureteropelvic junction obstruction • Vesicoureteral reflux
• Bacteria associated with acute pyelonephritis	Miscellaneous <ul style="list-style-type: none"> • Balkan nephropathy • Radiation • Sarcoidosis • Neoplasm
• BK virus	Idiopathic
• Brucella	
• Streptococcal species	
• Cytomegalovirus	
• Epstein-Barr virus	
• Hepatitis B virus	
• Histoplasmosis	
• Human immunodeficiency virus	
• Hantavirus	
• Leptospirosis	
• <i>Toxoplasma gondii</i>	
Disease-associated	
• Glomerulonephritis (e.g., systemic lupus erythematosus)	
• Acute allograft rejection	
• Tubulointerstitial nephritis and uveitis (TINU) syndrome	
Idiopathic	

Table 538-2 Sensitivity and Specificity of Components of Urinalysis, Alone and in Combination

TEST	SENSITIVITY (RANGE) %	SPECIFICITY (RANGE) %
Leukocyte esterase test	83 (67-94)	78 (64-92)
Nitrite test	53 (15-82)	98 (90-100)
Leukocyte esterase or nitrite test positive	93 (90-100)	72 (58-91)
Microscopy (white blood cells)	73 (32-100)	81 (45-98)
Microscopy (bacteria)	81 (16-99)	83 (11-100)
Leukocyte esterase test, nitrite test, or microscopy positive	99.8 (99-100)	70 (60-92)

From Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management: Clinical practice guideline. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in Febrile infants and children 2 to 24 months. Pediatrics 128:595-610, 2011.

Table 533-1 Renal Syndromes Produced by Nephrotoxins

NEPHROTIC SYNDROME	FANCONI SYNDROME
Angiotensin-converting enzyme inhibitors	Aminoglycosides
Gold salts	Chinese herbs (aristolochic)
Interferon	Cisplatin
Mercury compounds	Heavy metals (cadmium, lead, mercury, and uranium)
Nonsteroidal antiinflammatory drugs	Ifosfamide
Penicillamine	Lysol
	Outdated tetracycline
NEPHROGENIC DIABETES INSIPIDUS	RENAL TUBULAR ACIDOSIS
Amphotericin B	Amphotericin B
Cisplatin	Lead
Colchicine	Lithium
Demeclocycline	Toluene
Lithium	
Methoxyflurane	
Propoxyphene	
Vinblastine	
RENAL VASCULITIS	INTERSTITIAL NEPHRITIS
Hydralazine	Amidopyrine
Isoniazid	p-Aminosalicylate
Penicillins	Carbon tetrachloride
Propylthiouracil	Cephalosporins
Sulfonamides	Cimetidine
Numerous other drugs that can cause a hypersensitivity reaction	Cisplatin
	Colistin
	Copper
	Cyclosporine
	Ethylene glycol
	Foscarnet
	Gentamicin
	Gold salts
	Indomethacin
	Interferon-α
	Iron
	Kanamycin
	Lithium
	Mannitol
	Mercury salts
	Mitomycin C
	Neomycin
	Nonsteroidal antiinflammatory drugs
	Penicillins (especially methicillin)
	Pentamidine
	Phenacetin
	Phenylbutazone
	Poisonous mushrooms
	Polymyxin B
	Radiocontrast agents
	Rifampin
	Salicylate
	Streptomycin
	Sulfonamides
	Tacrolimus
	Tetrachloroethylene
	Trimethoprim-sulfamethoxazole
ACUTE RENAL FAILURE	
Acetaminophen	
Acyclovir	
Aminoglycosides	
Amphotericin B	
Angiotensin-converting enzyme inhibitors	
Biologic toxins (snake, spider, bee, wasp)	
Cisplatin	
Cyclosporine	
Ethylene glycol	
Halothane	
Heavy metals	
Ifosfamide	
Lithium	
Methoxyflurane	
Nonsteroidal antiinflammatory drugs	
Radiocontrast agents	
Tacrolimus	
Vancomycin	
OBSTRUCTIVE UROPATHY	
Sulfonamides	
Acyclovir	
Methotrexate	
Protease inhibitors	
Ethylene glycol	
Methoxyflurane	

Table 535-2 Common Causes of Acute Kidney Injury

PRERENAL	
Dehydration	
Hemorrhage	
Sepsis	
Hypoalbuminemia	
Cardiac failure	
INTRINSIC RENAL	
Glomerulonephritis	
• Postinfectious/poststreptococcal	
• Lupus erythematosus	
• Henoch-Schönlein purpura	
• Membranoproliferative	
• Anti-glomerular basement membrane	
Hemolytic-uremic syndrome	
Acute tubular necrosis	
Cortical necrosis	
Renal vein thrombosis	
Rhabdomyolysis	
Acute interstitial nephritis	
Tumor infiltration	
Tumor lysis syndrome	
POSTRENAL	
Posterior urethral valves	
Ureteropelvic junction obstruction	
Ureteroovesicular junction obstruction	
Ureterocele	
Tumor	
Urolithiasis	
Hemorrhagic cystitis	
Neurogenic bladder	

Table 535-5 Criteria for Definition of Chronic Kidney Disease (NKF KDOQI Guidelines)

Patient has CKD if either of the following criteria are present:

1. Kidney damage for ≥ 3 mo, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by 1 or more of the following features:
 - Abnormalities in the composition of the blood or urine
 - Abnormalities in imaging tests
 - Abnormalities on kidney biopsy
2. GFR <60 mL/min/1.73 m 2 for ≥ 3 mo, with or without the other signs of kidney damage described above

NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

Table 535-1 Pediatric-Modified RIFLE (pRIFLE) Criteria

CRITERIA	ESTIMATED CCL	URINE OUTPUT
Risk	eCCI decrease by 25%	<0.5 mL/kg/hr for 8 hr
Injury	eCCI decrease by 50%	<0.5 mL/kg/hr for 16 hr
Failure	eCCI decrease by 75% or eCCI <35 mL/min/1.73 m 2	<0.3 mL/kg/hr for 24 hr or anuric for 12 hr
Loss	Persistent failure >4 wk	
End-stage	End-stage renal disease (persistent failure >3 mo)	

CCI, creatinine clearance; eCCI, estimated creatinine clearance; pRIFLE, pediatric risk, injury, failure, loss, and end-stage renal disease.

Table 535-4 Comparison of Peritoneal Dialysis, Intermittent Hemodialysis, and Continual Renal Replacement Therapy

	PD	IHD	CRRT
BENEFITS			
Fluid removal	+	++	++
Urea and creatinine clearance	+	++	+
Potassium clearance	++	++	+
Toxin clearance	+	++	+
COMPLICATIONS			
Abdominal pain	+	-	-
Bleeding	-	+	+
Dysequilibrium	-	+	-
Electrolyte imbalance	+	+	+
Need for heparinization	-	+	+/-
Hyperglycemia	+	-	-
Hypotension	+	++	+
Hypothermia	-	-	+
Central line infection	-	+	+
Inguinal or abdominal hernia	+	-	-
Peritonitis	+	-	-
Protein loss	+	-	-
Respiratory compromise	+	-	-
Vessel thrombosis	-	+	+

PD, peritoneal dialysis; IHD, intermittent hemodialysis; CRRT, continual renal replacement therapy.

Adapted from Rogers MC: Textbook of pediatric intensive care, Baltimore, 1992, Williams & Wilkins.

Table 535-3 Urinalysis, Urine Chemistries, and Osmolality in Acute Kidney Injury

	HYPVOLEMIA	ACUTE TUBULAR NECROSIS	ACUTE INTERSTITIAL NEPHRITIS	GLOMERULONEPHRITIS	OBSTRUCTION
Sediment	Bland	Broad, brownish granular casts	White blood cells, eosinophils, cellular casts	Red blood cells, red blood cell casts	Bland or bloody
Protein	None or low	None or low	Minimal but may be increased with NSAIDs	Increased, >100 mg/dL	Low
Urine sodium, mEq/L*	<20	>30	>30	<20	<20 (acute) >40 (few days)
Urine osmolality, mOsm/kg	>400	<350	<350	>400	<350
Fractional excretion of sodium %†	<1	>1	Varies	<1	<1 (acute) >1 (few days)

*The sensitivity and specificity of urine sodium of <20 mEq/L in differentiating prerenal azotemia from acute tubular necrosis are 90% and 82%, respectively.

†Fractional excretion of sodium is the urine:plasma (U:P) ratio of sodium divided by U:P of creatinine $\times 100$. The sensitivity and specificity of fractional excretion of sodium of $<1\%$ in differentiating prerenal azotemia from acute tubular necrosis are 96% and 95%, respectively.

NSAIDs, nonsteroidal antiinflammatory drugs.

From Singri N, Ahya SN, Levin ML: Acute renal failure, JAMA 289:747-751, 2003.

2544 Part XXIII ◆ Nephrology

CAUSES	% OF RECIPIENTS
Aplasia, hypoplasia, dysplasia	15.9
Obstructive uropathy	15.6
Focal segmental glomerulosclerosis	11.7
Reflux nephropathy	5.2
Chronic glomerulonephritis	3.3
Polycystic disease	2.9
Medullary cystic disease	2.8
Hemolytic-uremic syndrome	2.6
Prune belly syndrome	2.6
Congenital nephrotic syndrome	2.6
Familial nephritis	2.3
Cystinosis	2.0
Idiopathic crescentic glomerulonephritis	1.7
MPGN type I	1.7
Berger (IgA) nephritis	1.3
Henoch-Schönlein nephritis	1.1
MPGN type II	0.8

TYPE	CAUSE
Primary	Congenital incompetence of the valvular mechanism of the vesicoureteral junction
Primary associated with other malformations of the ureterovesical junction	Ureteral duplication Ureterocele with duplication Ureteral ectopia Paraureteral diverticula
Secondary to increased intravesical pressure	Neuropathic bladder Nonneuropathic bladder dysfunction Bladder outlet obstruction
Secondary to inflammatory processes	Severe bacterial cystitis Foreign bodies Vesical calculi Clinical cystitis
Secondary to surgical procedures involving the ureterovesical junction	Surgery

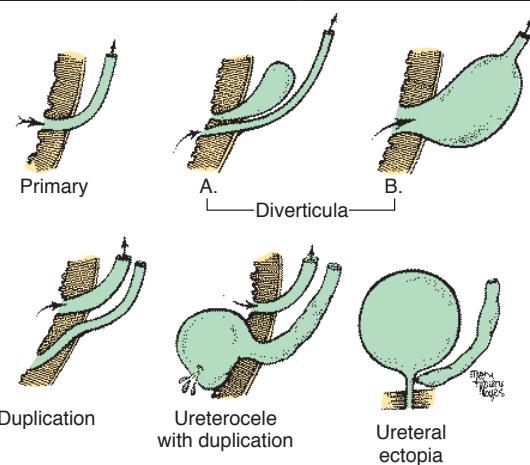


Figure 539-5 Various anatomic defects of the ureterovesical junction associated with vesicoureteral reflux.

MANIFESTATION	
Accumulation of nitrogenous waste products	Decrease in glomerular filtration rate
Acidosis	Decreased ammonia synthesis Impaired bicarbonate reabsorption Decreased net acid excretion
Sodium retention	Excessive renin production Oliguria
Sodium wasting	Solute diuresis Tubular damage
Urinary concentrating defect	Solute diuresis Tubular damage
Hyperkalemia	Decrease in glomerular filtration rate Metabolic acidosis Excessive potassium intake Hyporeninemic hypoaldosteronism
Renal osteodystrophy	Impaired renal production of 1,25-dihydroxycholecalciferol Hyperphosphatemia Hypocalcemia Secondary hyperparathyroidism
Growth retardation	Inadequate caloric intake Renal osteodystrophy Metabolic acidosis Anemia Growth hormone resistance
Anemia	Decreased erythropoietin production Iron deficiency Folate deficiency Vitamin B ₁₂ deficiency Decreased erythrocyte survival
Bleeding tendency	Defective platelet function
Infection	Defective granulocyte function Impaired cellular immune functions Indwelling dialysis catheters
Neurologic symptoms (fatigue, poor concentration, headache, drowsiness, memory loss, seizures, peripheral neuropathy)	Uremic factor(s) Aluminum toxicity Hypertension
Gastrointestinal symptoms (feeding intolerance, abdominal pain)	Gastroesophageal reflux Decreased gastrointestinal motility Serositis (uremia)
Hypertension	Volume overload Excessive renin production
Hyperlipidemia	Decreased plasma lipoprotein lipase activity
Pericarditis, cardiomyopathy	Uremic factor(s) Hypertension Fluid overload
Glucose intolerance	Tissue insulin resistance

Table 538-3 Guideline Recommendations for Diagnostic Evaluation Following a Febrile Urinary Tract Infection in Infants

GUIDELINE	ULTRASONOGRAPHY	VCUG	LATE DMSA SCAN
National Institute for Health And Care Excellence (NICE)*	(see Table 538-4)		
American Academy of Pediatrics	Yes	If abnormal ultrasonogram	No
Italian Society for Paediatric Nephrology (ISPN)	Yes	If abnormal ultrasonogram or if risk factors are present [†]	If abnormal ultrasonogram or VUR

*Upper urinary tract dilation on ultrasonography, poor urinary flow, infection with organism other than *E. coli*, or family history of vesicoureteral reflux.

[†]Abnormal antenatal ultrasonogram of fetal urinary tract, family history of reflux, septicemia, renal failure, age younger than 6 mo in a male infant, likely family noncompliance, incomplete bladder emptying, no clinical response to appropriate antibiotic therapy within 72 hr, or infection with organism other than *E. coli*.

DMSA, dimercaptosuccinic acid; VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux.

Table 538-4 Recommended Imaging Schedule for Children with Urinary Tract Infection

CHILD AGE AND TESTS	Type of Infection		
	RESPONDS WELL TO TREATMENT WITHIN 48 HR	ATYPICAL INFECTION	RECURRENT INFECTION
CHILDREN YOUNGER THAN 6 MO OLD			
Ultrasound scan during acute infection	No	Yes	Yes
Ultrasound scan within 6 wk of infection	Yes	No	No
DMSA scan 4-6 mo after acute infection	No	Yes	Yes
Micturating cystograms	Consider if ultrasound scan abnormal	Yes	Yes
CHILDREN 6 MO-3 YR OLD			
Ultrasound scan during acute infection	No	Yes	No
Ultrasound scan within 6 wk of infection	No	No	Yes
DMSA scan 4-6 mo after acute infection	No	Yes	Yes
Micturating cystograms	No	Not routine, consider if dilation on ultrasound, poor urine flow, non- <i>E. coli</i> infection, or family history of vesicoureteric reflux	
CHILDREN OLDER THAN AGE 3 YR			
Ultrasound scan during acute infection	No	Yes	No
Ultrasound scan within 6 wk of infection	No	No	Yes
DMSA scan 4-6 mo after acute infection	No	Yes	Yes
Micturating cystograms	No	No	No

DMSA, dimercaptosuccinic acid.

Adapted from National Institute for Health and Clinical Excellence. Urinary tract infection in children: diagnosis, treatment, and long-term management. NICE clinical guidelines, no. 54. London, 2007, RCOG Press, Tables 6-13, 6-14, and 6-15.

Table 540-3 The Etiology of Antenatal Hydronephrosis

ETIOLOGY	INCIDENCE
Transient hydronephrosis	41-88%
Ureteropelvic junction obstruction	10-30%
Vesicoureteral reflux	10-20%
Ureteroovesical junction obstruction/megaureters	5-10%
Multicystic dysplastic kidney	4-6%
Posterior urethral valve/urethral atresia	1-2%
Ureterocele/ectopic ureter/duplex system	5-7%
Others: prune belly syndrome, cystic kidney disease, congenital ureteric strictures, and megalourethra	Uncommon

From Nguyen HT, Herndon CDA, Cooper C, et al: The society for fetal urology consensus statement on the evaluation and management of antenatal hydronephrosis. *J Pediatr Urol* 6:212-231, 2010, Table 5, p. 217.

Table 540-4 Society for Fetal Urology Grading System for Hydronephrosis

GRADE OF HYDRONEPHROSIS	Renal Image	
	CENTRAL RENAL COMPLEX	RENAL PARENCHYMAL THICKNESS
0	Intact	Normal
1	Slight splitting	Normal
2	Evident splitting, complex confined within renal border	Normal
3	Wide splitting pelvis dilated outside renal border, calyces uniformly dilated	Normal
4	Further dilation of pelvis and calyces (calyces may appear convex)	Thin

After Maizels M, Mitchell B, Kass E, et al: Outcome of nonspecific hydronephrosis in the infant: a report from the registry of the Society for Fetal Urology. *J Urol* 152:2324-2327, 1994.

Table 543-1 Causes of Urinary Incontinence in Childhood

Overactive bladder (urge incontinence or diurnal urge syndrome)
Infrequent voiding (underactive bladder)
Voiding postponement
Detrusor-sphincter dyssynergia
Nonneurogenic neurogenic bladder (Hinman syndrome)
Vaginal voiding
Giggle incontinence
Cystitis
Bladder outlet obstruction (posterior urethral valves)
Ectopic ureter and fistula
Sphincter abnormality (epispadias, exstrophy; urogenital sinus abnormality)
Neuropathic
Overflow incontinence
Traumatic
Iatrogenic
Behavioral
Combinations

Table 540-2 Definition of Antenatal Hydronephrosis by Anterior-Posterior Diameter

DEGREE OF ANTEPARTUM HYDRONEPHROSIS	SECOND TRIMESTER	THIRD TRIMESTER
Mild	4 to <7 mm	7 to <9 mm
Moderate	7 to ≤10 mm	9 to ≤15 mm
Severe	>10 mm	>15 mm

From Nguyen HT, Herndon CDA, Cooper C, et al: The society for fetal urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol 6:212–231, 2010, Table 2, p. 215.

Table 540-1 Types and Causes of Urinary Tract Obstruction

LOCATION	CAUSE
Infundibula	Congenital Calculi Inflammatory (tuberculosis) Traumatic Postsurgical Neoplastic
Renal pelvis	Congenital (infundibulopelvic stenosis) Inflammatory (tuberculosis) Calculi Neoplasia (Wilms tumor, neuroblastoma)
Ureteropelvic junction	Congenital stenosis Calculi Neoplasia Inflammatory Postsurgical Traumatic
Ureter	Congenital obstructive megaureter Midureteral structure Ureteral ectopia Ureterocele Retrocaval ureter Ureteral fibroepithelial polyps Ureteral valves Calculi Postsurgical Extrinsic compression Neoplasia (neuroblastoma, lymphoma, and other retroperitoneal or pelvic tumors) Inflammatory (Crohn disease, chronic granulomatous disease) Hematoma, urinoma Lymphocele Retroperitoneal fibrosis
Bladder outlet and urethra	Neurogenic bladder dysfunction (functional obstruction) Posterior urethral valves Anterior urethral valves Diverticula Urethral strictures (congenital, traumatic, or iatrogenic) Urethral atresia Ectopic ureterocele Meatal stenosis (males) Calculi Foreign bodies Phimosis Extrinsic compression by tumors Urogenital sinus anomalies

Table 540-5 Classification of Megareter

Refluxing		Obstructed		Nonrefluxing and Nonobstructed	
PRIMARY	SECONDARY	PRIMARY	SECONDARY	PRIMARY	SECONDARY
Primary reflux	Neuropathic bladder	Intrinsic (primary obstructed megareter)	Neuropathic bladder	Nonrefluxing, nonobstructive	Diabetes insipidus
Megacystic-megareter syndrome	Hinman syndrome	Ureteral valve	Hinman syndrome		Infection
Ectopic ureter	Posterior urethral valves	Ectopic ureter	Posterior urethral valves		Persistent after relief of obstruction
Prune-belly syndrome	Bladder diverticulum Postoperative	Ectopic uterocele	Ureteral calculus Extrinsic Postoperative		

Patient name: Hospital number: Reason for referral: Date:					
Over the last month	Almost never	Less than half the time	About half the time	Almost every time	Not available
1. I have had wet clothes or wet underwear during the day.	0	1	2	3	NA
2. When I wet myself, my underwear is soaked.	0	1	2	3	NA
3. I miss having a bowel movement every day.	0	1	2	3	NA
4. I have to push for my bowel movements to come out.	0	1	2	3	NA
5. I only go to the bathroom one or two times each day.	0	1	2	3	NA
6. I can hold onto my pee by crossing my legs, squatting or doing the "pee dance."	0	1	2	3	NA
7. When I have to pee, I cannot wait.	0	1	2	3	NA
8. I have to push to pee.	0	1	2	3	NA
9. When I pee it hurts.	0	1	2	3	NA
10. Parents to answer. Has your child experienced something stressful like the example below?	No (0)			Yes (3)	
Total*					
<ul style="list-style-type: none"> • New baby. • New home. • New school. • School problems. • Abuse (sexual/physical). • Home problems (divorce/death). • Special events (birthday). • Accident/injury. • Others. 	*Females with a score ≥6 and males with a score ≥9 are most likely to have dysfunctional voiding.				

Figure 543-1 Dysfunctional Voiding Symptom Score questionnaire. (From Farhat W, Bagli DJ, Capolicchio G, et al: The dysfunctional voiding scoring system: quantitative standardization of dysfunctional voiding symptoms in children, J Urol 164:1011–1015, 2000.)

Table 543-3 Differential Diagnosis of Scrotal Swelling in Newborn Boys

Hydrocele	Scrotal hematoma
Inguinal hernia (reducible)	Testicular tumor
Inguinal hernia (incarcerated)*	Meconium peritonitis
Testicular torsion*	Epididymitis*

Table 546-1 Grading of Renal Injuries

GRADE	DESCRIPTION
1	Renal contusion or subcapsular hematoma
2	Nonexpanding perirenal hematoma, <1 cm parenchymal laceration, no urinary extravasation; all renal fragments viable; confined to renal retroperitoneum
3	Nonexpanding perirenal hematoma, >1 cm parenchymal laceration, no urinary extravasation; renal fragments may be viable or devitalized
4	Laceration extending into the collecting system with urinary extravasation; renal fragments may be vital or devitalized or Injury to the main renal vasculature with contained hemorrhage
5	Completely shattered kidney; by definition multiple major lacerations >1 cm associated with multiple devitalized fragments or Injury to the main renal vasculature with uncontrolled hemorrhage, renal hilar avulsion

Table 543-2 Nocturnal Enuresis

CAUSES

Delayed maturation of the cortical mechanisms that allow voluntary control of the micturition reflex
Defective sleep arousal
Reduced antidiuretic hormone production at night, resulting in an increased urine output (nocturnal polyuria)
Genetic factors, with chromosomes 12 and 13q the likely sites of the gene for enuresis
Bladder factors (lack of inhibition, reduced capacity, overactive)
Constipation
Organic factors, such as urinary tract infection or obstructive uropathy
Sleep disorders
Sleep disordered breathing secondary to enlarged adenoids
Psychologic factors more often implicated in secondary enuresis

OTHER FEATURES

Enuresis can occur in any stage of sleep (but usually non-rapid eye movement sleep)
All children are most difficult to arouse in the first third of the night and easiest to awaken in the last third, but enuretic children are more difficult to arouse than those with normal bladder control
Enuretic children often are described as "soaking the bed"
Family history in enuretic children often positive for enuresis
Risk increased with developmental delay, attention-deficit/hyperactivity disorder, autism spectrum disorders

Table 547-1 Classification of Urolithiasis

CALCIUM STONES (CALCIUM OXALATE AND CALCIUM PHOSPHATE)*	
Hypercalciuria	Absorptive: increased Ca absorption from gut; types I and II
Renal leak: decreased tubular reabsorption of Ca	
Resorptive	
Primary hyperparathyroidism (rare in children)	
Iatrogenic	
Loop diuretics	
Ketogenic diet	
Corticosteroids	
Adrenocorticotrophic hormone administration	
Methylxanthines (theophylline, aminophylline)	
Distal renal tubular acidosis, type 1 (calcium phosphate)	
Hypocitraturia—citrate most important inhibitor of Ca crystallization	
Vitamin D excess	
Immobilization	
Sarcoidosis	
Cushing disease	
Hyperuricosuria	
Heterozygous cystinuria	
Hyperoxaluria (calcium oxalate)	
Primary hyperoxaluria, types 1 and 2	
Secondary hyperoxaluria	
Enteric hyperoxaluria	
CYSTINE STONES	
Cystinuria	
STRUVITE STONES (MAGNESIUM AMMONIUM PHOSPHATE)	
Urinary tract infection (urea-splitting organism)	
Foreign body	
Urinary stasis	
URIC ACID STONES	
Hyperuricosuria	
Lesch-Nyhan syndrome	
Myeloproliferative disorders	
After chemotherapy	
Inflammatory bowel disease	
INDINAVIR STONES	
MELAMINE	
NEPHROCALCINOSIS	

Table 547-2 Laboratory Tests Suggested for Evaluation of Urolithiasis

SERUM	URINE
Calcium	Urinalysis
Phosphorus	Urine culture
Uric acid	Calcium: creatinine ratio
Electrolytes and anion gap	Spot test for cystinuria
Creatinine	24 hr collection for:
Alkaline phosphatase	Creatinine clearance
	Calcium
	Phosphate
	Oxalate
	Uric acid
	Dibasic amino acids (if cystine spot test result is positive)

Table 545-2 Differential Diagnosis of Scrotal Masses in Boys and Adolescents

PAINFUL	PAINLESS
Testicular torsion	Hydrocele
Torsion of appendix testis	Inguinal hernia*
Epididymitis	Varicocele*
Trauma: ruptured testis, hematocele	Spermatocele*
Inguinal hernia (incarcerated)	Testicular tumor*
Mumps orchitis	Henoch-Schönlein purpura*
Testicular vasculitis	Idiopathic scrotal edema

*May be associated with discomfort.

Table 545-1 American Urological Association Guidelines for Evaluation and Treatment of Boys with an Undescended Testis

DIAGNOSIS
Primary care providers should palpate testes for quality and position at each recommended well-child visit. (Standard)
Providers should refer infants with a history of cryptorchidism (detected at birth) who do not have spontaneous testicular descent by 6 mo (corrected for gestational age) to an appropriate surgical specialist for timely evaluation. (Standard)
Providers should refer boys with the possibility of newly diagnosed (acquired) cryptorchidism after 6 mo. (Standard)
Providers must immediately consult an appropriate specialist for all phenotypic male newborns with bilateral, nonpalpable testes for evaluation of a possible disorder of sex development (DSD). (Standard)
Providers should not perform ultrasound (US) or other imaging modalities in the evaluation of boys with cryptorchidism before referral because these studies rarely assist in decision making. (Standard)
Providers should assess the possibility of a disorder of sex development (DSD) when there is increasing severity of hypospadias with cryptorchidism. (Recommendation)
In boys with retractile testes, providers should monitor the position of the testes at least annually to monitor for secondary ascent. (Standard)
TREATMENT
Providers should not use hormonal therapy to induce testicular descent, since evidence shows low response rates and lack of evidence for long-term efficacy. (Standard)
In the absence of spontaneous testicular descent by 6 mo (corrected for gestational age), specialists should perform surgery within the next year. (Standard)
In prepubertal boys with nonpalpable testes, surgical specialists should perform examination under anesthesia to reassess for palpability of testes. If nonpalpable, surgical exploration and, if indicated, abdominal orchidopexy should be performed. (Standard)
In boys with a normal contralateral testis, surgical specialists may perform an orchiectomy (removal of the undescended testis) if a boy has a normal contralateral testis and either very short testicular vessels and vas deferens, dysmorphic or very hypoplastic testis, or postpubertal age. (Clinical Principle)
Providers should counsel boys with a history of cryptorchidism and/or monorchidism and their parents regarding potential long-term risks and provide education on infertility and cancer risk. (Clinical Principle)

Adapted from Kolon TF, Herndon CDA, Baker LA, et al: Evaluation and treatment of cryptorchidism: AUA Guideline. <http://www.auanet.org/common/pdf/education/clinical-guidance/Cryptorchidism.pdf>

URINE CONSTITUENT	AGE	RANDOM	TIMED	COMMENTS
Calcium	0-6 mo 7-12 mo ≥2 yr	<0.8 mg/mg creat <0.6 mg/mg creat <0.21 mg/mg creat	<4 mg/kg/24 hr	Prandial variation Sodium-dependent
Oxalate*	<1 yr	0.15-0.26 mmol/mmol creat	≥2 yr: <0.5 mmol/1.73 m ² /24 hr	Random urine mmol/mmol highly age-dependent Excretion rate/1.73 m ² constant through childhood and adulthood
	1-5 yr	0.11-0.12 mmol/mmol creat		
	5-12 yr >12 yr	0.006-0.15 mmol/mmol creat 0.002-0.083 mmol/mmol creat		
Uric acid	Term infant	3.3 mg/dL GFR [†]	<815 mg/1.73 m ² /24 hr	Excretion rate/1.73 m ² from >1 yr age; constant through childhood
	>3 yr	<0.53 mg/dL GFR		
Magnesium	>2 yr	<0.12 mg/mg creat	<88 mg/1.73 m ² /24 hr	Excretion rate/1.73 m ² constant through childhood
Citrate		>400 mg/g creat		Limited data available for children
Cystine		<75 mg/g creat	<60 mg/1.73 m ² /24 hr	Cystine >250 mg/g creat suggests homozygous cystinuria

*Oxalate oxidase assay.

[†](mg/dL uric acid) (serum creatinine concentration/urine creatinine concentration).

creat, Creatinine; GFR, glomerular filtration rate.

From Milliner DS: *Urolithiasis*. In Avner ED, Harmon WE, Naiudet P, editors: *Pediatric nephrology*, ed 5, Philadelphia, 2004, Lippincott Williams & Wilkins, p. 1103, with permission.

Table 547-4 Metabolic Evaluation of Children with Hypercalcemia

TYPE	SERUM CALCIUM	RESTRICTED CALCIUM (URINE)	FASTING CALCIUM (URINE)	CALCIUM LOAD (URINE)	PARATHYROID HORMONE (SERUM)
Absorptive	N	N or I	N	I	I
Renal	N	I	I	I	N
Resorptive	I	I	I	I	I

I, increased; N, normal.

Table 547-5 Primary Surgical Treatment Options vs Stone Size and Location

STONES	SHOCK WAVE LITHOTRIPSY	URETEROSCOPY	PERCUTANEOUS NEPHROLITHOTOMY
RENAL			
<1 cm	Most common	Optional	Optional
1-2 cm	Most common	Optional	Optional
>2 cm	Optional	Rare	Most common
LOWER POLE			
<1 cm	Most common	Optional	Optional
>1 cm	Optional	Optional	Most common
URETERAL			
Proximal	Most common	Optional	Occasional
Distal	Optional	Most common	Rare

Table 548-1 Suggested Indications for Pelvic Examination in Adolescents

- Age 21 yr for initial Pap test
- Unexplained menstrual irregularities, including pubertal aberrations
- Severe dysmenorrhea
- Unexplained abdominal pain
- Unexplained dysuria
- Abnormal vaginal discharge
- Placement of intrauterine device
- Removal of foreign body

Modified from The initial reproductive visit. Committee Opinion No. 460. American College of Obstetricians and Gynecologists. Obstet Gynecol 116:240-243, 2010.

Table 548-2 Recommendations for First Gynecologic Evaluation

- Between 13 and 15 yr of age
- First gynecologic encounter focuses on patient education; pelvic examination is generally not indicated
- First pelvic examination with Pap test at 21 yr of age, unless otherwise indicated by Table 548-1

Table 547-6 Suggested Therapy for Urolithiasis Caused by Metabolic Abnormalities

METABOLIC ABNORMALITY	INITIAL TREATMENT	SECOND-LINE TREATMENT
Hypercalciuria	Reduction of dietary Na ⁺ Dietary calcium at RDA Thiazides	Potassium citrate Neutral phosphate
Hyperoxaluria	Adjustment of dietary oxalate Potassium citrate	Neutral phosphate* Magnesium Pyridoxine*
Hypocitruc aciduria	Potassium citrate Bicarbonate	
Hyperuricosuria	Alkalization	Allopurinol
Cystinuria	Alkalization Reduction of dietary Na ⁺	Tiopronin (Thiola) D-Penicillamine Captopril

*Initial therapy in primary hyperoxaluria.

Gynecologic Problems of Childhood

Table 549-1 Specific Vulvar Disorders in Children

ORGANISM	PRESENTATION	DIAGNOSIS	TREATMENT
Molluscum contagiosum (Fig. 549-7)	1-5 mm discrete, skin-colored, dome-shaped, umbilicated lesions with a central cheesy plug	Diagnosis usually is made by visual inspection	The disease generally is self-limited and the lesions can resolve spontaneously. Treatment choices in children may include cryosurgery, laser, application of topical anesthetic and curettage, podophyllotoxin, and topical silver nitrate. Use of topical 5% imiquimod cream and 10% potassium hydroxide has been reported with similar effects.
Condyloma acuminata	Skin-colored papules, some with a shaggy, cauliflower-like appearance	Diagnosis usually is made by visual inspection. Biopsy should be reserved for when the diagnosis is in question. Human papillomavirus DNA testing is not helpful	Many lesions in children resolve spontaneously, "wait and see" often utilized in children (60 days). Topical treatment with imiquimod cream and podophyllotoxin is the most studied (daily qhs 3 times/wk × 16 wk, wash 6-10 hr after application). General anesthesia is usually required for surgical/ablative procedures (cryotherapy, laser therapy, electrocautery)—reserve for symptomatic or large lesions. Other treatments have been utilized in adults, including trichloroacetic acid, 5-fluorouracil, sinecatechins, topical cidofovir, and cimetidine. The efficacy and safety of these treatments in children has not been established
Herpes simplex	Blisters that break, leaving tender ulcers	Visual inspection confirmed by culture from lesion	Infants: Acyclovir 20 mg/kg body weight IV q8 hr × 21 days for disseminated and central nervous system disease or × 14 days for disease limited to the skin and mucous membranes <i>Genital/mucocutaneous disease:</i> Age 3 mo–2 yr: 15 mg/kg/day IV divided in q8h × 5-7 days Age 2–12 yr (1st episode): Same as above or 1,200 mg/day divided in q8h dosing × 7–10 days Age 2–12 yr (Recurrence): 1,200 mg/day in q8h dosing or 1,600 mg/day in bid dosing × 5 days (give 3–5 days for children older than 12 yr)

Table 552-4 Causes of Hirsutism

PERIPHERAL
Idiopathic
Partial androgen insensitivity (5α-reductase deficiency)
HAIR-AN syndrome (hirsutism, androgenization, insulin resistance, and acanthosis nigricans)
Hyperprolactinemia
GONADAL
Polycystic ovary syndrome (polycystic ovaries, chronic anovulation)
Ovarian neoplasm (Sertoli-Leydig cell, granulosa cell, thecoma, gynandroblastoma, lipoid cell, luteoma, hypernephroma, Brenner tumor)
Gonadal dysgenesis (Turner mosaic with XY or H-Y antigen-positive)
ADRENAL
Cushing syndrome
Adrenal hyperresponsiveness
Congenital adrenal hyperplasia (classic, cryptic, adult onset)
21-Hydroxylase deficiency
11-Hydroxylase deficiency
3β-Hydroxysteroid deficiency
17β-Hydroxylase deficiency
Adrenal neoplasm (adenoma, cortical carcinoma)
EXOGENOUS
Minoxidil
Dilantin
Cyclosporine
Anabolic steroids
Acetazolamide (Diamox)
Penicillamine
Oral contraceptives with androgenic progestins
Danazol
Androgenic steroids
Psoralens
Hydrochlorothiazide
Phenothiazines
CONGENITAL ANOMALIES
Trisomy 18 (Edwards syndrome)
Cornelia de Lange syndrome
Hurler syndrome
Juvenile hypothyroidism

Table 549-1 Specific Vulvar Disorders in Children—cont'd

ORGANISM	PRESENTATION	DIAGNOSIS	TREATMENT
Labial agglutination (see Fig. 549-1)	May be asymptomatic or can cause vulvitis, urinary dribbling, urinary tract infection, or urethritis	Diagnosis is made by visual inspection of the adherent labia, often with a central semitranslucent line	Does not require treatment if the patient is asymptomatic <i>Symptomatic patients:</i> Topical estrogen cream or betamethasone ointment applied alone or in combination daily for 6 wk directly to the line of adhesion, using a cotton swab while applying gentle labial traction Estrogen should be interrupted if breast budding occurs Mechanical or surgical separation of the adhesions is rarely indicated The adhesions usually resolve in 6-12 wk; unless good hygiene measures are followed, reoccurrence is common To decrease the risk of recurrence, an emollient (petroleum jelly, A and D ointment) should be applied to the inner labia for 1 mo or longer at bedtime
Lichen sclerosus (Fig. 549-4)	A sclerotic, atrophic, parchment-like plaque with an hourglass or keyhole appearance of vulvar, perianal, or perineal skin, subepithelial hemorrhages may be misinterpreted as sexual abuse or trauma The patient can experience perineal itching, soreness, or dysuria	Diagnosis usually is made by visual inspection Biopsy should be reserved for when the diagnosis is in question	Utrapotent topical corticosteroids are the first-line therapy (clobetasol propionate ointment 0.05%) once or twice a day for 4-8 wk Once symptoms are under control, the patient should be tapered off the drug unless therapy is required for a flare-up In many girls, the condition resolves with puberty; however, this is not always the case and patients may require long-term follow-up
Psoriasis	Children are more likely than adults to have vulvar psoriasis noted as pruritic, well-demarcated, nonscaly, brightly erythematous, symmetrical plaques. The classic extragenital lesion are similar but with a silver scaly appearance	Diagnosis may be confirmed by locating other affected areas on the scalp or in nasolabial folds or behind the ears	Vulvar lesions may be treated with low to medium potency topical corticosteroids, increasing strength as necessary
Atopic dermatitis	Chronic cases can result in crusty, weepy lesions that are accompanied by intense pruritus and erythema Scratching often results in excoriation of the lesions and secondary bacterial or candidal infection	It may be seen in the vulvar area but characteristically affects the face, neck, chest, and extremities	Children with this condition should avoid common irritants and use topical corticosteroids (such as 1% hydrocortisone) for flare-ups If dry skin is present, lotion or bath oil can be used to seal in moisture after bathing
Contact dermatitis	Erythematous, edematous, or weepy vulvar vesicles or pustules can result, but more often the skin appears inflamed	Associated with exposure to an irritant, such as perfumed soaps, bubble bath, talcum powder, lotions, elastic bands of undergarments, or disposable diaper components	Avoidance of irritant Topical corticosteroids for flare-ups
Seborrheic dermatitis	Erythematous and greasy, yellowish scaling on vulva and labial crural folds associated with greasy dandruff-type rash of scalp, behind ears and face	Diagnosis usually is made by visual inspection	Gentle cleaning, topical clotrimazole with 1% hydrocortisone added
Vitiligo (Fig. 549-5)	Sharply demarcated hypopigmented patches, often symmetric in vaginal and anal regions. May be present in periphery at body orifices and extensor surfaces	Clinical. Test for associated illness if clinically warranted (thyroid disease, Addison disease, pernicious anemia, diabetes mellitus)	If desired, treat limited lesions with low-potency corticosteroids or tacrolimus. See dermatologist for extensive lesions.

2610 Part XXV ◆ Gynecologic Problems of Childhood

Table 549-2 Antibiotic Recommendations for Specific Vulvovaginal Infections

ETIOLOGY	TREATMENT
<i>Streptococcus pyogenes</i> <i>Streptococcus pneumoniae</i>	Penicillin V, 250 mg PO bid-tid × 10 days Amoxicillin 50 mg/kg/day (max: 500 mg/dose) divided into 3 doses daily × 10 days Erythromycin ethyl succinate, 30-50 mg/kg/day (max: 400 mg/dose) divided into 4 doses daily TMP-SMX 6-10 mg/kg/day (TMP component) divided into 2 doses daily × 10 days Clarithromycin 7.5 mg/kg bid (max: 1 g/day) × 5-10 days Reoccurrence most likely from asymptomatic pharyngeal carriage in child or family member. However, failure of penicillin regimens can occur For penicillin resistance: Rifampin 10 mg/kg every 12 hr × 2 days
<i>Staphylococcus aureus</i>	Topical mupirocin 2% 3 times daily to the affected skin area If systemic therapy required: Amoxicillin-clavulanate, 45 mg/kg/day (amoxicillin) PO divided into 2 or 3 doses daily × 7 days (first-line treatment because of high penicillin resistance) Extensive resistance to common antibiotics noted, recommend susceptibility testing for further antibiotic use MRSA: TMP-SMX double-strength 8-10 mg/kg/day; culture abscesses, incision and drainage
<i>Haemophilus influenzae</i>	Amoxicillin, 40 mg/kg/day divided into 3 doses daily × 7 days Cases of treatment failure or non-encapsulated <i>H. influenzae</i> , amoxicillin-clavulanate is recommended
<i>Yersinia</i>	TMP-SMX 6 mg/kg (TMP component) daily for 3 days
<i>Shigella</i>	TMP-SMX 10/50 mg/kg/day (max: 160/600) divided into 2 doses daily × 5 days Ampicillin 50-100 mg/kg/day divided into 4 doses daily (adult max: 4 g/day) × 5 days Azithromycin 12 mg/kg (max: 500) × 1 day, then 6 mg/kg/day (max: 250 mg) × 4 days (in areas of high resistance to above regimens or when sensitivities are unknown) For resistant organisms: Ceftriaxone 50-75 mg/kg/day IV or IM divided into 1 or 2 doses (max: 2 g/day) × 2-5 days
<i>Chlamydia trachomatis</i>	Children weighing <45 kg: Erythromycin base or ethylsuccinate 50 mg/kg/day PO divided into 4 daily doses × 14 days Children weighing >45 kg but age younger than 8 yr: azithromycin 1 g PO in a single dose Children age older than 8 yr (treat per adult regimens): Preferred regimens: Azithromycin 1 g PO in a single dose or Doxycycline 100 mg PO twice daily × 7 days Alternative regimens: Erythromycin base 500 mg PO 4 times daily × 7 days Erythromycin ethylsuccinate 800 mg PO 4 times daily × 7 days Levofloxacin 500 mg PO daily × 7 days Ofloxacin 300 mg PO twice daily for 7 days
<i>Neisseria gonorrhoeae</i>	Children weighing <45 kg: Ceftriaxone, 125 mg IM in a single dose Children weighing ≥45 kg: Treat with adult regimen of 250 mg IM in a single dose Children with bacteremia or arthritis: Ceftriaxone, 50 mg/kg (max dose for children weighing <45 kg: 1 g) IM or IV in a single dose daily × 7 days Dual treatment: Addition of either azithromycin 1 g PO in a single dose or doxycycline 100 mg PO twice daily × 7 days to the above regimens may assist in hindering the development of antibiotic resistance. Note: The CDC removed cefixime 400 mg PO in a single dose from recommended medications because of increasing resistance; however, can be used as part of a dual therapy if ceftriaxone is unavailable
<i>Trichomonas</i>	Metronidazole, 15-30 mg/kg/day tid (max: 250 mg tid) × 5-7 days or Tinidazole 50 mg/kg (<2 g) as a single dose for children older than 3 yr
Pinworms (<i>Enterobius vermicularis</i>)	Mebendazole (Vermox), 1 chewable 100 mg tablet, repeated in 2 wk or Albendazole, 100 mg for child younger than age 2 yr or 400 mg for older child, repeated in 2 wk Pyrantel pamoate 10 mg/kg in a single administration

MRSA, methicillin-resistant *Staphylococcus aureus*; TMP-SMX, trimethoprim-sulfamethoxazole.

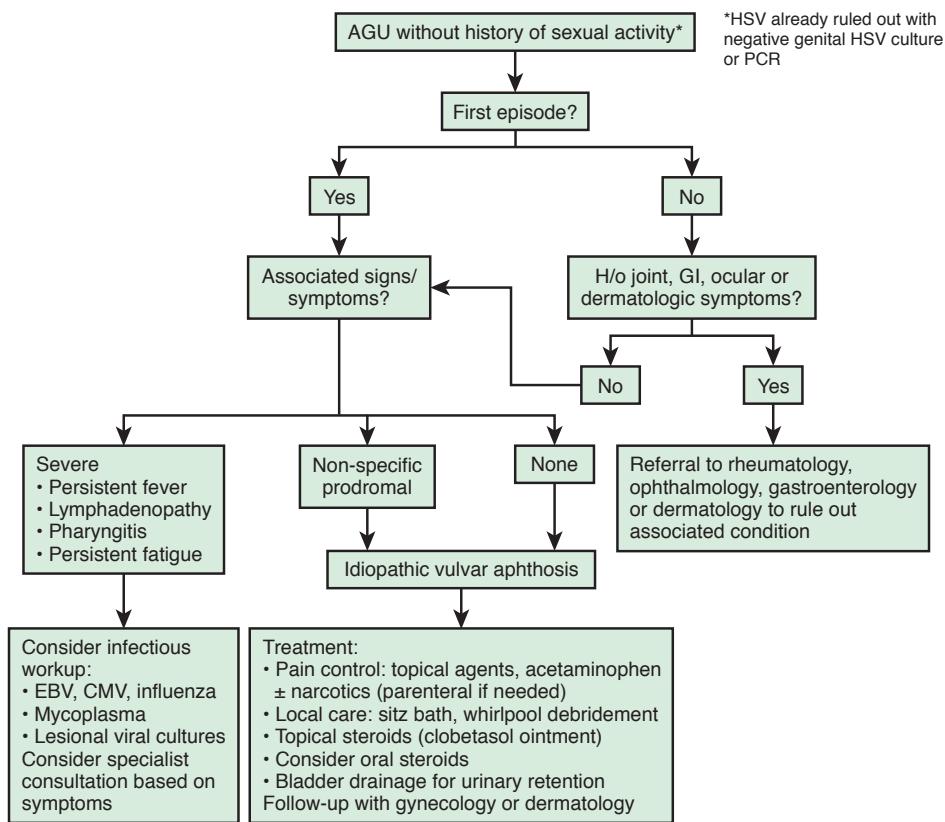


Figure 549-3 Algorithm for evaluation and management of acute genital ulcers in nonsexually active young girls. (From Rosman IS, Berk DR, Bayliss SJ, et al: Acute genital ulcers in nonsexually active young girls: case series, review of the literature, and evaluation and management recommendations. *Pediatr Dermatol* 29(2):147–153, 2012.)

Table 551-2 Common Causes of Nipple Discharge

Pregnancy
Medicines
Hormones (oral contraceptives, estrogen, progesterone)
Blood pressure drugs (methyldopa, verapamil)
Tricyclic antidepressants
Tranquilizers (antipsychotics)
Antinausea drugs (metoclopramide)
Herbs (nettle, fennel, blessed thistle, anise, fenugreek seed)
Illicit drugs (marijuana, opiates)
Stimulation of the breast (sexual or from exercise)
Thyroid abnormalities
Chronic emotional stress
Hypothalamic tumors
Chest wall conditions
Herpes zoster
Trauma
Burns
Tumors
Breast conditions
Mammary duct ectasia
Chronic cystic mastitis
Intraductal cysts
Intraductal papillomas

Table 551-3 Breast Masses in the Adolescent Girl

BENIGN
Fibroadenoma
Fibrocystic changes or cysts
Unilateral thelarche
Hemangioma
Intramammary lymph node
Fat necrosis
Abscess
Mastitis
Lipoma
Hematoma
Hamartoma
Macromastia (juvenile hypertrophy)
Galactocele
Intraductal papilloma
Juvenile papillomatosis
Lymphangioma
MALIGNANT
Malignant cystosarcoma phyllodes
Breast carcinoma
Metastatic disease
Lymphoma, neuroblastoma, sarcoma, rhabdomyosarcoma, acute leukemia

Table 553-2 Malignant Ovarian Tumors in Children and Adolescents

TUMOR	OVERALL 5-YR SURVIVAL	CLINICAL FEATURES
GERM CELL TUMORS		
Dysgerminoma	85%	10-20% bilateral Most common ovarian malignancy Gonadal dysgenesis/androgen insensitivity Sensitive to chemotherapy/radiation
Immature teratoma	97-100%	All 3 germ layers present
Endodermal sinus tumor	80%	Almost always large (>15 cm) Schiller-Duval bodies
Choriocarcinoma	30%	Rare Can mimic ectopic pregnancy
Embryonal carcinoma	25%	Endocrinologic symptoms (precocious puberty) Highly malignant
Gonadoblastoma	100%	Primary amenorrhea Virilization 45,X or 45,X/46,XY mosaicism
SEX CORD STROMAL TUMORS		
Juvenile granulosa stroma cell tumor	92%	Produce estrogen Menstrual irregularities Isosexual precocious pseudopuberty Call-Exner bodies rare
Sertoli-Leydig cell tumor	70-90%	Virilization in 40% Produce testosterone
Lipoid cell tumors	~80%	Rare heterogeneous group with lipid-filled parenchyma
Gynandroblastoma	90% or greater	Rare low-grade mixed tumors that produce either estrogen or androgen

Table 553-3 Serum Tumor Markers

TUMOR	CA-125	AFP	hCG	LDH	E2	T	INHIBIN	MIS	VEGF	DHEA
Epithelial tumor	+									
Immature teratoma	+	+			+					+
Dysgerminoma			+	+	+					
Endodermal sinus tumor		+								
Embryonal carcinoma	+	+			+					
Choriocarcinoma			+							
Mixed germ cell		+	+	+						
Granulosa cell tumor	+				+		+	+		
Sertoli-Leydig						+	+			
Gonadoblastoma					+	+	+			+
Theca-fibroma										+

AFP, α -fetoprotein; CA-125, cancer antigen 125; DHEA, dehydroepiandrosterone; E2, estradiol; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; T, testosterone, MIS, müllerian inhibiting substance; VEGF, vascular endothelial growth factor.

Table 554-1 Common Müllerian Anomalies

ANOMALY	DESCRIPTION
Hydrocolpos	Accumulation of mucus or nonsanguineous fluid in the vagina
Hemihematometra	Aretic segment of vagina with menstrual fluid accumulation
Hydrosalpinx	Accumulation of serous fluid in the fallopian tube, often an end result of pyosalpinx
Didelphic uterus	Two cervixes, each associated with 1 uterine horn
Bicornuate uterus	One cervix associated with 2 uterine horns
Unicornuate uterus	Result of failure of 1 müllerian duct to descend

Table 555-1 Health Consequences of Female Genital Mutilation**IMMEDIATE RISKS**

Pain, shock (caused by pain or hemorrhage, or both), excessive bleeding, difficulty passing urine or feces, infection (including tetanus inoculation and the transmission of bloodborne viruses such as HIV, hepatitis B, and hepatitis C), psychologic consequences (as a result of pain, shock, or physical restraint), unintended labial fusion, death (caused by hemorrhage or infection).

LONG-TERM RISKS

Pain (chronic neuropathic pain), keloid scarring, infections (including chronic pelvic infections, recurrent urinary tract infections, and an increased incidence of certain genital infections), birth complications (cesarean section, postpartum hemorrhage, and episiotomy), danger to the newborn (including death), decreased quality of sexual life, psychologic consequences (including posttraumatic stress disorder, depression, and anxiety)

LONG-TERM RISKS PARTICULAR TO TYPE 3 FEMALE GENITAL MUTILATION

Need for later surgery (deinfibulation), urinary and menstrual problems, painful sexual intercourse, and infertility

From Simpson J, Robinson K, Creighton SM, Hodes D: Female genital mutilation: the role of health professionals in prevention, assessment, and management. BMJ 344:e1361, 2012, Box 3.

The Endocrine System

2636 Part XXVI ◇ The Endocrine System

Table 557-4 Proposed Classification of Growth Hormone Insensitivity

Primary GH insensitivity (hereditary defects)
GH receptor defect (may be positive or negative for GH-binding protein)
• Extracellular mutation (e.g., Laron syndrome)
• Cytoplasmic mutation
• Intracellular mutation
GH signal transduction defects (distal to cytoplasmic domain of GH receptor)
• Stat5b mutations
Insulin-like growth factor-1 defects
• IGF-1 gene deletion
• IGF-1 transport defect (ALS mutation)
• IGF-1 receptor defect
Bioactive GH molecule (responds to exogenous GH)
Secondary GH insensitivity (acquired defects)
• Circulating antibodies to GH that inhibit GH action
• Antibodies to the GH receptor
• GH insensitivity caused by malnutrition, liver disease, catabolic states, diabetes mellitus
• Other conditions that cause GH insensitivity

GH insensitivity: Clinical and biochemical features of IGF-1 deficiency and insensitivity to exogenous GH, associated with GH secretion that would not be considered abnormally low.

GH insensitivity syndrome: GH insensitivity associated with the recognizable dysmorphic features described by Laron.

Partial GH insensitivity: GH insensitivity in the absence of dysmorphic features described by Laron.

ALS, acid labile subunit; GH, growth hormone; IGF, insulin-like growth factor.

From Sperling MA: Pediatric endocrinology, ed 4, Philadelphia, 2014, Elsevier, Box 10-4, p. 347.

Table 557-5 Causes of Acquired Hypopituitarism**BRAIN DAMAGE***

- Traumatic brain injury
- Subarachnoid hemorrhage
- Neurosurgery
- Irradiation
- Stroke

PITUITARY TUMORS*

- Adenomas
- Others

NONPITUITARY TUMORS

- Craniopharyngiomas
- Meningiomas
- Gliomas
- Chordomas
- Ependymomas
- Metastases

INFECTION

- Abscess
- Hypophysitis
- Meningitis
- Encephalitis

INFARCTION

- Apoplexy
- Sheehan syndrome

AUTOIMMUNE DISORDER

- Lymphocytic hypophysitis

OTHER

- Hemochromatosis, granulomatous diseases, histiocytosis
- Empty sella
- Perinatal insults

*Pituitary tumors are classically the most common cause of hypopituitarism. However, new findings imply that causes related to brain damage might outnumber pituitary adenomas in causing hypopituitarism.

From Schneider HJ, Aimaretti G, Kreitschmann-Andermahr I, et al: Hypopituitarism, Lancet 369:1461–1470, 2007.

Table 556-1 Hormones of the Hypothalamus and Pituitary Gland

HORMONES	LOCATION	S/I	FUNCTION
ACTH	Anterior pituitary	S	Production and secretion of GCs, MCs, and androgens from adrenal gland
ADH	Posterior pituitary	S	Reabsorption of water into the bloodstream via renal collecting ducts
CRH	Hypothalamus	S	Secretion of ACTH
Dopamine	Hypothalamus	S	Secretion of PRL
FSH (females)	Anterior pituitary	I	Secretion of estrogen from ovary
FSH (males)	Anterior pituitary	S	Production of sperm from testis
GH	Anterior pituitary	S	Secretion of IGF-1
GHRH	Hypothalamus	S	Secretion of GH
Ghrelin	Hypothalamus	S	Secretion of GH
GnRH	Hypothalamus	S	Secretion of FSH and LH
LH (females)	Anterior pituitary	S	Ovulation and development of the corpus luteum
LH (males)	Anterior pituitary	S	Production and secretion of testosterone
Oxytocin	Posterior pituitary	S	Contractions of uterus at birth and release of milk from breast
PRL	Anterior pituitary	S	Promotion of milk synthesis
Somatostatin	Hypothalamus	I	Secretion of GH and TSH
TRH	Hypothalamus	S	Secretion of TSH and PRL
TSH	Anterior pituitary	S	Secretion of T ₄ and T ₃

ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GC, glucocorticoids; GH, growth hormone; GHRH, growth hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; IGF-1, insulin-derived growth factor 1; LH, luteinizing hormone; MC, mineralocorticoids; PRL, prolactin; S/I, stimulate/inhibit; T₃, triiodothyronine; T₄, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone (thyrotropin).

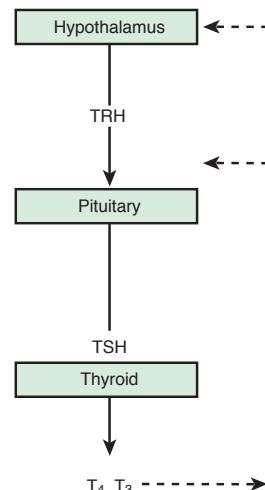


Figure 556-1 Hypothalamic-pituitary-thyroid (HPT) axis. Thyroid-releasing hormone (TRH) from the hypothalamus stimulates the pituitary gland to secrete thyroid-stimulating hormone (TSH). TSH stimulates the thyroid gland to produce and secrete thyroid hormones (T₄ and T₃). High circulating levels of T₃ and T₄ inhibit further TRH and TSH secretion through a negative feedback mechanism (dashed lines). T₃, triiodothyronine; T₄, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone (thyrotropin); <-->, inhibits; <-->, stimulates.

2642 Part XXVI ◇ The Endocrine System

Table 557-7 Evaluation of Suspected Growth Hormone Deficiency

Growth-related history and patient physical exam	<ul style="list-style-type: none"> Infants and children with GHD have growth failure Short stature and growth failure may be the only clinical features present GHD affects ~1 in 3,500 children
Imaging and other evaluations	<ul style="list-style-type: none"> Diagnosis is based on clinical, auxologic, and biochemical parameters Radiologic evaluation of bone age Central nervous system MRI or CT scan to evaluate the hypothalamic-pituitary region and to exclude other conditions Evaluation and management by a pediatric endocrinologist
Laboratory evaluation	<ul style="list-style-type: none"> Measurements of GH, IGF-1, and IGF-1-binding protein levels Determination of peak GH levels after stimulation test
Special testing (if applicable)	<ul style="list-style-type: none"> Family history and genetic analyses (e.g., search for <i>PROP1</i> and <i>POU1F1</i> mutations)
Rationale for treatment and treatment modalities	<ul style="list-style-type: none"> Replacement therapy with rhGH (GHT) Predictors of greater benefit with GHT in GHD include early initiation of treatment, higher rhGH dose, and IGF-1-guided dosing GHT should be started as soon as GHD is diagnosed

GH, growth hormone; GHD, growth hormone deficiency; GHT, growth hormone therapy; IGF, insulin-like growth factor; *POU1F1*, POU class 1 homeobox 1; *PROP1*, homeobox protein prophet of Pit1; rhGH, human recombinant growth hormone.

From Rogol AD, Hayden GF: Etiologies and early diagnosis of short stature and growth failure in children and adolescents. *J Pediatr* 164(5):S1-S14, 2014, Table XIII, p. S10.

Table 558-1 Differential Diagnosis of Polyuria and Polydipsia

Diabetes insipidus (DI)	
• Central DI	
Genetic (autosomal dominant)	
Acquired	
Trauma (surgical or accidental)	
Congenital malformations (holoprosencephaly, septo-optic dysplasia, encephalocele)	
Neoplasms (cranioopharyngioma, germinoma, metastasis)	
Infiltrative (Langerhans cell histiocytosis), autoimmune (lymphocytic infundibuloneurohypophysis), and infectious diseases	
Drugs (chemotherapy)	
Idiopathic	
• Nephrogenic DI	
Genetic (X-linked, autosomal recessive, autosomal dominant)	
Acquired	
Hypercalcemia, hypokalemia	
Drugs (lithium, demeclocycline)	
Kidney disease	
Primary polydipsia	
Sickle cell anemia	
• Diabetes mellitus	

Figure 558-1 Regulation of vasopressin (VP) secretion and serum osmolality. Hyperosmolality, hypovolemia, and hypotension are sensed by osmosensors, volume sensors, and barosensors, respectively. These stimulate both VP secretion and thirst. VP, acting on the kidney, causes increased reabsorption of water (antidiuresis). Thirst causes increased water ingestion. The results of these dual negative feedback loops cause a reduction in hyperosmolality or in hypotension or hypovolemia. Additional stimuli for VP secretion include nausea, hypoglycemia, and pain. (From Muglia LJ, Majzoub JA: Disorders of the posterior pituitary. In Sperling MA, editor: Pediatric endocrinology, ed 4, Philadelphia, 2014, Elsevier, Fig. 6.)

Table 557-6 Clinical Features of Growth Hormone Insensitivity

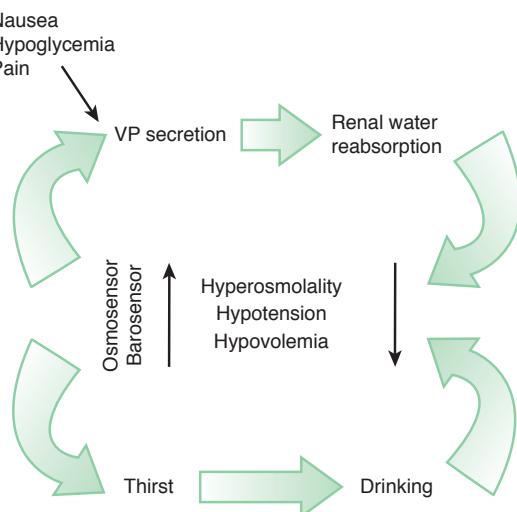
Growth and development	
Birthweight: near-normal	
Birth length: may be slightly decreased	
Postnatal growth: severe growth failure	
Bone age: delayed, but may be advanced relative to height age	
Genitalia: micropenis in childhood; normal for body size in adults	
Puberty: delayed 3-7 yr	
Sexual function and fertility: normal	
Craniofacies	
Hair: sparse before the age of 7 yr	
Forehead: prominent; frontal bossing	
Skull: normal head circumference; craniofacial disproportion due to small facies	
Facies: small	
Nasal bridge: hypoplastic	
Orbits: shallow	
Dentition: delayed eruption	
Sclerae: blue	
Voice: high pitched	
Musculoskeletal/metabolic/miscellaneous	
Hypoglycemia: in infants and children; fasting symptoms in some adults	
Walking and motor milestones: delayed	
Hips: dysplasia; avascular necrosis of femoral head	
Elbow: limited extensibility	
Skin: thin, prematurely aged	
Osteopenia	

From Sperling MA: Pediatric endocrinology, ed 4, Philadelphia, 2014, Elsevier, Table 10-5, p. 355.

Table 559-1 Differential Diagnosis of Hyponatremia

DISORDER	INTRAVASCULAR VOLUME STATUS	URINE SODIUM
Systemic dehydration	Low	Low
Decreased effective plasma volume	Low	Low
Primary salt loss (nonrenal)	Low	Low
Primary salt loss (renal)	Low	High
SIADH	High	High
Cerebral salt wasting	Low	Very high
Decreased free water clearance	Normal or high	Normal or high
Primary polydipsia	Normal or high	Normal
Runner's hyponatremia	Low	Low
NSIAD	High	High
Pseudohyponatremia	Normal	Normal
Factitious hyponatremia	Normal	Normal

NSIAD, nephrogenic syndrome of inappropriate antidiuresis; SIADH, syndrome of inappropriate antidiuretic hormone secretion.



Chapter 559 ◇ Other Abnormalities of Arginine Vasopressin Metabolism and Action 2647

Table 559-2 Clinical Parameters to Distinguish Among SIADH, Cerebral Salt Wasting, and Central Diabetes Insipidus

CLINICAL PARAMETER	SIADH	CEREBRAL SALT WASTING	CENTRAL DI
Serum sodium	Low	Low	High
Urine output	Normal or low	High	High
Urine sodium	High	Very high	Low
Intravascular volume status	Normal or high	Low	Low
Vasopressin level	High	Low	Low

DI, diabetes insipidus; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Table 559-3 Genetic Mutations Associated with Hypoaldosteronism/Pseudohypoaldosteronism (Type IV Renal Tubular Acidosis)

GENE CHROMOSOME OMIM	PATHOPHYSIOLOGY	MUTATION-CLINICAL MANIFESTATIONS-OMIM-INHERITANCE
PRIMARY HYPOALDOSTERONISM		
CYP21A2—cytochrome P450, subfamily XXIA, polypeptide 2 6p21.3 613815	P450c21—steroid 21-hydroxylase that converts 17 α -hydroxyprogesterone to 11-deoxycortisol and progesterone to 11-deoxycorticosterone in the adrenal zona fasciculata	Loss-of-function mutations decrease synthesis of cortisol and aldosterone, the latter resulting in the salt-losing form of classical congenital adrenal hyperplasia, AR-201910
CYP11B2—cytochrome P450, subfamily XIB, polypeptide 2 8q21 124080	P450c11B2—aldosterone synthase/corticosterone methyloxidase types I and II expressed only in the zona glomerulosa; hydroxylates deoxycorticosterone at carbon-11 and corticosterone at carbon-18 and oxidizes 18-hydroxycorticosterone to aldosterone	Loss-of-function mutations associated with severe salt loss and volume depletion but not with abnormalities of genital formation or glucocorticoid synthesis AR (CMO1 203400; CMOII 610600)
PSEUDOHYPOALDOSTERONISM TYPE I		
NR3C2—nuclear receptor subfamily 3, group C, member 2 (MR-mineralocorticoid receptor), 4q31.1 600983	Ligand-activated nuclear transcription factor that transmits aldosterone-mediated control of gene expression by binding to the mineralocorticoid response element in the promoter region of the target gene	Loss-of-function mutations lead to mineralocorticoid resistance and pseudohypoaldosteronism type I, AD-177735
SCNN1A—sodium channel, non-voltage-gated, α -subunit 12p13.31 600228	Inactivating mutation of α -subunit of the epithelial sodium channel	Pseudohypoaldosteronism type I, AR-264350
SCNN1B—sodium channel, non-voltage-gated, β -subunit 16p12.2 600760	Inactivating mutation of β -subunit of the epithelial sodium channel	Pseudohypoaldosteronism type I, AR-264350
SCNN1G—sodium channel, non-voltage-gated, γ -subunit 16p12.2 600761	Inactivating mutation of γ -subunit of the epithelial sodium channel	Pseudohypoaldosteronism type I, AR-264350
PSEUDOHYPOALDOSTERONISM TYPE II		
WNK4—protein kinase, lysine-deficient 4 17q21.31 601844	Multifunctional serine-threonine protein kinase whose substrate is SLC12A3, the thiazide-sensitive sodium/chloride cotransporter (NCCT)—OMIM 600968—that also regulates lysosomal degradation of NCCT and endocytosis of the KCNJ1 potassium channel	Pseudohypoaldosteronism type IIB, AD-614491
WNK1—protein kinase, lysine-deficient 1 12p13.33 605232	Serine-threonine protein kinase that inactivates WNK4 by phosphorylating its kinase domain	Pseudohypoaldosteronism type IIC, AD-614492
KLH3—Kelch-like 3 5q31.2 605775	Adaptor protein within the ubiquitination sequence that links WNK1 and WNK4 to CUL3	Pseudohypoaldosteronism type IID, AD/AR-614495
CUL3—Cullin 3 2q36.2 603136	Scaffold protein that links to RING-box E3 ligase facilitating WNK4 ubiquitination and proteasomal destruction of WNK4	Pseudohypoaldosteronism type IIE, AD-614496

AD, autosomal dominant; AR, autosomal recessive; CMO, corticosterone methyloxidase; OMIM, Online Mendelian Inheritance in Man.

From Root AW: Disorders of aldosterone synthesis, secretion, and cellular function. *Curr Opin Pediatr* 26:480-486, 2014, Table 1, p. 483.

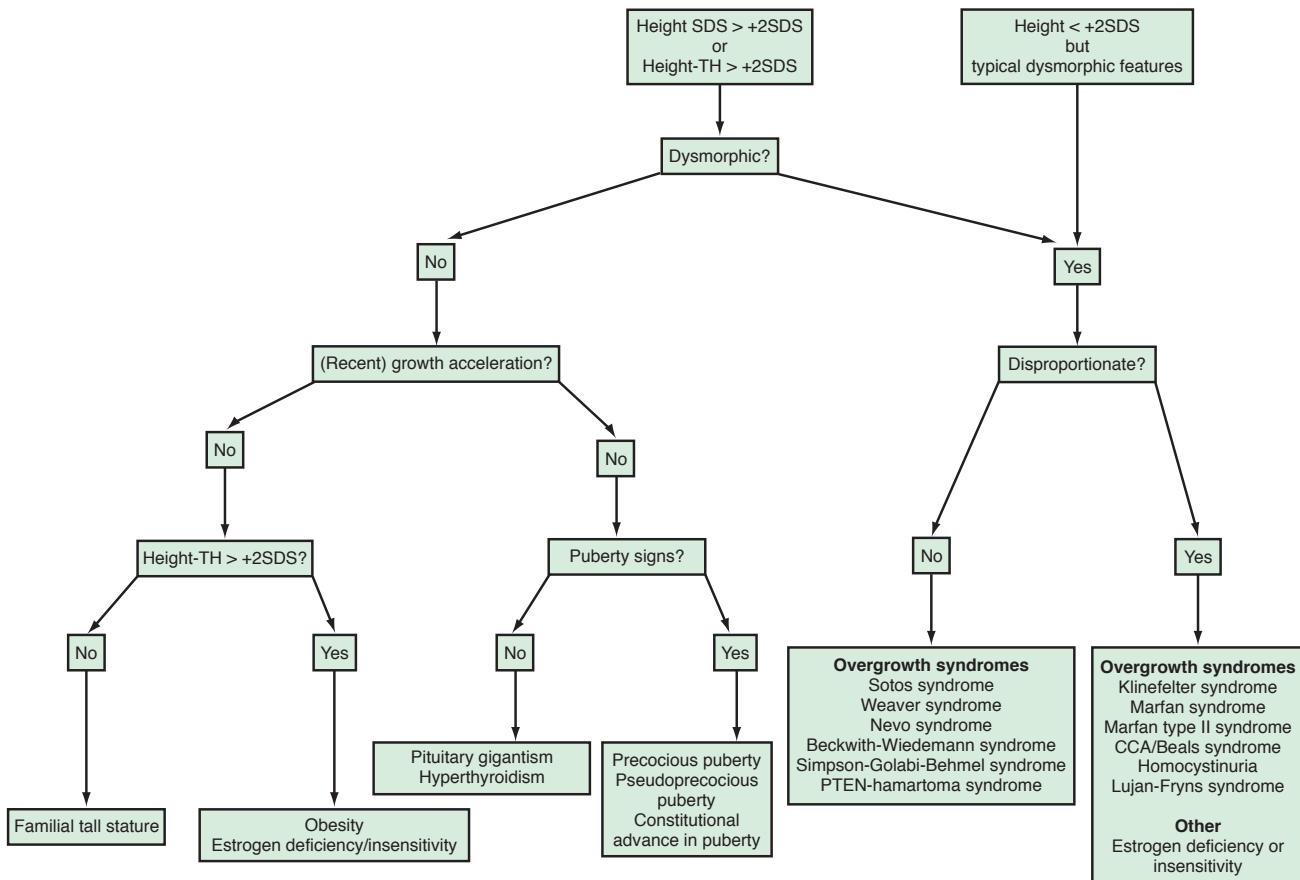


Figure 560-1 Diagnostic flow chart for the differential diagnosis of tall stature and overgrowth syndromes. Height-TH, current height percentile >2 SDS from target height percentile, the latter based on midparental height calculation; SDS, standard deviation score. (From Neylon OM, Werther GA, Sabin MA: Overgrowth syndromes. *Curr Opin Pediatr* 24:505–511, 2012, Fig. 1, p. 507.)

Table 560-1 Differential Diagnosis of Tall Stature and Overgrowth Syndromes

FETAL OVERGROWTH

Maternal diabetes mellitus
Cerebral gigantism (Sotos syndrome)
Weaver syndrome
Beckwith-Wiedemann syndrome
Other IGF-2 excess syndromes

POSTNATAL OVERGROWTH LEADING TO CHILDHOOD TALL STATURE

Nonendocrine Causes

Familial (constitutional) tall stature
Exogenous obesity
Cerebral gigantism (Sotos syndrome)
Weaver syndrome
Marfan syndrome
Fragile X syndrome
Beckwith-Wiedemann syndrome
Klinefelter syndrome (XXY)
SHOX excess syndromes
Homocystinuria
XY

Endocrine Causes

Excess GH secretion (pituitary gigantism)
McCune-Albright syndrome or MEN associated with excess GH secretion
Precocious puberty
Hyperthyroidism

POSTNATAL OVERGROWTH LEADING TO ADULT TALL STATURE

Familial (constitutional) tall stature
Marfan syndrome
Klinefelter syndrome (XXY)
XY
Androgen or estrogen deficiency or estrogen resistance
Androgen insensitivity syndrome (testicular feminization)
ACTH or cortisol deficiency or resistance
Excess GH secretion (pituitary gigantism)

Table 564-1 Causes of Acquired Thyroxine-Binding Globulin (TBG) Deficiency and Excess

DECREASED TBG

Androgens
Anabolic steroids
Glucocorticoids
Hepatocellular disease
Severe illness
Protein-losing nephropathies
Protein-losing enteropathies
Nicotinic acid
L-Asparaginase

INCREASED TBG

Estrogens
Selective estrogen receptor modulators
Pregnancy
Hepatitis
Porphyria
Heroin, methadone
Mitotane
5-Fluorouracil
Perphenazine

2652 Part XXVI ◇ The Endocrine System

Table 560-2 Genetic Overgrowth Syndromes

GENETIC SYNDROMES	CLINICAL FEATURES	INCIDENCE OF MALIGNANCY (%)	ETOLOGY	INVESTIGATIONS AND MANAGEMENT
Beckwith-Wiedemann syndrome*	Hypoglycemia, large tongue, ear pits, omphalocele or umbilical hernia, hemihyperplasia	~7.5		US heart, kidneys Chromosomes 11p FISH and/or MLPA, methylation studies Tumor surveillance justified
Perlman syndrome*	Macrosomia, unusual facies Nephroblastosis		Rare autosomal recessive	US brain (ACC), heart (coarctation), kidneys
Simpson-Golabi-Behmel syndrome*	Coarse facial features, macroglossia, central groove lower lip, supernumerary nipples	~7.5	X-linked recessive (glypican-3 mutations)	US heart, kidney X-ray spine (vertebral segmentation anomaly) Tumor surveillance justified
Sotos syndrome	Facial gestalt (long, thin face, broad forehead) Feeding difficulties Hypotonia	~4	Usually de novo dominant <i>NSD1</i> deletion or mutation Rare familial cases	US heart, kidneys Monitor development
PTEN-hamartoma syndrome (Bannayan-Ruvalcaba-Riley)	Macrocephaly (>97th percentile) often progressive from birth, hypotonia, pigmented skin, penile macules, lipomas	Uncertain	Sporadic or autosomal dominant <i>PTEN</i> mutation	US head, heart, and kidney Monitor development
Weaver syndrome	Broad forehead, hypertelorism, small chin, long philtrum, camptodactyly, fetal finger pads	~5-6	Rare, unknown	US heart, brain, kidney
Marfan syndrome type I	Facial gestalt, arachnodactyly, scoliosis, pectus carinatum or excavatum, aortic root dilation, lens dislocation		Autosomal dominant fibrillin-1 (<i>FBN1</i>)	Eye examination and follow-up Heart US and cardiology follow-up Monitor scoliosis
Marfan syndrome type II or Loeys-Dietz syndrome	Marfan-like habitus, aortic root dilation, aortic dissection, vasculopathy		Autosomal dominant, TGF-β pathway anomaly <i>TGFBR1</i> and <i>TGFBR2</i> genes	Eye examination usually normal Heart US and follow-up Monitor scoliosis
Beals syndrome	Congenital distal arthrogryposis Crumpled ears		Autosomal dominant fibrillin 2 (<i>FBN2</i>)	Eye examination and heart US usually normal
Homocystinuria	Marfan-like habitus Developmental delay Lens dislocation		Autosomal recessive Cystathione β-synthase (CBS) mutation	Urine metabolic screen Eye examination Monitor development
Lujan syndrome	Marfanoid habitus plus intellectual disability		X-linked recessive <i>MED12</i> gene	Eye examination usually normal Heart US usually normal
Sex chromosome aneuploidy Klinefelter 47XXY, 47XYY, 47XXX	Tall stature, small testes, gynecomastia Tall stature, ± learning disability			Androgen replacement from puberty in Klinefelter syndrome Monitor development
Autosomal anomaly Tetrasomy 12p mosaicism,* pat 11pdup, 4pdub, 22q13del, 15q26-qter dup	Congenital overgrowth or childhood tall stature with intellectual disability			Monitor development

*Overgrowth often presenting at birth.

ACC, agenesis of the corpus callosum; FISH, fluorescence in situ hybridization; MLPA, multiple ligation probe amplification; PTEN, phosphatase and tensin homolog; TGF, transforming growth factor; TGFBR, transforming growth factor β receptor; US, ultrasound.

From Verge CF, Mowat D: Overgrowth, Arch Dis Child 95:458–463, 2010.

2656 Part XXVI ◆ The Endocrine System

Table 565-1 Etiologic Classification of Congenital Hypothyroidism**PRIMARY HYPOTHYROIDISM**

Defect of fetal thyroid development (dysgenesis)

- Aplasia
 - Hypoplasia
 - Ectopia
- Defect in thyroid hormone synthesis (dyshormonogenesis)
- Iodide transport defect from blood into follicular cell: mutation in sodium-iodide symporter gene
 - Defective iodide transport from follicular cell into colloid: mutation in Pendrin transport protein
 - Thyroid organization, or coupling defect: mutation in thyroid peroxidase gene
 - Defects in H_2O_2 generation: mutations in DUOX2 maturation factor or *DUOX2* gene
 - Thyroglobulin synthesis defect: mutation in thyroglobulin gene
 - Deiodination defect: mutation in *DEHAL1* gene

TSH unresponsiveness

- Mutation in TSH receptor
- Defective TSH signaling: $G_s\alpha$ mutation (e.g., type IA pseudohypoparathyroidism)

Defect in thyroid hormone transport: mutation in monocarboxylate transporter 8 (*MCT8*) gene

Resistance to thyroid hormone

Maternal antibodies: thyrotropin receptor-blocking antibody (TRAb, measured as *thyrotropin-binding inhibitor immunoglobulin*)

Iodine deficiency (endemic goiter)

Maternal medications

- Iodides, amiodarone
- Propylthiouracil, methimazole
- Radioiodine

CENTRAL (HYPOPITUITARY) HYPOTHYROIDISMIsolated TSH deficiency: mutation in TSH β -subunit gene (depending on mutation, TSH may be undetectable, measurable ["normal"], or elevated)

Isolated TRH deficiency: mutation in TRH gene

TRH unresponsiveness: mutation in TRH receptor gene

Multiple congenital pituitary hormone deficiencies (e.g., septooptic dysplasia)

PIT-1 mutations

- Deficiency of TSH
 - Deficiency of growth hormone
 - Deficiency of prolactin
- PROP-1* mutations
- Deficiency of TSH
 - Deficiency of growth hormone
 - Deficiency of prolactin
 - Deficiency of LH
 - Deficiency of FSH
 - \pm Deficiency of ACTH

Table 562-1 Conditions Causing Precocious Puberty**CENTRAL (GONADOTROPIN-DEPENDENT, TRUE PRECOCIOUS) PUBERTY**

- Idiopathic
- Organic brain lesions
- Hypothalamic hamartoma
- Brain tumors, hydrocephalus, severe head trauma, myelomeningocele
- Hypothyroidism, prolonged and untreated*

COMBINED PERIPHERAL AND CENTRAL

- Treated congenital adrenal hyperplasia
- McCune-Albright syndrome, late
- Familial male precocious puberty, late

PERIPHERAL (GONADOTROPIN-INDEPENDENT, PRECOCIOUS) PSEUDOPUBERTY**GIRLS****Isosexual (feminizing) conditions**

- McCune-Albright syndrome
- Autonomous ovarian cysts
- Ovarian tumors
- Granulosa-theca cell tumor associated with Ollier disease
- Teratoma, chorionepithelioma

SCTAT associated with Peutz-Jeghers syndrome

Feminizing adrenocortical tumor

Exogenous estrogens

Heterosexual (masculinizing) conditions

- Congenital adrenal hyperplasia
- Adrenal tumors
- Ovarian tumors
- Glucocorticoid receptor defect
- Exogenous androgens

BOYS**Isosexual (masculinizing) conditions**

- Congenital adrenal hyperplasia
- Adrenocortical tumor
- Leydig cell tumor
- Familial male precocious puberty
- Isolated

Associated with pseudohypoparathyroidism

hCG-secreting tumors

- Central nervous system
- Hepatoblastoma

Mediastinal tumor associated with Klinefelter syndrome

Teratoma

Glucocorticoid receptor defect

Exogenous androgen

Heterosexual (feminizing) conditions

- Feminizing adrenocortical tumor
- SCTAT associated with Peutz-Jeghers syndrome

Exogenous estrogens

INCOMPLETE (PARTIAL) PRECOCIOUS PUBERTY

Premature thelarche

Premature adrenarche

Premature menarche

*Central puberty without true gonadotropin dependency (see text).
hCG, human chorionic gonadotropin; SCTAT, sex-cord tumor with annular tubules.

Table 566-1 Characteristics of Thyroiditis Syndromes

CHARACTERISTIC	HASHIMOTO THYROIDITIS	PAINLESS POSTPARTUM THYROIDITIS	PAINLESS SPORADIC THYROIDITIS	PAINFUL SUBACUTE THYROIDITIS	ACUTE SUPPURATIVE THYROIDITIS	RIEDEL THYROIDITIS
Sex ratio (F:M)	4-6:1	—	2:1	5:1	1:1	3-4:1
Cause	Autoimmune	Autoimmune	Autoimmune	Unknown (probably viral)	Infectious (bacterial)	Unknown
Pathologic findings	Lymphocytic infiltration, germinal centers, fibrosis	Lymphocytic infiltration	Lymphocytic infiltration	Giant cells, granulomas	Abscess formation	Dense fibrosis
Thyroid function	Usually euthyroidism; some hypothyroidism	Hyperthyroidism, hypothyroidism, or both	Hyperthyroidism, hypothyroidism, or both	Hyperthyroidism, hypothyroidism, or both	Usually euthyroidism	Usually euthyroidism
TPO antibodies	High titer, persistent	High titer, persistent	High titer, persistent	Low titer, or absent, or transient	Absent	Usually present
ESR	Normal	Normal	Normal	High	High	Normal
24 hr ^{123}I uptake	Variable	<5%	<5%	<5%	Normal	Low or normal

ESR, erythrocyte sedimentation rate; ^{123}I , iodine 123; TPO, thyroid peroxidase.

Data from Farwell AP, Braverman LE. Inflammatory thyroid disorders. Otolaryngol Clin North Am 4:541-556, 1996.

2670 Part XXVI ◇ The Endocrine System

AGE	U.S. REFERENCE VALUE	CONVERSION FACTOR	SI REFERENCE VALUE
THYROID THYROGLOBULIN, SERUM			
Cord blood	14.7-101.1 ng/mL	×1	14.7-101.1 µg/L
Birth to 35 mo	10.6-92.0 ng/mL	×1	10.6-92.0 µg/L
3-11 yr	5.6-41.9 ng/mL	×1	5.6-41.9 µg/L
12-17 yr	2.7-21.9 ng/mL	×1	2.7-21.9 µg/L
THYROID-STIMULATING HORMONE, SERUM			
<i>Premature Infants (28-36 wk)</i>			
1st wk of life	0.7-27.0 mIU/L	×1	0.7-27.0 mIU/L
<i>Term Infants</i>			
Birth to 4 days	1.0-17.6 mIU/L	×1	1.0-17.6 mIU/L
2-20 wk	0.6-5.6 mIU/L	×1	0.6-5.6 mIU/L
5 mo-20 yr	0.5-5.5 mIU/L	×1	0.5-5.5 mIU/L
THYROXINE-BINDING GLOBULIN, SERUM			
Cord blood	1.4-9.4 mg/dL	×10	14-94 mg/L
1-4 wk	1.0-9.0 mg/dL	×10	10-90 mg/L
1-12 mo	2.0-7.6 mg/dL	×10	20-76 mg/L
1-5 yr	2.9-5.4 mg/dL	×10	29-54 mg/L
5-10 yr	2.5-5.0 mg/dL	×10	25-50 mg/L
10-15 yr	2.1-4.6 mg/dL	×10	21-46 mg/L
Adult	1.5-3.4 mg/dL	×10	15-34 mg/L
THYROXINE, TOTAL, SERUM			
<i>Full-Term Infants</i>			
1-3 days	8.2-19.9 µg/dL	×12.9	106-256 nmol/L
1 wk	6.0-15.9 µg/dL	×12.9	77-205 nmol/L
1-12 mo	6.1-14.9 µg/dL	×12.9	79-192 nmol/L
<i>Prepubertal Children</i>			
1-3 yr	6.8-13.5 µg/dL	×12.9	88-174 nmol/L
3-10 yr	5.5-12.8 µg/dL	×12.9	71-165 nmol/L
<i>Pubertal Children and Adults</i>			
>10 yr	4.2-13.0 µg/dL	×12.9	54-167 nmol/L
THYROXINE, FREE, SERUM			
Full-term (3 days)	2.0-4.9 ng/dL	×12.9	26-63.1 pmol/L
Infants	0.9-2.6 ng/dL	×12.9	12-33 pmol/L
Prepubertal children	0.8-2.2 ng/dL	×12.9	10-28 pmol/L
Pubertal children and adults	0.8-2.3 ng/dL	×12.9	10-30 pmol/L
THYROXINE, TOTAL, WHOLE BLOOD			
Newborn screen (filter paper)	6.2-22 µg/dL	×12.9	80-283 nmol/L
TRIIODOTHYRONINE, FREE, SERUM			
Cord blood	20-240 pg/dL	×0.01536	0.3-0.7 pmol/L
1-3 days	180-760 pg/dL	×0.01536	2.8-11.7 pmol/L
1-5 yr	185-770 pg/dL	×0.01536	2.8-11.8 pmol/L
5-10 yr	215-700 pg/dL	×0.01536	3.3-10.7 pmol/L
10-15 yr	230-650 pg/dL	×0.01536	3.5-10.0 pmol/L
>15 yr	210-440 pg/dL	×0.01536	3.2-6.8 pmol/L
TRIIODOTHYRONINE RESIN UPTAKE TEST (RT₃U), SERUM			
Newborn	26-36%	×0.01	0.26-0.36 fractional uptake
Thereafter	26-35%	×0.01	0.26-0.35 fractional uptake
TRIIODOTHYRONINE, TOTAL, SERUM			
Cord blood	30-70 ng/dL	×0.0154	0.46-1.08 nmol/L
1-3 days	75-260 ng/dL	×0.0154	1.16-4.00 nmol/L
1-5 yr	100-260 ng/dL	×0.0154	1.54-4.00 nmol/L
5-10 yr	90-240 ng/dL	×0.0154	1.39-3.70 nmol/L
10-15 yr	80-210 ng/dL	×0.0154	1.23-3.23 nmol/L
>15 yr	115-190 ng/dL	×0.0154	1.77-2.93 nmol/L

Adapted from Nicholson JF, Pesce MA: Reference ranges for laboratory tests and procedures. In Behrman RE, Kliegman RM, Jenson HB, editors: Nelson textbook of pediatrics, ed 17, Philadelphia, 2004, WB Saunders, pp. 2412-2413; TSH from Lem AJ, de Rijke YB, van der Hoorn H, et al: Serum thyroid hormone levels in healthy children from birth to adulthood and in short children born small for gestational age. J Clin Endocrinol Metab 97:3170-3178, 2012; free T₃ from Elmlinger MW, Kuhnel W, Lambrecht H-G, Ranke MB: Reference intervals from birth to adulthood for serum thyroxine (T₄), triiodothyronine (T₃), free T₃, free T₄, thyroxine binding globulin (TBG), and thyrotropin (TSH). Clin Chem Lab Med 39:973-979, 2001.

2672 Part XXVI ◇ The Endocrine System

Table 565-6 Pathogenesis of General Complications in Management of Complicated Hypothyroidism

COMPLICATION	PATHOGENESIS
Heart failure	Impaired ventricular systolic and diastolic functions and increased peripheral vascular resistance
Ventilatory failure	Blunted hypercapnic and hypoxic ventilatory drives
Hyponatremia	Impaired renal free water excretion and syndrome of inappropriate antidiuretic hormone secretion
Ileus	Bowel hypomotility
Medication sensitivity	Reduced clearance rate and increased sensitivity to sedative, analgesic, and anesthetic agents
Hypothermia and lack of febrile response to sepsis	Decreased calorigenesis
Delirium, dementia, seizure, stupor, and coma	Decreased central nervous system thyroid hormone actions, and encephalopathy from hyponatremia and hypercapnia
Adrenal insufficiency	Associated intrinsic adrenal or pituitary disease, or reversible impairment of hypothalamic-pituitary-adrenal stress response
Coagulopathy	Acquired von Willebrand syndrome (type 1) and decreased factors VIII, VII, V, IX, and X

Table 565-4 Autoimmune Polyglandular Syndromes 1 and 2

	APS-1	APS-2
Incidence	<1 in 100,000 population/yr	1-2 in 10,000 population/yr
Onset	Infancy/early childhood	Late childhood/adulthood
Male:female ratio	3:4	1:3
Inheritance	Monogenic (AIRE gene)	Polygenic (HLA-associated)
Mucocutaneous candidiasis	73-100%	None
Hypoparathyroidism	77-89%	None
Addison disease	60-86%	70-100%
Type 1 diabetes	4-18%	41-52%
Autoimmune thyroid disease	8-40%	70%
GONADAL FAILURE		
Male	7-17%	5%
Female	30-60%	3.5-10%
Ectodermal dysplasia	77%	None
Vitiligo	4-13%	4-5%
Pernicious anemia	12-15%	2-25%
Alopecia	27%	2%
Autoimmune hepatitis	10-15%	Rare
Malabsorption	10-18%	Rare

HLA, human leukocyte antigen.

From Nambam B, Winter WE, Schatz DA: IgG₄ antibodies in autoimmune polyglandular disease and IgG₄-related endocrinopathies: pathophysiology and clinical characteristics. *Curr Opin Pediatr* 26:493-499, 2014, Table 1, p. 494.**Table 565-3** Etiologic Classification of Acquired Hypothyroidism

Autoimmune	
• Hashimoto thyroiditis	
• Autoimmune polyglandular syndromes types 1 and 2 (APS-1, APS-2)	
Drug-induced	
• Excess iodide: amiodarone, nutritional supplements, expectorants	
• Anticonvulsants: phenytoin, phenobarbital, valproate	
• Antithyroid drugs: methimazole, propylthiouracil	
• Miscellaneous: lithium, tyrosine kinase inhibitors, interferon alfa, stavudine, thalidomide, aminoglutethimide	
Postablative	
• Irradiation	
• Radioiodine	
• Thyroidectomy	
Systemic infiltrative disease	
• Cystinosis	
• Langerhans cell histiocytosis	
Hemangiomas (large) of the liver (type 3 iodothyronine deiodinase)	
Hypothalamic-pituitary disease with multiple pituitary hormone deficiencies	
• Hypothalamic-pituitary tumors (e.g., craniopharyngioma)	
• Meningoencephalitis	
• Cranial radiation	
• Head trauma	
• Langerhans cell histiocytosis	

Table 565-5

DISEASE	AUTOANTIGENS
Addison disease	P450c21, P450c17, P450scc
Hashimoto thyroiditis	Thyroid peroxidase, thyroglobulin
Graves disease	TSH receptor
Hypoparathyroidism	Calcium-sensing receptor, NALP-5
Type 1 diabetes	IA-2A, ZnT8
Hypogonadism	P450c17, P450scc
Immune gastritis	H+, K+-ATPase
Pernicious anemia	Intrinsic factor
Celiac disease	Transglutaminase, gliadin
Immune hepatitis	P450D6, P4502C9, P4501A2
Alopecia areata	Tyrosine hydroxylase
Vitiligo	Tyrosinase

ATPase, adenosine triphosphatase; TSH, thyroid-stimulating hormone.

From Nambam B, Winter WE, Schatz DA: IgG₄ antibodies in autoimmune polyglandular disease and IgG₄-related endocrinopathies: pathophysiology and clinical characteristics. *Curr Opin Pediatr* 26:493-499, 2014, Table 2, p. 495.

Table 568-2 Major Symptoms and Signs of Hyperthyroidism and of Graves Disease and Conditions Associated with Graves Disease

MANIFESTATIONS OF HYPERTHYROIDISM

Symptoms

- Hyperactivity, irritability, altered mood, insomnia, anxiety, poor concentration
 - Heat intolerance, increased sweating
 - Palpitations
 - Fatigue, weakness
 - Dyspnea
 - Weight loss with increased appetite (weight gain in 10% of patients)
 - Puritus
 - Increased stool frequency
 - Thirst and polyuria
 - Oligomenorrhea or amenorrhea
- Signs**
- Sinus tachycardia, atrial fibrillation (rare in children), supraventricular tachycardia
 - Fine tremor, hyperkinesis, hyperreflexia
 - Warm, moist skin
 - Palmar erythema, onycholysis
 - Hair loss or thinning
 - Osteoporosis
 - Muscle weakness and wasting
 - High-output heart failure
 - Chorea
 - Periodic (hypokalemic) paralysis (primarily in Asian men)
 - Psychosis (rare)

MANIFESTATIONS OF GRAVES DISEASE

- Diffuse goiter
- Ophthalmopathy
 - A feeling of grittiness and discomfort in the eye
 - Retrobulbar pressure or pain
 - Eyelid lag or retraction
 - Periorbital edema, chemosis, scleral or conjunctival injection
 - Exophthalmos (proptosis)
 - Extraocular muscle dysfunction
 - Exposure keratitis
 - Optic neuropathy
- Localized dermatopathy (rare in children)
- Lymphoid hyperplasia
- Thyroid acropachy (rare in children)

CONDITIONS ASSOCIATED WITH GRAVES DISEASE

- Type 1 diabetes mellitus
- Addison disease
- Vitiligo
- Pernicious anemia
- Alopecia areata
- Myasthenia gravis
- Celiac disease

Table 567-1 Goitrogens and Their Mechanism

GOITROGEN	MECHANISM
FOODS	
Cassava, lima beans, linseed, sorghum, sweet potato	Contain cyanogenic glucosides that are metabolized to thiocyanates that compete with iodine for uptake by the thyroid
Cruciferous vegetables such as cabbage, kale, cauliflower, broccoli, turnips, rapeseed	Contain glucosinolates; metabolites compete with iodine for uptake by the thyroid
Soy, millet	Flavonoids impair thyroid peroxidase activity
INDUSTRIAL POLLUTANTS	
Perchlorate	Competitive inhibitor of the sodium-iodine symporter, decreasing iodine transport into the thyroid
Others (e.g., disulfides from coal processes)	Reduce thyroidal iodine uptake
Smoking	An important goitrogen; smoking during breastfeeding is associated with reduced iodine concentrations in breast milk; high serum concentration of thiocyanate from smoking might compete with iodine for active transport into the secretory epithelium of the lactating breast
NUTRIENTS	
Selenium deficiency	Accumulated peroxides can damage the thyroid, and deiodinase deficiency impairs thyroid hormone activation
Iron deficiency	Reduces heme-dependent thyroperoxidase activity in the thyroid and might blunt the efficacy of iodine prophylaxis
Vitamin A deficiency	Increases TSH stimulation and goiter through decreased vitamin A-mediated suppression of the pituitary TSH- β gene

Table 568-3 Treatments for Hyperthyroidism Caused by Graves Disease

TREATMENT	ADVANTAGE	DISADVANTAGE	COMMENT
Antithyroid drugs	Noninvasive Less initial cost Low risk of permanent hypothyroidism Possible remission	Cure rate 30-80% (average: 40-50%) Adverse drug reactions Drug compliance required	First-line treatment in children and adolescents and in pregnancy Initial treatment in severe cases or preoperative preparation
Radioactive iodine (^{131}I)	Cure of hyperthyroidism Most cost-effective	Permanent hypothyroidism is almost inevitable Might worsen ophthalmopathy Pregnancy must be deferred for 6-12 mo, mother cannot breastfeed; small potential risk of exacerbation of hyperthyroidism	No evidence for infertility, birth defects, cancer when currently recommended doses are applied
Surgery	Rapid, effective treatment especially in patients with large goiter	Most invasive therapy Potential complications (recurrent laryngeal nerve damage, hypoparathyroidism) Most costly therapy Permanent hypothyroidism; pain; scarring	Potential use in pregnancy if major side effect from antithyroid drugs Useful when coexisting suspicious nodule is present or thyromegaly is massive Option for patients who refuse radioiodine

From Cooper DS: Hyperthyroidism, Lancet 362:459-468, 2003.

Table 568-1 Causes of Hyperthyroidism

CAUSES OF HYPERTHYROIDISM	PATHOPHYSIOLOGIC FEATURES	INCIDENCE
CIRCULATING THYROID STIMULATORS		
Graves disease	Thyroid-stimulating immunoglobulins	Common
Neonatal Graves disease	Thyroid-stimulating immunoglobulins	Rare
Thyrotropin-secreting tumor	Pituitary adenoma	Very rare
Choriocarcinoma	Human chorionic gonadotropin secretion stimulating the thyroid-stimulating hormone receptor	Rare
THYROIDAL AUTONOMY		
Toxic multinodular goiter	Activating mutations in thyrotropin receptor or G-protein	Common
Toxic solitary adenoma	Activating mutations in thyrotropin receptor or G-protein	Common
Congenital hyperthyroidism	Activating mutations in thyrotropin receptor	Very rare
Iodine-induced hyperthyroidism (Jod-Basedow phenomenon)	Unknown; excess iodine results in unregulated thyroid hormone production	Uncommon in United States and other iodine-sufficient areas
DESTRUCTION OF THYROID FOLLICLES (THYROIDITIS)		
Subacute painful thyroiditis	Probable viral infection	Uncommon
Painless sporadic thyroiditis (or postpartum thyroiditis)	Autoimmune	Common
Amiodarone-induced thyroiditis	Direct toxic drug effects	Uncommon
Acute (infectious) thyroiditis	Thyroid infection (e.g., bacterial, fungal) and release of preformed hormone	Uncommon
EXOGENOUS THYROID HORMONE		
Iatrogenic	Overtreatment with thyroid hormone	Common
Factitious	Excess ingestion of thyroid hormone	Rare
Hamburger thyrotoxicosis	Thyroid gland included in ground beef	Probably rare
ECTOPIC THYROID TISSUE		
Struma ovarii	Ovarian teratoma containing thyroid tissue	Rare
Metastatic follicular thyroid cancer	Large tumor mass capable of secreting thyroid hormone autonomously	Rare
Pituitary resistance to thyroid hormone	Mutated thyroid hormone receptor-β	Rare

Table 568-4 Management of Thyroid Storm in Adolescents

GOAL	TREATMENT
Inhibition of thyroid hormone formation and secretion	Propylthiouracil, 400 mg every 8 hr PO or by nasogastric tube Saturated solution of potassium iodide, 3 drops every 8 hr
Sympathetic blockade	Propranolol, 20-40 mg every 4-6 hr or 1 mg IV slowly (repeat doses until heart rate slows); not indicated in patients with asthma or heart failure that is not rate related
Glucocorticoid therapy	Prednisone 20 mg bid
Supportive therapy	Intravenous fluids (depending on indication: glucose, electrolytes, multivitamins) Temperature control (cooling blankets, acetaminophen; avoid salicylates) O_2 if required Digitalis for heart failure and to slow ventricular response; pentobarbital for sedation Treatment of precipitating event (e.g., infection)

Table 569-1 Etiologic Classification of Solitary Thyroid Nodules

Lymphoid follicle, as part of chronic lymphocytic thyroiditis
Thyroid developmental anomalies
Intrathyroidal thyroglossal duct cyst
Thyroid abscess (acute suppurative thyroiditis)
Simple cyst
Neoplasms
Benign
Colloid (adenomatous) nodule
Follicular adenoma
Toxic adenoma
Nonthyroidal (e.g., lymphohemangioma)
Malignant
Papillary carcinoma
Follicular carcinoma
Mixed papillary-follicular carcinoma
Undifferentiated (anaplastic)
Medullary carcinoma
Nonthyroidal
Lymphoma
Teratoma

Table 571-1 Causes of Hypocalcemia

I. Neonatal	4. CaSR-activating mutation a. Sporadic b. Autosomal dominant (G protein subunit $\alpha 11$ mutation)
A. Maternal Disorders	
Diabetes mellitus	
Toxemia of pregnancy	
Vitamin D deficiency	
High intake of alkali or magnesium sulfate	
Use of anticonvulsants	
Hyperparathyroidism	
B. Neonatal Disorders	
Low birthweight: prematurity, intrauterine growth restriction	
Peripartum asphyxia, sepsis, critical illness	
Hyperbilirubinemia, phototherapy, exchange transfusion	
Hypomagnesemia, hypermagnesemia	
Acute/chronic renal failure	
Nutrients/medications: high phosphate intake, fatty acids, phytates, bicarbonate infusion, citrated blood, anticonvulsants, aminoglycosides	
Hypoparathyroidism	
Vitamin D deficiency or resistance	
Osteopetrosis type II	
II. Hypoparathyroidism	
A. Congenital	
1. Transient neonatal	
2. Congenital hypoparathyroidism	
a. Familial isolated hypoparathyroidism	
(1) Autosomal recessive hypoparathyroidism (GCMB, PTH)	
(2) Autosomal dominant hypoparathyroidism (CaSR)	
(3) X-linked hypoparathyroidism (SOX3)	
b. DiGeorge syndrome (<i>TBX1</i>)	
c. Sanjad-Sakati syndrome (short stature, retardation, dysmorphism; HRD); Kenny-Caffey syndrome 1 (short stature, medullary stenosis) (<i>TBCE</i>)	
d. Barakat syndrome (sensorineural deafness, renal dysplasia; HDR) (<i>GATA3</i>)	
e. Lymphedema-hypoparathyroidism-nephropathy, nerve deafness	
f. Mitochondrial fatty acid disorders (Kearns-Sayre, Pearson, MELAS)	
3. Insensitivity to PTH	
a. Blomstrand chondrodyplasia (<i>PTHR1</i>)	
b. Pseudohypoparathyroidism type IA (<i>GNAS</i>)	
Pseudohypoparathyroidism type IB	
Pseudohypoparathyroidism type IC	
Pseudohypoparathyroidism type II	
Pseudopseudohypoparathyroidism	
c. Acrodysostosis with hormone resistance (<i>PRKAR1A</i>)	
d. Hypomagnesemia	
	III. Vitamin D Deficiency
	IV. Other Causes of Hypocalcemia
	A. Calcium Deficiency
	1. Nutritional deprivation
	2. Hypercalciuria
	B. Disorders of Magnesium Homeostasis
	1. Congenital hypomagnesemia
	2. Acquired
	a. Acute renal failure
	b. Chronic inflammatory bowel disease, intestinal resection
	c. Diuretics
	C. Hyperphosphatemia
	1. Renal failure
	2. Phosphate administration (intravenous, oral, rectal)
	3. Tumor cell lysis
	4. Muscle injuries (crush, rhabdomyolysis)
	D. Miscellaneous
	1. Hypoproteinemia
	2. Hyperventilation
	3. Drugs: furosemide, aminoglycosides, bisphosphonates, calcitonin, anticonvulsants, ketoconazole, antineoplastic agents (placamycin, asparaginase, cisplatin, cytosine arabinoside, doxorubicin), citrated blood products
	4. Hungry bone syndrome
	5. Acute and critical illness: sepsis, acute pancreatitis, toxic shock
	a. Organic acidemia: propionic, methylmalonic, isovaleric

HRD, hypoparathyroidism, sensorineural deafness, and renal anomaly; HRD, hypoparathyroidism, retardation, dysmorphism; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episode; PTH, parathyroid hormone.

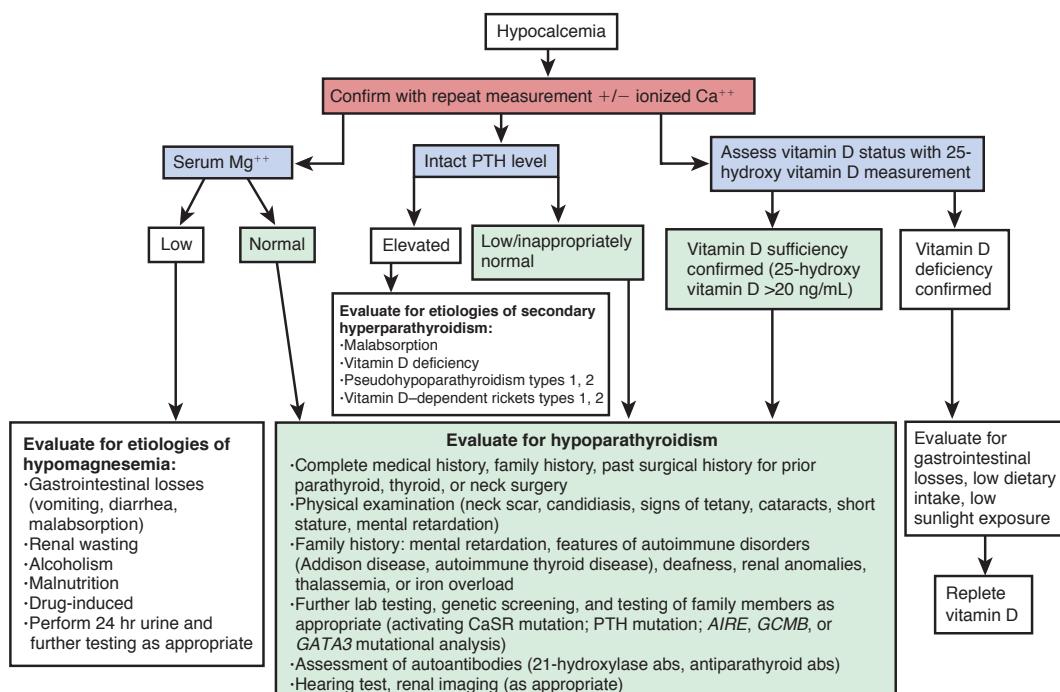


Figure 571-1 Evaluation of hypocalcemia. Abs, autoantibodies; CaSR, calcium-sensing receptor; PTH, parathyroid hormone. (From Bilezikian JP, Khan A, Potts JT Jr, et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. J Bone Miner Res 26:2317–2337, 2011, Fig. 1.)

2696 Part XXVI ◇ The Endocrine System

Table 573-1 Causes of Hypercalcemia

I.	Neonate/Infant
A.	Maternal Disorders
1.	Excessive vitamin D ingestion, hypoparathyroidism, pseudohypoparathyroidism
B.	Neonate/Infant
1.	Iatrogenic: excessive intake of calcium, vitamin D, vitamin A
2.	Phosphate depletion
3.	Subcutaneous fat necrosis
4.	Williams-Beuren syndrome (del7q11.23/BAZ1B) (transient receptor potential; 3-channel defect)
5.	Neonatal severe hyperparathyroidism (CaSR)
6.	Metaphyseal chondrodysplasia, Murk-Jansen type (PTH1R)
7.	Idiopathic infantile hypercalcemia (CYP24A1) (25-hydroxyvitamin D 24-hydroxylase)
8.	Persistent parathyroid hormone-related protein
9.	Lactase/disaccharidase deficiency (LCT)
10.	Infantile hypophosphatasia (TNSALP)
11.	Mucolipidosis type II (GNPTAB)
12.	Blue diaper syndrome
13.	Antenatal Bartter syndrome types 1 and 2 (SLC12A1, KCNJ1)
14.	Distal renal tubular acidosis
15.	IMAGe syndrome (CDKN1C)
16.	Post bone marrow transplantation for osteopetrosis
17.	Endocrinopathies: primary adrenal insufficiency, severe congenital hypothyroidism, hyperthyroidism
II.	Hyperparathyroidism
A.	Sporadic
1.	Parathyroid hyperplasia, adenoma, carcinoma
B.	Familial
1.	Neonatal severe hyperparathyroidism (CaSR)
2.	Multiple endocrine neoplasia, type I (MEN1)
3.	Multiple endocrine neoplasia, type IIA (RET)
4.	Multiple endocrine neoplasia, type IIB (RET)
5.	Multiple endocrine neoplasia, type IV (CDKN1B)
6.	McCune-Albright syndrome (GNAS)
7.	Familial isolated hyperparathyroidism 1 (CDC73)
8.	Familial isolated hyperparathyroidism 2 (jaw tumor syndrome) (CDC73)
9.	Familial isolated hyperparathyroidism 3
10.	Jansen metaphyseal dysplasia (PTH1R)
C.	Secondary/Tertiary
1.	Postrenal transplantation
2.	Chronic hyperphosphatemia
D.	Hypercalcemia of Malignancy
1.	Ectopic production of parathyroid hormone-related peptide
2.	Metastatic dissolution of bone
III.	Familial Hypocalciuric Hypercalcemia
A.	Familial Hypocalciuric Hypercalcemia I (CaSR)
1.	Loss-of-function mutations in CaSR
a.	Monoallelic: familial benign hypercalcemia
b.	Biallelic: neonatal severe hyperparathyroidism
B.	Familial Hypocalciuric Hypercalcemia II (GNA11)
C.	Familial Hypocalciuric Hypercalcemia III, Oklahoma Variant (AP2S1)
D.	CaSR-blocking autoantibodies
IV.	Excessive Calcium or Vitamin D
A.	Milk-Alkali Syndrome
B.	Exogenous Ingestion of Calcium or Vitamin D or Topical Application of Vitamin D (calcitriol or analog)
C.	Ectopic Production of Calcitriol Associated with Granulomatous Diseases (sarcoidosis, cat-scratch fever; tuberculosis, histoplasmosis, coccidioidomycosis, leprosy; human immunodeficiency virus; cytomegalovirus; chronic inflammatory bowel disease)
D.	Neoplasia
1.	Primary bone tumors
2.	Metastatic tumors with osteolysis
3.	Lymphoma, leukemia
4.	Dysgerminoma
5.	Pheochromocytoma
6.	Tumors secreting parathyroid hormone-related peptide, growth factors, cytokines, prostaglandins, osteoclast-activating factors
E.	Williams-Beuren Syndrome (del7q11.23)
V.	Immobilization
VI.	Other Causes
A.	Drugs: Thiazides, Lithium, Vitamin A and Analogs, Calcium, Alkali, Antiestrogens, Aminophylline
B.	Total Parenteral Nutrition
C.	Endocrinopathies: Hyperthyroidism, Addison disease, Pheochromocytoma
D.	Vasoactive Intestinal Polypeptide-Secreting Tumor
E.	Acute or Chronic Renal Failure/Administration of Aluminum
F.	Hypophosphatasia
G.	Juvenile Rheumatoid Arthritis: Cytokine Mediated

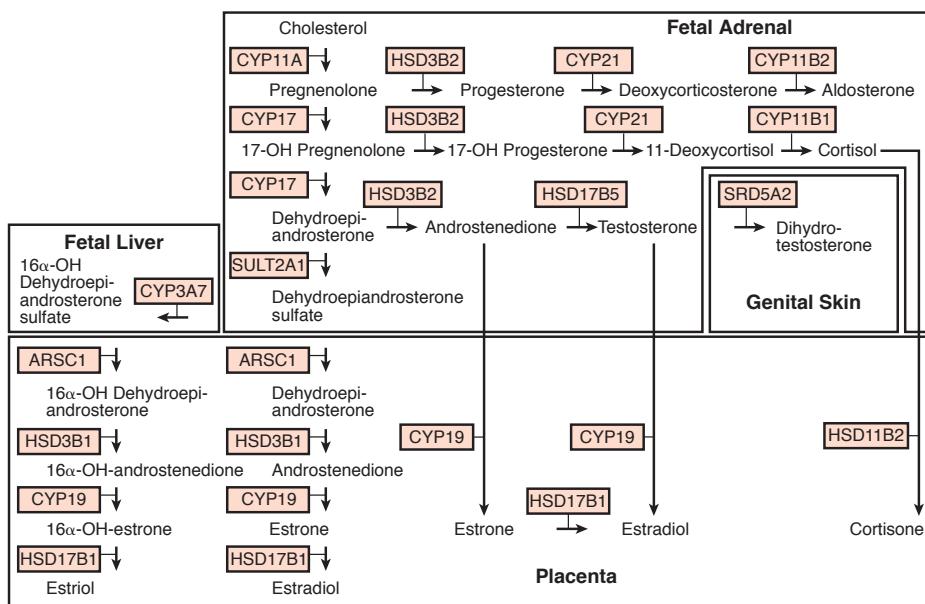


Figure 574-1 Steroid biosynthesis and metabolism during gestation. Conversions within the fetal adrenal cortex, fetal liver, male (i.e., testosterone-exposed) genital skin, and placenta are denoted by arrows; the enzyme mediating each conversion is also shown. Enzymatic conversions in the adrenal cortex are the same postnatally as prenatally, but cortisol and aldosterone biosynthesis are more prominent, and normally little testosterone is synthesized. Many of the involved enzymes are cytochromes P450 (CYPs). Adrenal enzymes include CYP 11A, cholesterol side-chain cleavage enzyme (P450ccc in older terminology); HSD3B2, 3 β -hydroxysteroid dehydrogenase/ Δ 5, Δ 4 isomerase type 2; CYP 17, 17 β -hydroxylase/17,20-lyase (P450c17); CYP 21, 21-hydroxylase (P450c21); CYP 11B1, 11 β -hydroxylase (P450c11); CYP 11B2, aldosterone synthase (P450aldo; this enzyme mediates successive 11 β -hydroxylase, 18-hydroxylase, and 18-oxidase reactions in the zona glomerulosa for the conversion of deoxycorticosterone to aldosterone). Other enzymes important in the fetoplacental unit include ARSC1, arylsulfatase; CYP 19, aromatase (P450arom); HSD3B1, 3 β -hydroxysteroid dehydrogenase/ Δ 5, Δ 4 isomerase type 1; HSD11B2, 11 β -hydroxysteroid dehydrogenase type 2; HSD17B1 and HSD17B5 are 2 different 17-hydroxysteroid dehydrogenase enzymes; SRD5A2, steroid 5 α -reductase type 2; SULT2A1, steroid sulfotransferase.

Table 575-3 Frequencies of Etiologies of Primary Adrenal Insufficiency

ETIOLOGY	AGE AT DIAGNOSIS
Congenital adrenal hyperplasia	59% Infancy
Autoimmune	16% Childhood-adolescence
APECED (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy)	6% Childhood-adolescence
Adrenoleukodystrophy	4% Childhood-adolescence
Isolated glucocorticoid deficiency	4% Infancy
Idiopathic	4% Childhood
Syndromes	3% Infancy
X-linked adrenal hypoplasia congenita	2% Infancy-childhood
Hemorrhage	1% Infancy

Data from Perry R, Kecha O, Paquette J, et al. Primary adrenal insufficiency in children: twenty years' experience at the Sainte-Justine Hospital, Montreal. *J Clin Endocrinol Metab* 90:3243–3250, 2005; Hsieh S, White PC. Presentation of primary adrenal insufficiency in childhood. *J Clin Endocrinol Metab* 96:E925–E928, 2011.

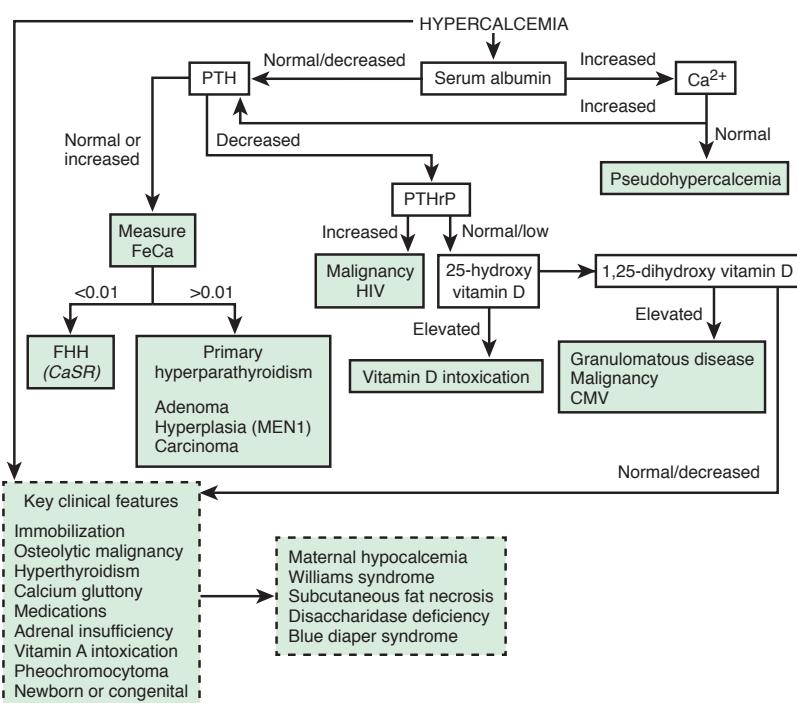


Figure 573-1 Evaluation of hypercalcemia. Ca²⁺, calcium ions; CaSR, calcium-sensing receptor; CMV, cytomegalovirus; FeCa, fractional excretion of urinary calcium. (From Lietman SA, Germain-Lee EL, Levine MA. Hypercalcemia in children and adolescents. *Curr Opin Pediatr* 22:508–515, 2010.)

2704 Part XXVI ◇ The Endocrine System

Table 575-1 Causes of Primary Adrenal Insufficiency

	PATHOGENESIS OR GENETICS	CLINICAL FEATURES IN ADDITION TO ADRENAL INSUFFICIENCY
CONGENITAL ADRENAL HYPERPLASIA		
21-Hydroxylase deficiency	CYP21A2 mutations	Hyperandrogenism
11β-Hydroxylase deficiency	CYP11B1 mutations	Hyperandrogenism, hypertension
3β-Hydroxysteroid dehydrogenase type 2 deficiency	HSD3B2 mutations	Ambiguous genitalia in boys, postnatal virilization in girls
17α-Hydroxylase deficiency	CYP17A1 mutations	
P450 oxidoreductase deficiency	POR mutations	XY sex reversal, pubertal delay in both sexes, hypertension
P450 side-chain cleavage deficiency	CYP11A1 mutations	Skeletal malformation (Antley-Bixler syndrome), abnormal genitalia
Congenital lipoid adrenal hyperplasia	STAR mutations	XY sex reversal
OTHER GENETIC DISORDERS		
Adrenoleukodystrophy or adrenomyeloneuropathy	ABCD1 mutations	Weakness, spasticity, dementia, blindness, quadripareisis. Adrenomyeloneuropathy is a milder variant of adrenoleukodystrophy with slower progression
Triple A syndrome (Allgrove syndrome)	AAAS mutations	Achalasia, alacrima, cognitive deficits, neuromuscular deficits, hyperkeratosis
Smith-Lemli-Opitz syndrome	DHCR7 mutations	Craniofacial malformations, developmental delay growth failure, cholesterol deficiency
Wolman disease	LIPA mutations	Bilateral adrenal calcification, hepatosplenomegaly
Kearns-Sayre syndrome	Mitochondrial DNA deletions	External ophthalmoplegia, retinal degeneration, cardiac conduction defects, other endocrine disorders
Pallister-Hall syndrome	GLI3 mutations	hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and postaxial polydactyly
IMAGe syndrome	CDKN1C mutations	Intrauterine growth retardation, metaphyseal dysplasia, genital abnormalities
<i>Adrenal Hypoplasia Congenita</i>		
X-linked	NR0B1 mutations	Hypogonadotropic hypogonadism in boys
Xp21 contiguous gene syndrome	Deletion of genes for Duchenne muscular dystrophy, glyceral kinase, and NR0B1	Duchenne muscular dystrophy, glyceral kinase deficiency, psychomotor retardation
SF-1 linked	NR5A1 mutations	XY sex reversal
<i>Familial Glucocorticoid Deficiency or Corticotropin Insensitivity Syndromes</i>		
Type 1	MC2R mutations	Tall stature, characteristic facial features, such as hypertelorism and frontal bossing
Type 2	MRAP mutations	
Variant of familial glucocorticoid deficiency	MCM4 mutations	Growth failure, increased chromosomal breakage, natural killer cell deficiency
Variant of familial glucocorticoid deficiency	NNT mutations	
AUTOIMMUNE		
Isolated	Sporadic; associations with HLA-DR3-DQ2, HLA-DR4-DQ8, MICA, CTLA4, PTPN22, CIITA, CLEC16A	None
APS type 1 (APECED)	AIRE mutations	Chronic mucocutaneous candidosis, hypoparathyroidism, other autoimmune diseases
APS type 2	Sporadic; associations with HLA-DR3, HLA-DR4, CTLA4	Thyroid autoimmune disease, type 1 diabetes, other autoimmune diseases
APS type 4	Sporadic; associations with HLA-DR3, CTLA4	Other autoimmune diseases (autoimmune gastritis, vitiligo, coeliac disease, alopecia), excluding thyroid disease and type 1 diabetes
INFECTIOUS		
Tuberculous adrenalitis	Tuberculosis	Tuberculosis-associated manifestations in other organs
AIDS	HIV-1	Other AIDS-associated diseases
Fungal adrenalitis	Histoplasmosis, cryptococcosis, coccidioidomycosis	Opportunistic infections
Meningococcal sepsis (Waterhouse-Friderichsen syndrome), African trypanosomiasis	Neisseria meningitidis	
	Trypanosoma brucei	Other trypanosomiasis-associated organ involvement
OTHER ACQUIRED CAUSES		
Bilateral adrenal hemorrhage	Meningococcal sepsis (Waterhouse-Friderichsen syndrome), primary antiphospholipid syndrome, traumatic birth, anticoagulation	Symptoms and signs of underlying disease
Bilateral adrenal metastases	Mainly cancers of the lung, stomach, breast, and colon	Symptoms and signs of underlying disease
Bilateral adrenal infiltration	Primary adrenal lymphoma, amyloidosis, hemochromatosis, sarcoidosis (rare)	Symptoms and signs of underlying disease
Bilateral adrenalectomy		Symptoms and signs of underlying disease

Table 575-1 Causes of Primary Adrenal Insufficiency—cont'd

	PATHOGENESIS OR GENETICS	CLINICAL FEATURES IN ADDITION TO ADRENAL INSUFFICIENCY
DRUG-INDUCED		
Mitotane (o,p-DDD)	Cytotoxicity	None, unless related to drug
Aminoglutethimide	Inhibition of cholesterol side chain cleavage enzyme (CYP11A1)	None, unless related to drug
Trilostane	Inhibition of 3β-hydroxysteroid dehydrogenase type 2	None, unless related to drug
Etomidate	Inhibition of 11β-hydroxylase (CYP11B1)	None, unless related to drug
Ketoconazole, fluconazole	Inhibition of mitochondrial cytochrome P450 enzymes (e.g., CYP11A1, CYP11B1)	None, unless related to drug

AAAS, achalasia, adrenocortical insufficiency, alacrima syndrome; ABCD, ATP-binding cassette, subfamily D; ABCG5, ATP-binding cassette, subfamily G, member 5; ABCG8, ATP-binding cassette, subfamily G, member 8; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; APS, autoimmune polyendocrinopathy syndrome; CIITA, class II transactivator; CTLA-4, cytotoxic T-lymphocyte antigen 4; DHCR7, 7-dehydrocholesterol reductase; HLA, human leukocyte antigen; IMAGe, intrauterine growth restriction (IUGR), metaphyseal dysplasia, adrenal hypoplasia congenita (AHC), and genitourinary abnormalities; LIPA, lipase A; MC2R, melanocortin 2 receptor; MCM4, minichromosome maintenance complex component 4; MICA, major histocompatibility complex class I chain-related gene A; MRAP, melanocortin 2 receptor accessory protein; PTPN22, protein tyrosine phosphatase, non-receptor type 22; StAR, steroidogenic acute regulatory protein.

Adapted from: Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. Lancet 383:2152–2164, 2014, Table 1, pp. 2153–2154.

Table 575-2 Causes of Secondary Adrenal Insufficiency

	ETOLOGIES	CLINICAL MANIFESTATIONS IN ADDITION TO ADRENAL INSUFFICIENCY
DRUG-INDUCED		
Abrupt cessation of glucocorticoid therapy (systemic or topical)	Suppression of CRH and ACTH secretion leading to atrophy of the adrenal cortex	Primary disease-associated symptoms
OTHER ACQUIRED CAUSES		
Hypothalamic or pituitary tumors	Adenomas, cysts, craniopharyngiomas, ependymomas, meningiomas, rarely carcinomas, metastasis	Panhypopituitarism*; primary disease-associated symptoms
Traumatic brain injury		Panhypopituitarism*; primary disease-associated symptoms
Hypothalamic or pituitary surgery or irradiation		Panhypopituitarism*; primary disease-associated symptoms
Infections or infiltrative processes	Lymphocytic hypophysitis, hemochromatosis, tuberculosis, meningitis, sarcoidosis, actinomycosis, histiocytosis X, Wegener granulomatosis	Panhypopituitarism*; primary disease-associated symptoms
Pituitary apoplexy (when occurring in a peripartum mother, termed Sheehan syndrome)	High blood loss or hypotension	Abrupt onset of severe headache, visual disturbance, nausea, vomiting; panhypopituitarism*; primary disease-associated symptoms
CONGENITAL OR GENETIC CAUSES		
<i>Abnormal Central Nervous System Development</i>		
Anencephaly	Multiple	Primary disease-associated symptoms
Holoprosencephaly	Multiple	Primary disease-associated symptoms
<i>Combined Pituitary Hormone Deficiency (CPHD)†</i>		
CPHD2	Mutations in <i>PROP1</i> (paired-like homeobox 1)	Panhypopituitarism; corticotropin deficiency occurs in adolescence
CPHD3	Mutations in <i>LHX3</i> (LIM homeobox 3)	Panhypopituitarism; deafness, short neck
CPHD4	Mutations in <i>LHX4</i> (LIM homeobox 4)	Panhypopituitarism; small sella, cerebellar defects
Septooptic dysplasia, CPHD5	Mutations in <i>HESX1</i> (HESX homeobox 1)	Panhypopituitarism; septooptic dysplasia (blindness owing to hypoplastic optic nerves, absence of the septum pellucidum); developmental delay
CPHD6	Mutations in <i>OTX2</i> (orthodenticle homeobox 2)	Panhypopituitarism; ectopic posterior pituitary gland
X-linked panhypopituitarism	Mutations in <i>SOX3</i> (SRY(sex-determining region Y box 3)	Panhypopituitarism; infundibular hypoplasia, developmental delay
<i>Other Genetic Syndromes Affecting Corticotropin Secretion</i>		
Congenital proopiomelanocortin deficiency	Mutations in <i>POMC</i> (proopiomelanocortin)	Early-onset severe obesity, hyperphagia, red hair
Prohormone convertase 1/3 deficiency	Mutations in <i>PC1</i> (prohormone convertase 1/3)	Obesity, malabsorption or diarrhea, hypogonadotropic hypogonadism
Isolated ACTH (corticotropin) deficiency	Mutations in <i>TBX19</i> (T-box 19)	
Prader-Willi syndrome	Deletion or silencing of genes on the parental copy of genes within the imprinted chromosome region 15q11-q13 including <i>SNRPN</i> (small nuclear ribonucleoprotein polypeptide N) and <i>NDN</i> (necidin, melanoma antigen (MAGE) family member)	Dysmorphic features, hypotonia, developmental delay, obesity, growth hormone deficiency, hypogonadotropic hypogonadism

*The associated anterior and/or posterior hormone deficiencies may vary.

†CPHD1 (mutations in *POU1F1*) is not associated with corticotropin deficiency.

2716 Part XXVI ◇ The Endocrine System

Table 576-1 Diagnosis and Treatment of Congenital Adrenal Hyperplasia

DISORDER	AFFECTED GENE AND CHROMOSOME	SIGNS AND SYMPTOMS	LABORATORY FINDINGS	THERAPEUTIC MEASURES
21-Hydroxylase deficiency, classic form	CYP21 6p21.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated 17-hydroxyprogesterone	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
21-Hydroxylase deficiency, nonclassic form	CYP21 6p21.3	May be asymptomatic; precocious adrenarche, hirsutism, acne, menstrual irregularity, infertility	↑ Baseline and ACTH-stimulated 17-hydroxyprogesterone ↑ Serum androgens	Suppression with glucocorticoids
11β-Hydroxylase deficiency	CYP11B1 8q24.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated 11-deoxycortisol and deoxycorticosterone	Glucocorticoid (hydrocortisone) replacement
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
		Hypertension	↓ Plasma renin, hypokalemia	Suppression with glucocorticoids
3β-Hydroxysteroid dehydrogenase deficiency, classic form	HSD3B2 1p13.1	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated Δ5 steroids (pregnenolone, 17-hydroxy-pregnenolone, DHEA)	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females and males	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing
		Precocious adrenarche, disordered puberty	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Suppression with glucocorticoids
17α-Hydroxylase/ 17,20-lyase deficiency	CYP17 10q24.3	Cortisol deficiency (corticosterone is an adequate glucocorticoid)	↓ Cortisol, ↑ ACTH ↑ DOC, corticosterone Low 17α-hydroxylated steroids; poor response to ACTH	Glucocorticoid (hydrocortisone) administration
		Ambiguous genitalia in males	↓ Serum androgens; poor response to hCG	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Sexual infantilism	↓ Serum androgens or estrogens	Sex hormone replacement consonant with sex of rearing
		Hypertension	↓ Plasma renin; hypokalemia	Suppression with glucocorticoids
Congenital lipoid adrenal hyperplasia	STAR 8p11.2	Glucocorticoid deficiency	↑ ACTH Low levels of all steroid hormones, with decreased or absent response to ACTH	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↓ Aldosterone, ↑ plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in males	Decreased or absent response to hCG in males	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Poor pubertal development or premature ovarian failure in females	↑ FSH, ↑ LH, ↓ estradiol (after puberty)	Estrogen replacement

Table 576-1 Diagnosis and Treatment of Congenital Adrenal Hyperplasia—cont'd

DISORDER	AFFECTED GENE AND CHROMOSOME	SIGNS AND SYMPTOMS	LABORATORY FINDINGS	THERAPEUTIC MEASURES
P450 oxidoreductase deficiency	POR 7q11.3	Glucocorticoid deficiency Ambiguous genitalia in males and females Maternal virilization Antley-Bixler syndrome	↓ Cortisol, ↑ ACTH ↑ Pregnenolone, ↑ progesterone ↑ Serum androgens prenatally, ↓ androgens and estrogens at puberty Decreased ratio of estrogens to androgens	Glucocorticoid (hydrocortisone) replacement Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing

↓, Decreased; ↑, increased; ↑↑, markedly increased; ACTH, adrenocorticotrophic hormone; DHEA, dehydroepiandrosterone; DOC, 11-deoxycorticosterone; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone.

Table 576-2 Genotype-Phenotype Correlations in Congenital Adrenal Hyperplasia Owing to 21-Hydroxylase Deficiency

MUTATION GROUP	A	B	C
Enzymatic activity, % normal	Nil	1-2%	20-50%
CYP21 mutations (phenotype generally corresponds to the least affected allele)	Gene deletion Exon 3 del 8 bp Exon 6 cluster Q318X R356W Intron 2 splice	I172N	P30L V281L P453S
Severity	Salt wasting	Simple virilizing	Nonclassic
Aldosterone synthesis	Low	Normal	Normal
Age at diagnosis (without newborn screening)	Infancy	Infancy (females) Childhood (males)	Childhood to adulthood, or asymptomatic
Virilization	Severe	Moderate to severe	None to Mild
Incidence	1/20,000	1/50,000	1/500

Table 575-4 Clinical Manifestations and Biochemical Findings in Adrenal Insufficiency

	PATHOPHYSIOLOGIC MECHANISM	PREVALENCE (%)*
SYMPTOMS		
Fatigue	Glucocorticoid deficiency	90
Anorexia, weight loss	Glucocorticoid deficiency	90
Nausea, vomiting	Glucocorticoid deficiency, mineralocorticoid deficiency	90
Salt craving (primary adrenal insufficiency only)	Mineralocorticoid deficiency	20
Myalgia or joint pain	Glucocorticoid deficiency	
SIGNS		
Low blood pressure, orthostatic hypotension	Mineralocorticoid deficiency, glucocorticoid deficiency	70-100%
Skin or mucosal hyperpigmentation (primary adrenal insufficiency only)	Excess of proopiomelanocortin-derived peptides	70
LABORATORY FINDINGS		
Hyponatremia	Mineralocorticoid deficiency, glucocorticoid deficiency (leading to decreased free water excretion)	90
Hyperkalemia (primary adrenal insufficiency only)	Mineralocorticoid deficiency	50
Hypoglycemia	Glucocorticoid deficiency	30
Ketosis	Glucocorticoid deficiency	30
Low random cortisol level	Glucocorticoid deficiency	80
Eosinophilia, lymphocytosis	Glucocorticoid deficiency	
High ACTH level (primary adrenal insufficiency only)	Glucocorticoid deficiency	100
High plasma renin activity (primary adrenal insufficiency only)	Mineralocorticoid deficiency	100

*Prevalence data are for primary insufficiency only. Blanks indicate that no pediatric prevalence data are available.

Data from Hsieh S, White PC. Presentation of primary adrenal insufficiency in childhood. J Clin Endocrinol Metab 96:E925-E928, 2011.

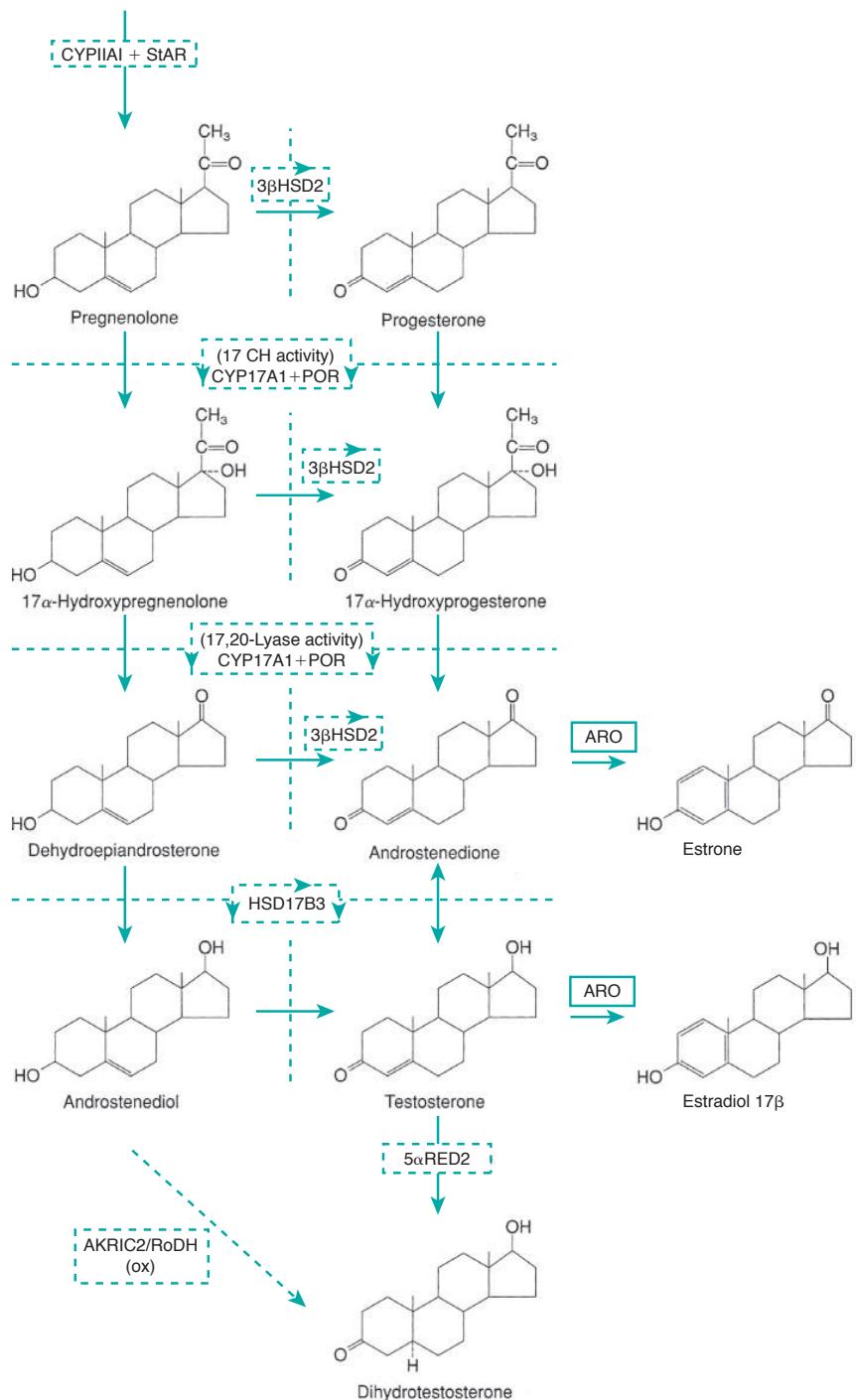


Figure 582-1 Biosynthesis of sex steroids. Dashed lines indicate enzymatic defects associated with 46,XY disorder of sex differentiation. 3β HSD2, 3β -hydroxysteroid dehydrogenase type 2; AKR1C2/RoDH (Ox), one of the enzymes in the recently described alternative androgen biosynthetic pathway; ARO, aromatase; CYP17A1, the enzyme that catalyzes both 17α -hydroxylase (17-OH) and 17,20-lyase activities; HSD17B3, enzyme that catalyzes the 17-ketoreductase reaction; POR, P450 oxidoreductase; StAR, steroidogenic acute regulatory protein.

Table 585-1 Causes of Gynecomastia

SYMPTOMS	SIGNS
FETAL ANDROGEN DEFICIENCY	
Ambiguous genitalia	Ambiguous genitalia (47,XY disorders of sex development)
	Normal female genitalia
	Microphallus (resembling clitoromegaly)
	Pseudovaginal perineoscrotal hypospadias
	Bifid scrotum
	Cryptorchidism
PREPUBERTAL ANDROGEN DEFICIENCY	
Delayed puberty	Eunuchoidism
Lack of sexual interest or desire (libido)	Infantile genitalia
Reduced nighttime or morning spontaneous erections	Small testes
Breast enlargement and tenderness	Lack of male hair pattern growth, no acne
Reduced motivation and initiative	Disproportionately long arms and legs relative to height
Diminished strength and physical performance	Pubertal fat distribution
No ejaculate or ejaculation (spermarche)	Poorly developed muscle mass
Inability to father children (infertility)	High-pitched voice
	Reduced peak bone mass, osteopenia, or osteoporosis
	Gynecomastia
	Small prostate gland
	Aspermia, severe oligozoospermia, or azoospermia
ADULT ANDROGEN DEFICIENCY	
Incomplete sexual development	Eunuchoidism
Lack of sexual interest or desire (libido)	Small or shrinking testes
Reduced nighttime or morning spontaneous erections	Loss of male hair (axillary and pubic hair)
Breast enlargement and tenderness	Gynecomastia
Inability to father children (infertility)	Aspermia or azoospermia or severe oligozoospermia
Height loss, history of minimal-trauma fracture	Low bone mineral density (osteopenia or osteoporosis)
Hot flushes, sweats	Height loss, minimal-trauma or vertebral compression fracture
Reduced shaving frequency	Unexplained reduction in prostate size or prostate-specific antigen
Less-Specific Symptoms	
Decreased energy, vitality	Less-Specific Signs
Decreased motivation, self-confidence	Mild normocytic, normochromic anemia (normal female range)
Feeling sad or blue, irritability	Depressed mood, mild depression or dysthymia
Weakness, decreased physical or work performance	Reduced muscle bulk and strength
Poor concentration and memory	Increased body fat or body mass index
Increased sleepiness	Fine facial skin wrinkling (lateral to orbits and mouth)

Table 589-2 Diagnostic Criteria for Impaired Glucose Tolerance and Diabetes Mellitus

IMPAIRED GLUCOSE TOLERANCE	DIABETES MELLITUS
Fasting glucose 100–125 mg/dL (5.6–7.0 mmol/L)	Symptoms* of diabetes mellitus plus random or casual plasma glucose ≥200 mg/dL (11.1 mmol/L) or
2-hr plasma glucose during the OGTT ≥140 mg/dL, but <200 mg/dL (11.1 mmol/L)	Fasting (at least 8 hr) plasma glucose ≥126 mg/dL (7.0 mmol/L) or 2 hr plasma glucose during the OGTT ≥200 mg/dL or Hemoglobin A _{1C} ≥6.5% [†]

*Symptoms include polyuria, polydipsia, and unexplained weight loss with glucosuria and ketonuria.

[†]Results should be confirmed by repeat testing if in absence of unequivocal hyperglycemia.

OGTT, oral glucose tolerance test.

Table 583-1 Etiologic Classification of Male Hypogonadism

HYPERGONADOTROPIC HYPOGONADISM (PRIMARY HYPOGONADISM; TESTES)	
Congenital	Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) resistance
	Mutations in steroid synthetic pathways
	Gonadal dysgenesis
	Klinefelter syndrome (47,XXY)
	Noonan syndrome (PTPN-11 gene mutation in many cases)
	Cystic fibrosis (infertility)
Acquired	Cryptorchidism (some cases)
	Vanishing testes
	Chemotherapy
	Radiation
	Infection (e.g., mumps)
	Infarction (testicular torsion)
	Trauma
HYPOGONADOTROPIC HYPOGONADISM (SECONDARY HYPOGONADISM; HYPOTHALAMIC-PITUITARY)	
Congenital	Genetic defects causing Kallmann syndrome and/or normosmic hypogonadotropic hypogonadism (HH)
	Other genetic disorders associated with HH: leptin gene, leptin receptor, DAX1 (dosage-sensitive/sex-reversal adrenal hypoplasia on the X chromosome), SF-1 (steroidogenic factor-1)
	Inherited syndromes: Prader-Willi, Bardet-Biedl, Laurence-Moon-Biedl, Alström
	Isolated HH at pituitary level (gonadotropin-releasing hormone receptor, FSH and LH β-subunit)
	Multiple pituitary hormone deficiencies: septooptic dysplasia (HESX-1 in some cases) and other disorders of pituitary organogenesis (e.g., PROP1, LHX3, LHX4, SOX-3)
Idiopathic	
Acquired	
	Anorexia nervosa
	Drug use
	Malnutrition
	Chronic illness, especially Crohn disease
	Hyperprolactinemia
	Pituitary tumors
	Pituitary infarction
	Infiltrative disorders (e.g., histiocytosis, sarcoidosis)
	Hemosiderosis and hemochromatosis
	Radiation

Table 577-1 Etiologic Classification of Adrenocortical Hyperfunction

EXCESS ANDROGEN	
Congenital adrenal hyperplasia	
21-Hydroxylase (P450c21) deficiency	
11β-Hydroxylase (P450c11) deficiency	
3β-Hydroxysteroid dehydrogenase defect (deficiency or dysregulation)	
Tumor	
EXCESS CORTISOL (CUSHING SYNDROME)	
Bilateral adrenal hyperplasia	
Adenoma	
Hypersecretion of corticotropin (Cushing disease)	
Ectopic secretion of corticotropin	
Exogenous corticotropin	
Adrenocortical nodular dysplasia	
Pigmented nodular adrenocortical disease (Carney complex)	
Tumor	
McCune-Albright syndrome	
EXCESS MINERALOCORTICOID	
Primary hyperaldosteronism	
Aldosterone-secreting adenoma	
Bilateral micronodular adrenocortical hyperplasia	
Glucocorticoid-suppressible aldosteronism	
Tumor	
Deoxycorticosterone excess	
Congenital adrenal hyperplasia	
11β-Hydroxylase (P450c11)	
17α-Hydroxylase (P450c17)	
Tumor	
Apparent mineralocorticoid excess (deficiency of 11β-hydroxysteroid dehydrogenase type 2)	
EXCESS ESTROGEN	
Tumor	

Table 588-1 Revised Nomenclature

PREVIOUS	CURRENTLY ACCEPTED
Intersex	Disorders of sex development (DSD)
Male pseudohermaphrodite	46,XY DSD
Undervirilization of an XY male	46,XY DSD
Undermasculinization of an XY male	46,XY DSD
46,XY intersex	46,XY DSD
Female pseudohermaphrodite	46,XX DSD
Overvirilization of an XX female	46,XX DSD
Masculinization of an XX female	46,XX DSD
46,XX intersex	46,XX DSD
True hermaphrodite	Ovotesticular DSD
Gonadal intersex	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

Table 588-4 Sources of Maternal-Derived Androgens

ENDOGENOUS	EXOGENOUS
BENIGN	SYNTHETIC ANDROGENS
Luteoma of pregnancy	Danazol
Adrenal adenoma	Progesterins (medroxyprogesterone acetate)
Hyperreactio luteinalis	Potassium-sparing diuretics
Thecoma/fibroma	
Stromal hyperthecosis	
Brenner tumor	
Serous cystadenoma	
Mature cystic teratoma (dermoid cyst)	
MALIGNANT	
Metastatic carcinomas (Krukenberg tumor)	
Sex-cord stromal tumors— granulosa cell and Sertoli-Leydig tumors	
Adrenal cortical carcinoma	
Cystadenocarcinoma	
Hilar cell tumor	

From Auchus RJ, Chang AY: 46,XX DSD: the masculinized female. Best Pract Res Clin Endocrinol Metab 24:219–242, 2010, Table 2, p. 237.

Table 588-5 Causes of a PAIS-Like Phenotype**DEFECTS IN ANDROGEN PRODUCTION**

- Partial gonadal dysgenesis
 - Mutations in SRY, NR5A1, WT1
- Mutations of the luteinizing hormone receptor
- Biosynthetic enzyme deficiencies
- 17,20-Lyase deficiency
- P450 oxidoreductase deficiency
- 17 β -hydroxysteroid dehydrogenase deficiency type 3
- 5 α -Reductase deficiency type 2

GENETIC

- Klinefelter syndrome
- Smith-Lemli-Opitz syndrome
- Denys-Drash syndrome
- Frasier syndrome

PAIS

- Mutations of the androgen receptor gene
- Normal androgen receptor gene with fetal growth restriction

NR5A1, nuclear receptor subfamily 5 A1; PAIS, partial androgen insensitivity syndrome; SRY, sex-determining region Y; WT1, Wilms tumor 1.

From Hughes IA, Davies JD, Bunch TI, et al: Androgen insensitivity syndrome. Lancet 380:1419–1428, 2012, Panel 1, p. 1421.

Table 588-2 Etiologic Classification of Disorders of Sex Development (DSD)

46,XX DSD
<i>Androgen Exposure</i>
<i>Fetal/Fetoplacental Source</i>
21-Hydroxylase (P450c21 or CYP21) deficiency
11 β -Hydroxylase (P450c11 or CYP11B1) deficiency
3 β -Hydroxysteroid dehydrogenase II (3 β -HSD II) deficiency
Cytochrome P450 oxidoreductase (POR)
Aromatase (P450arom or CYP19) deficiency
Glucocorticoid receptor gene mutation
<i>Maternal Source</i>
Virilizing ovarian tumor
Virilizing adrenal tumor
Androgenic drugs
<i>Disorder of Ovarian Development</i>
XX gonadal dysgenesis
Testicular DSD (SRY+, SOX9 duplication)
<i>Undetermined Origin</i>
Associated with genitourinary and gastrointestinal tract defects
46,XY DSD
<i>Defects in Testicular Development</i>
Denys-Drash syndrome (mutation in WT1 gene)
WAGR syndrome (Wilms tumor, aniridia, genitourinary malformation, retardation)
Deletion of 11p13
Campomelic syndrome (autosomal gene at 17q24.3-q25.1) and SOX9 mutation
XY pure gonadal dysgenesis (Swyer syndrome)
Mutation in SRY gene
XY gonadal agenesis
Unknown cause
<i>Deficiency of Testicular Hormones</i>
Leydig cell aplasia
Mutation in LH receptor
Lipoid adrenal hyperplasia (P450scC or CYP11A1) deficiency; mutation in StAR (steroidogenic acute regulatory protein)
3 β -HSD II deficiency
17-Hydroxylase/17,20-lyase (P450c17 or CYP17) deficiency
Persistent müllerian duct syndrome because of antimüllerian hormone gene mutations or receptor defects for antimüllerian hormone
<i>Defect in Androgen Action</i>
Dihydrotestosterone deficiency because of 5 α -reductase II mutations or AKR1C2/AKR1C4 mutations
Androgen receptor defects: <ul style="list-style-type: none"> • Complete androgen insensitivity syndrome • Partial androgen insensitivity syndrome (Reifenstein and other syndromes)
Smith-Lemli-Opitz syndrome (defect in conversion of 7-dehydrocholesterol to cholesterol, DHCR7)
<i>Ovotesticular DSD</i>
XX
XY
XX/XY chimeras
<i>Sex Chromosome DSD</i>
45,X (Turner syndrome and variants)
47,XXX (Klinefelter syndrome and variants)
45,X/46,XY (mixed gonadal dysgenesis, sometimes a cause of ovotesticular DSD)
46,XX/46,XY (chimeric, sometimes a cause of ovotesticular DSD)