**Chapter 435** ◆ Disturbances of Rate and Rhythm of the Heart **2251**

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| **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 Oral: 30-60 mg/kg/24 hr Nausea, vomiting, diarrhea, fibrillation, divided q6h (sulfate) or fever, cinchonism, QRS atrial flutter, q8h (gluconate) and QT prolongation,  VT. In atrial In adults, 10 mg/kg/day AV nodal block, flutter, an divided q6h asystole syncope, AV node Max dose: 2.4g/24 hr thrombocytopenia,  blocking drug hemolytic anemia, SLE,  (digoxin, blurred vision, convulsions,  verapamil, allergic reactions,  propranolol) exacerbation of periodic  must be paralysis  given first to prevent 1 : 1 conduction  Procainamide SVT, atrial Oral: 15-50 mg/kg/24 hr PR, QRS, QT interval fibrillation, divided q4h prolongation, anorexia,  atrial flutter, Max dose: 4 g/24 hr nausea, vomiting, rash, VT IV: 10-15 mg/kg over fever, agranulocytosis,  30-45 min load followed by thrombocytopenia,  20-80 μg/kg/min Coombs-positive hemolytic  Max dose: 2 g/24 hr anemia, SLE, hypotension,  exacerbation of periodic paralysis, proarrhythmia  Disopyramide SVT, atrial Oral: <2 yr: 20-30 mg/ Anticholinergic effects, fibrillation, kg/24 hr divided q6h or urinary retention, blurred atrial flutter q12h (long-acting form); vision, dry mouth, QT and  2-10 yr: 9-24 mg/kg/24 hr QRS prolongation, hepatic divide q6h or q12h toxicity, negative inotropic (long-acting form); 11 yr: effects, agranulocytosis,  5-13 mg/kg/24 hr divided psychosis, hypoglycemia, q6h or q12h (long-acting) proarrhythmia  Max dose: 1.2 g/24 hr | | | Enhances digoxin, may increase PTT when given with warfarin  Toxicity increased by amiodarone and cimetidine | 2-6 μg/mL  4-8 μg/mL With NAPA  <40 μg/mL  2-5 μg/ml |
| CLASS IB: INHIBITS NA**+** FAST CHANNEL, SHORTENS REPOLARIZATION  Lidocaine VT, VF IV: 1 mg/kg repeat q 5 min 2 CNS effects, confusion,  times followed by convulsions, high grade AV  20-50 μg/kg/min (max block, asystole, coma,  dose: 3 mg/kg) paresthesias, respiratory  failure  Mexiletine VT Oral: 6-15 mg/kg/24 hr GI upset, skin rash,  divided q8h neurologic  Phenytoin Digitalis Oral: 3-6 mg/kg/24 hr Rash, gingival hyperplasia, intoxication divided q12h ataxia, lethargy, vertigo,  Max dose: 600 mg tremor, macrocytic anemia,  IV: 10-15 mg/kg over 1 hr bradycardia with rapid load push | | | Propranolol, cimetidine, increases toxicity | 1-5 μg/mL |
| Cimetidine | 0.8-2 μg/mL |
| Amiodarone, oral anticoagulants, cimetidine, nifedipine, disopyramide, increase toxicity | 10-20 μg/mL |
| CLASS IC: INHIBITS NA**+** CHANNEL  Flecainide SVT, atrial tachycardia, VT  Propafenone SVT, atrial tachycardia, atrial fibrillation, VT | Oral: 6.7-9.5 mg/kg/24 hr divided q8h  In older children, 50-200 mg/ m2/day divided q12h  Oral: 150-300 mg/m2/24 hr divided q6h | Blurred vision, nausea, decrease in contractility, proarrhythmia  Hypotension, decreased contractility, hepatic toxicity, paresthesia, headache, proarrhythmia | Amiodarone increases toxicity | 0.2-1 μg/mL |
| Increases digoxin levels | 0.2-1 μg/mL |

### Continued

**2252 Part XX** ◆ The Cardiovascular System

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| **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  Coadministration with disopyramide, flecainide or verapamil may decrease ventricular function  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 |
| 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 |
| 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 Oral/load instructions:  WPW), atrial Premature: 20 μg/kg flutter, atrial Newborn: 30 μg/kg fibrillation >6 mo: 40 μg/kg  Give 1 total dose followed  2  by 14 q8-12h × 2 doses Maintenance: 10 μg/kg/24 hr  divide q12h  Max dose: 0.5 mg  IV: 3 4 PO dose Max dose: 0.5 mg  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  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 | | PAC, PVC, bradycardia, AV block, nausea, vomiting, anorexia, prolongs PR interval | Quinidine Amiodarone,  verapamil, increase digoxin levels | 1-2 mg/mL |
| Bradycardia, asystole, high degree AV block, PR prolongation, hypotension, CHF  Chest pain, flushing, dyspnea, bronchospasm, atrial fibrillation, bradycardia, asystole | Use with  β-blocker or disopyramide exacerbates  CHF, increases digoxin level and toxicity |  |

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.

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| **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) |

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| **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) | IKs | Exercise (swimming), emotion | 42-54% |
| 2 7q35-36 *KCNH2* | | HERG, (Kv11.1) | IKr | Rest, emotion, exercise | 35-45% |
|  | |  |  | (acoustic, postpartum), |  |
|  | |  |  | surprise (sudden loud noise) |  |
| 3 3p24-21 *SCN5A* | | Nav1.5 | INa | Rest, sleep, emotion | 1.7-8%; high lethality |
| 4 4q24-27 *ANK2* | | Ankyrin-B | INa-K, INa-Ca, INa | Exercise | <1% |
| 5 21q22 *KCNE1* | | MinK | IKs | Exercise, emotion | <1% |
| 6 21q22 *KCNE2* | | MiRP1 | IKr | Rest, exercise | <1% |
| 7 17q23 *KCNJ2* | | Kir2.1 | IK1 | Rest, exercise | Periodic paralysis, |
|  | |  |  |  | dysmorphic feature |
| 8 12p13.3 *CACNA1C* | | Cav1.2 | ICa | Exercise, emotion | Rare, syndactyly |
| 9 3p25.3 *CAV3* | | Caveolin-3 | INa | Nonexertional, sleep | Rare |
| 10 11q23.3 *SCN4B* | | NaVβ4 | INa | Exercise, postpartum | <0.1% |
| 11 7q21-22 *AKAP9* | | Yotiao | IKs | Poorly characterized | <1% |
| 12 2q11.2 *SNTA1* | | Syntrophin α1 | INa | Poorly characterized | <1% |
| 13 11q24 *KCNJ5* | | Kir3.4 | KIr | Poorly characterized | <1% |
| SHORT QT SYNDROME TYPE  1 7q35-36 *KCNH2*  2 11p15.5 *KCNQ1*   1. 17q23 *KCNJ2* 2. 12p13.3 *CACNA1C* 3. 10p12.33 *CACNB2b* | | HERG (Kv11.1) KvLQT1 (Kv7.1)  Kir2.1 Cav1.2  CaV β2b | IKr IKs IK1  ICa ICa | Exercise, rest (acoustic)  —  Sleep  —  — | —  —  —  —  — |
| JERVELL AND LANGE-NIELSEN SYNDROME TYPE  1 11p15.5 *KCNQ1* KvLQT1 (Kv7.1)  2 21q22 *KCNE1* MinK | | | IKs IKs | Exercise (swimming), emotion Exercise (swimming), emotion | 1-7%; deafness  <1%; deafness |

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

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| **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.azcert.org).](http://www.azcert.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.*

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| **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).

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| **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 16SrRNA (bacteria) or 18SrRNA (fungi), or serologic tests.

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| **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 | |

†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.*

SIDS, sudden infant death syndrome.

\*Common.

## Priority: blood specimen Valvular specimen available

|  |  |
| --- | --- |
| Q fever and *Bartonella* serology  +  Determination of rheumatoid factors and antinuclear antibodies | |
|  | If negative |

If negative

Primer extension Autoimmunohistochemistry

enrichment reaction

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

+

Histological examination

**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 nonin- fective endocarditis.

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

**Chapter 437** ◆ Infective Endocarditis **2265**

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| **Table 437-3** | Diagnostic Approach to Uncommon Pathogens Causing Endocarditis | |
| **PATHOGEN** | | **DIAGNOSTIC PROCEDURE** |
| *Brucella* spp. | | Blood cultures; serology; culture, immunohistology, and PCR of surgical material |
| *Coxiella burnetii* | | Serology (IgG phase I >1 in 800); tissue culture, immunohistology, and PCR of surgical material |
| *Bartonella* spp. | | Blood cultures; serology; culture, immunohistology, and PCR of surgical material |
| *Chlamydia* spp. | | Serology; culture, immunohistology, and PCR of surgical material |
| *Mycoplasma* spp. | | Serology; culture, immunohistology, and PCR of surgical material |
| *Legionella* spp. | | Blood cultures; serology; culture, immunohistology, and PCR of surgical material |
| *Tropheryma whipplei* | | Histology and PCR of surgical material |

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| **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.

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| **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 | |

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

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| **Table 440-1** | Etiology of Pericardial Disease |
| CONGENITAL  Absence (partial, complete) Cysts  Mulibrey nanism (*TRIM 37* gene mutation)  Camptodactyly-arthropathy-coxa vara-pericarditis syndrome (*PRG4* gene mutation) | |
| INFECTIOUS  Viral (coxsackievirus B, Epstein-Barr virus, influenza, adenovirus, parvovirus, HIV, mumps)  Bacterial (*Haemophilus influenzae*, streptococcus, pneumococcus, staphylococcus, meningococcus, mycoplasma, tularemia, listeria, leptospirosis, tuberculosis, Q-fever, salmonella)  Immune complex (meningococcus, *H. influenzae*) 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, Behçet 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 | |

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

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| **Table 437-4** | Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and Streptococcus bovis | | | |
| **REGIMEN** | | **DOSAGE\* AND ROUTE** | **DURATION, WK** | **COMMENTS** |
| Aqueous crystalline penicillin G sodium | | 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 |
| *or* | | | | |
| Ceftriaxone sodium | | 2 g/24 hr IV/IM in 1 dose  *Pediatric dose*†: 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 | | 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 *Abiotrophia, Granulicatella,* or *Gemella* 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 |
| *or* | | | | |
| Ceftriaxone sodium | | 2 g/24 hr IV/IM in 1 dose | 2 |  |
| *plus* | | | | |
| Gentamicin sulfate‡ | | 3 mg/kg per 24 hr IV/IM in 1 dose, or 3 equally divided doses  *Pediatric dose:* 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  *Pediatric dose:* 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–*

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| **Table 439-3** | Causes of Myocarditis | | | |
| **INFECTIOUS** |  |  | **IMMUNE-MEDIATED** | **TOXIC** |
| Viral  Bacterial | Adenovirus Parvovirus  Coxsackie B virus Epstein-Barr virus  Hepatitis C virus Measles virus Human herpes virus Varicella-zoster virus  Human immunodeficiency virus Influenza viruses  *Mycobacteria Streptococcus* spp. *Mycoplasma pneumoniae Treponema pallidum*  *Corynebacterium diphtheriae Borrelia burgdorferi*  *Ehrlichia Aspergillus Candida Coccidioides Cryptococcus Histoplasma Trypanosoma cruzi Toxoplasma gondii Babesia*  Schistosomiasis  Larva migrans (visceral) | Autoantigens | Churg-Strauss syndrome Inflammatory bowel disease Giant cell myocarditis Diabetes mellitus Sarcoidosis  Systemic lupus erythematosus  Thyrotoxicosis Takayasu arteritis Kawasaki syndrome Celiac disease Whipple disease | Anthracyclines Cocaine Interleukin-2 Ethanol  Heavy metals Spider bite Snake bite Scorpion bite Electric shock |
| Fungal  Protozoal | Hypersensitivity | Granulomatosis with polyangiitis  Sulfonamides Cephalosporins Diuretics  Tricyclic antidepressants Dobutamine |  |
| Parasitic |  |  |  |

*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.*

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| **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  *with*  Optional addition of 3 mg/kg per 24 hr IV/IM in 2 or 3 equally gentamicin sulfate‡ divided doses  *Pediatric dose*§: 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  For penicillin-allergic (nonanaphylactoid- type) patients:  Cefazolin 6 g/24 hr IV in 3 equally divided doses | | 6 wk  3-5 day  6 wk | For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk  Clinical benefit of aminoglycosides has not been established  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 3 mg/kg per 24 hr IV/IM in 2 or 3 equally gentamicin sulfate divided doses  *Pediatric dose:* 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  *Pediatric dose:* 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 μg/mL and trough concentration of 10-15 μg/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 ≤0.1 μg/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 Baddour LM, Wilson WR, Bayer AS, et al: Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications,* Circulation *111:e394–*

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| **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  1 g | IM or IV IM or IV | 50  50 | mg/kg IM or IV mg/kg IM or IV |
| Allergic to penicillins or ampicillin—oral | | Cephalexin\*† *or* Clindamycin *or*  Azithromycin or clarithromycin | 2 g  600  500 | mg mg | 50  20  15 | mg/kg mg/kg mg/kg |
| Allergic to penicillins or ampicillin and unable to take oral medication | | Cefazolin or ceftriaxone†  *or*  clindamycin | 1 g  600 | IM or IV  mg IM or IV | 50  20 | mg/kg IM or IV 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.*

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

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

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| **Table 442-2** | Dosage of Drugs Commonly Used for the Treatment of Congestive Heart Failure | |
| **DRUG** | | **DOSAGE** |
| DIGOXIN  Digitalization ( 1 initially, followed by  2  14 q12h × 2)  Maintenance digoxin | | 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 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)  Bumetanide (Bumex)  Chlorothiazide (Diuril) Spironolactone (Aldactone) Nesiritide (B-type natriuretic peptide) | | IV: 0.5-2 mg/kg/dose  PO: 1-4 mg/kg/day, divided qd-qid IV: 0.01-0.1 mg/kg/dose  PO: 0.01-0.1 mg/kg/day q24-48h  PO: 20-40 mg/kg/day, divided bid or tid PO: 1-3 mg/kg/day, divided bid or tid  IV: 0.001-0.03 μg/kg/min |
| ADRENERGIC AGONISTS (ALL IV)  Dobutamine Dopamine Isoproterenol Epinephrine Norepinephrine | | 2-20 μg/kg/min  2-30 μg/kg/min  0.01-0.5 μg/kg/min  0.1-1.0 μg/kg/min  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  Enalapril (Vasotec), all PO Hydralazine (Apresoline)  Nitroglycerin Nitroprusside (Nipride) | | 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 0.08-0.5 mg/kg/day, divided q12-24h  IV: 0.1-0.5 mg/kg/dose (maximum: 20 mg) PO: 0.75-5 mg/kg/day, divided q6-12h  IV: 0.25-0.5 μg/kg/min start; increase to 20 μg/kg/min maximum IV: 0.5-8 μg/kg/min |
| β-ADRENERGIC BLOCKERS  Carvedilol (Coreg)  Metoprolol (Lopressor, Toprol-XL) | | 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  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 ≈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.

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| **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 O2 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 thermodilation 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 thermodilation 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 × stroke volume.

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**Diagnostic workup Include evaluation for target-organ damage‡**

≥95%

**Diagnostic workup Include evaluation for target-organ damage‡**

90-<95%

or 120/80 mm Hg

<90%

90-<95% or 120/80 mm Hg

**Educate on heart-healthy lifestyle†**

*For the family*

**Normotensive**

**Repeat BP**

*In 6 months*

**Prehypertensive**

**Therapeutic lifestyle changes†**

**Stage 1 Hypertension**

**Repeat BP**

*Over 3 visits*

**Measure BP and height and calculate BMI**

*Determine BP category for gender, age, and height*

**Stage 2 Hypertension**

Secondary hypertension

or primary hypertension

**Consider referral**

Secondary hypertension

**Rx specific for cause**

Primary hypertension

**Consider diagnostic workup and evaluation for target- organ damage‡**

*If overweight and comorbidity*

*To provider with expertise*

*in pediatric hypertension*

*exists*

Normal BMI

**Drug Rx**

**Weight**

Overweight

≥95%

**Drug Rx‡**

Still ≥95%

|  |  |  |
| --- | --- | --- |
|  | **Therapeutic lifestyle changes†** | |
|  | |  |
| Normal BMI | | |

Overweight

**Weight**

Normal BMI

**Monitor**

Overweight

**Weight**

**reduction and drug Rx**

**reduction**

**Q 6 Mo**

**reduction**

**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 Educa- tion 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.)*

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| **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  Thyrotoxicosis  Hemochromatosis-hemosiderosis Cancer therapy (radiation, doxorubicin) Sickle cell anemia  Endocarditis  Cor pulmonale (cystic fibrosis)  Genetic or metabolic cardiomyopathy (hypertrophic, dilated) |

Endocrine Renovascular lesion Essential hypertension

Documented hypertension

Coarctation Abnormal urinalysis

of aorta

Yes No

Predominant Predominant white blood cells red blood cells

Reflux nephritis Postinfectious Recurrent urinary nephritis

tract infections Lupus nephritis Renal anomaly Henoch Schönlein

(and infection) purpura Nephrocalcinosis Nephrolithiasis Other nephritis

Renal vein thrombosis

Thromboembolism Tumor

No

Yes

Gradient between upper and lower blood pressures

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

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| **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 (Ask-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 for 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 mineralcorticoid excess  Glucocorticoid remedial aldosteronism (familial aldosteronism type 1) Glucocorticoid resistance (Chrousos syndrome) Pseudohypoaldosteronism 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 | |

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| **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 Hypervolemia  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 adrenocorticotropic 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 | |

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| **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 |

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

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| **Table 445-5** | Clinical Evaluation of Confirmed Hypertension | | |
| **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  Blood urea nitrogen, creatinine, electrolytes, urinalysis, and urine culture  Complete blood count Renal ultrasound | | History and physical examination help focus subsequent evaluation  R/O renal disease and chronic pyelonephritis, mineralocorticoid excess states  R/O anemia, consistent with chronic renal disease  R/O renal scar, congenital anomaly, or disparate renal size | All children with persistent BP ≥95th percentile All children with persistent BP ≥95th percentile  All children with persistent BP ≥95th percentile All children with persistent BP ≥95th percentile |
| EVALUATION FOR COMORBIDITY  Fasting lipid panel, fasting glucose  Drug screen Polysomnography | | Identify hyperlipidemia, identify metabolic abnormalities  Identify substances that might cause hypertension  Identify sleep disorder in association with hypertension | 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  History suggestive of possible contribution by substances or drugs.  History of loud, frequent snoring |
| EVALUATION FOR TARGET-ORGAN DAMAGE  Echocardiogram  Retinal exam | | Identify left ventricular hypertrophy and other indications of cardiac involvement  Identify retinal vascular changes | Patients with comorbid risk factors\* and BP  90th-94th percentile; all patients with BP ≥95th percentile  Patients with comorbid risk factors and BP 90th-94th  percentile; all patients with BP ≥95th percentile |
| ADDITIONAL EVALUATION AS INDICATED  Ambulatory blood pressure monitoring Plasma renin determination  Renovascular imaging  Isotopic scintigraphy (renal scan) Magnetic resonance angiography Duplex Doppler flow studies  3-Dimensional CT  Arteriography: digital subtraction arteriography or classic  Plasma and urine steroid levels Plasma and urine catecholamines | | Identify white coat hypertension, abnormal diurnal BP pattern, BP load  Identify low renin, suggesting mineralocorticoid-related disease  Identify renovascular disease  Identify steroid-mediated hypertension  Identify catecholamine-mediated hypertension | Patients in whom white coat hypertension is suspected, and when other information on BP pattern is needed  Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension  Positive family history of severe hypertension Young children with stage 1 hypertension and any  child or adolescent with stage 2 hypertension  Young children with stage 1 hypertension and any child or adolescent with stage 2 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.*

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| **Table 445-6** | Causes of Renovascular Hypertension in Children | |
| Fibromuscular dysplasia Syndromic   * Neurofibromatosis type 1 * Tuberous sclerosis * Williams syndrome * Marfan syndrome * Other syndromes Vasculitis * Takayasu disease * Polyarteritis nodosa * Kawasaki disease * Other systemic vasculitides | | Extrinsic compression   * Neuroblastoma * Wilms tumor * Other tumors Other causes * 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.*

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Step 1

Begin with the recommended initial dose of desired medication

*If BP control is not achieved:*

Step 2

Increase dose until desired BP target is reached, or maximum dose is reached

*If BP control is not achieved:*

Proceed to highest recommended dose if necessary and desirable

Step 3

Add a second medication with

a complementary mechanism of action

*If BP control is not achieved:*

Step 4 OR

Add a third antihypertensive drug of a different class

Consult a physician experienced in treating childhood and adolescent hypertension

**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.)*

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| --- | --- | --- | --- | --- | --- |
| **Table 445-7** Recommended Doses  and Adolescents | | for | Selected Antihypertensive Agents | for Use in Hypertensive Children | |
| **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- | Benazepril† | 0.2 mg·kg−1 ·day−1 up to 10 mg/day | | qd | 0.6 mg·kg−1 ·day−1 up to 40 mg/day |
| converting enzyme | Captopril† | 0.3-0.5 mg/kg/dose | | bid-tid | 6 mg·kg−1 ·day−1 up to 450 mg/day |
| inhibitors | Enalapril† | 0.08 mg·kg−1 ·day−1 | | qd | 0.6 mg·kg−1 ·day−1 up to 40 mg/day |
|  | Fosinopril | 0.1 mg·kg−1 ·day−1 up to 10 mg/day | | qd | 0.6 mg/kg/day up to 40 mg/day |
|  | Lisinopril† | 0.07 mg·kg−1 ·day−1 up to 5 mg/day | | qd | 0.6 mg/kg/day up to 40 mg/day |
|  | Quinapril | 5-10 mg/day | | qd | 80 mg/day |
| Angiotensin receptor blockers | Candesartan | 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 qdqd  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 | 1-6 yr, 0.4 mg/kg; 6-17 yr, <50 kg  16 mg qd; >50 kg 32 mg qd |
|  | Losartan† | qd | 1.4 mg·kg−1 ·day−1 up to 100 mg/day |
|  | Olmesartan Valsartan† | qd qd | 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 | Amlodipine† | 0.06 mg·kg−1 ·day−1 | | qd | 0.3 mg·kg−1 ·day−1 up to 10 mg/day |
| blockers | Felodipine | 2.5 mg/day | | qd | 10 mg/day |
|  | Isradipine† | 0.05-0.15 mg/kg/dose | | tid-qid | 0.8 mg·kg−1 ·day−1 up to 20 mg/day |
|  | Extended- | 0.25-0.5 mg·kg−1 ·day−1 | | qd-bid | 3 mg·kg−1 ·day−1 up to 120 mg/day |
|  | release |  | |  |  |
|  | nifedipine |  | |  |  |
| 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.*

**2302 Part XX** ◆ The Cardiovascular System

Signs suggesting renovascular hypertension

Discharge

Blood pressure <90th percentile

Digital subtraction angiography and renal vein renin sampling

Findings suggestive of renovascular hypertension OR strong clinical suspicion of renovascular hypertension

Pre-captopril and post-captopril scintigraphy and/or CT and/or magnetic resonance angiography

(depending on local availability and preferences)

Blood pressure not well controlled on ≥2 drugs

At present, no further investigation

Blood pressure well controlled on 1-2 drugs

Repeat ausculatory blood pressure measurement if still >90th percentile for age, sex, and height confirm with 24 h ambulatory blood-pressure monitoring if possible

Blood pressure measurement >90th percentile for age, sex, and height

Blood pressure 90-95th percentile

Continue to monitor

Confirmed hypertension Blood pressure >95th percentile

Undertake primary investigation for hypertension focusing on secondary causes (coarctation, renal, and endocrine), including renal Doppler ultrasound

No cause for hypertension recorded and no signs suggesting renovascular hypertension

**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.)*

**Chapter 445** ◆ Systemic Hypertension **2303**

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

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| **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 | |  |  | Hepatocytes, macrophages, lymphocytes T cells, cytotoxic lymphocytes  CFU-MIX, CFU-Meg, CFU-GM, BFU-E, macrophage T cells, B cells, dendritic cells  CFU-Eo, B cells  CFU-MIX, CFU-GM, BFU-E, monocytes, B cells, T cells, cytotoxic lymphocytes  B cells  Neutrophils, endothelial cells, T cells BFU-E, CFU-MIX  Macrophages, lymphocytes CFU-Meg, B cells, keratinocytes  3 (p35) and 11 (p40) T cells, NK cells, macrophages Pre-B lymphocytes, macrophages  B cells  B cells, T cells T cells  Marrow stromal cells CD4+ T cells, NK cells T cells  CD4+ T cells  T cells, monocytes, marrow stromal cells  T cells, hematopoietic progenitors Monocytes, macrophages |
| IL-1 | | 17 | Alpha 2q13 Beta 2q13-21 |
| IL-2 | | 15-20 | 4q26-27 |
| IL-3 | | 14-30 | 5q23-31 |
| IL-4 | | 16-20 | 5q23-31 |
| IL-5 | | 46 (Dimer of 2 subunits) | 5q23-31 |
| IL-6 | | 19-26 | 7p21-24 |
| IL-7 | | 35 | 8q12-13 |
| IL-8 | | 8-10 | 4q13.3 |
| IL-9 | | 16 | 5q31-32 |
| IL-10 | | 18.7 | 1q32.1 |
| IL-11 | | 23 | 19q13 |
| IL-12 | | 70-75 (Dimer of 2 subunits) | p35/p40 |
| IL-13 | | 9 | 5q23-31 |
| IL-14 | | 53 | 5q31 |
| IL-15 | | 14-15 | 4q25-35 |
| IL-16 | | 12-14 | 15q23-26 |
| IL-17 | | 20-30 | 2q31 |
| IL-18 | | 24 | 9p13 |
| IL-21 | |  | 4q26-q27 |
| IL-23 | | Dimer of subunits | p19/IL-12p40 |
| IL-25 | |  | 14q11.2 |
| IL-31 | | 4-Helix bundle | 12q24.31 |
| IL-34 | | 222 Amino acid protein | 16q22.1 |
| 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

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| **Table 447-1** | Normal Mean and Lower Limits of Normal for Hemoglobin, Hematocrit, and Mean Corpuscular Volume | | | | |
| **Age (yr)** | **HEMOGLOBIN (g/dL)**  **Mean Lower Limit** | **Mean** | **HEMATOCRIT (%)**  **Lower Limit** | **MEAN CORPUSCULAR VOLUME (µM3)** | |
| **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**  **Mean −2 SD** | | **AFRICAN- AMERICAN** | |
| **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.*

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

|  |  |  |  |
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| **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 Median Range | | 10  2  0-408 | 26  23  1-120 |
| AGE AT DIAGNOSIS, FEMALE (MO)  Mean Median Range  Boys >1 yr  Girls >1 yr Etiology  Antecedent history  Physical examination abnormal (congenital anomalies present) | | 14  3  0-768  9%  12%  Genetic None 25% | 26  23  1-192  82%  80%  Acquired Viral illness 0% |
| LABORATORY  Hemoglobin (g/dL) WBCs <5,000/μL  Platelets >400,000/μL  Adenosine deaminase  MCV increased at diagnosis MCV increased during recovery MCV increased in remission HbF increased at diagnosis HbF increased during recovery HbF increased in remission  i Antigen increased  i Antigen increased during recovery i Antigen increased in remission | | 1.2-14.8  15%  20%  Increased 80%  100%  100%  100%  100%  85%  100%  100%  90% | 2.2-12.5  20%  45%  Normal 5%  90%  0%  20%  100%  0%  20%  60%  0% |

*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.*

**Chapter 447** ◆ The Anemias **2311**

## Microcytic Normocytic Macrocytic

**Reticulocyte count**

**Reticulocyte count**

**Reticulocyte count**

**Low/Inadequate High Low/Inadequate High Low/Inadequate High**

* Iron deficiency
* Thalassemia trait
* Chronic disease/
* Thalassemia syndromes
* Hemoglobin C and E disorders
* Chronic disease/ inflammation
* RBC aplasia
  + Antibody mediated hemolysis
  + Hypersplenism
    - Folate deficiency
    - Vitamin B12 deficiency
    - Acquired aplastic anemia
    - Dyserythropoietic anemia I, III
    - Active hemolysis

inflammation

* + - * Pyropoikilocytosis

(TEC, Infection, Drugs) • Microangiopathy

* + - * + Congenital aplastic anemia

with very elevated

Lead poisoning

Sideroblastic anemias

Copper deficiency

Malignancy

Endocrinopathies

Renal failure

(HUS, TTP, DIC,

Kasabach-Merritt)

* Membranopathies

(Diamond-Blackfan, Fanconi anemia, Pearson syndrome)

reticulocyte count

* + Iron refractory iron
  + Acute bleeding

(spherocytosis, elliptocytosis, • Drug induced

deficiency anemia

* + - Hypersplenism
    - Dyserythropoietic Anemia II
    - Hemophagocytic syndrome

ovalocytosis)

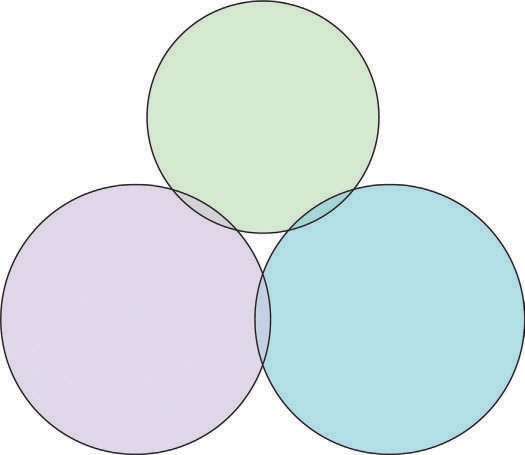
* Enzymopathies

(G6PD, PK deficiencies)

* Hemoglobinopathies (HBSS, SC)
* Trisomy 21
* Hypothyroidism
* Oroticaciduria

**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.)*

|  |  |
| --- | --- |
| **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 Epicanthus 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 |



**Genetic hemoglobin**

**disorders** Thalassemias Hemoglobin variants Glucose-6-phosphate

dehydrogenase deficiency Ovalocytosis

**Nutrition**

Iron deficiency Folic acid deficiency

Vitamin B12 deficiency Vitamin A deficiency Protein energy malnutrition

**Infectious disease**

Soil-transmitted helminths Malaria

Schistosomiasis Tuberculosis AIDS

Leishmaniasis Tropical sprue

Malabsorption and disorders of the small intestine

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

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.

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| **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 When used alone, it has low specificity and sensitivity. Use appropriate age 0.5-4 yr specific normal values found in Table 447-1. Normal values for African-  Americans are found in Table 447-2. | |
| Mean corpuscular volume (MCV) (μm3) | | <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) (μg/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 In infants and young children <27.5 A sensitive indicator that falls within days of onset of iron-deficient  content (CHr) (pg) In adults ≤28.0 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) (μmol/mol heme) | | ≤5 yr >70 It can be measured directly on a drop of blood with a portable  Children >5 yr >80 hematofluorometer.  Children >5 yr on washed red cells A useful screening test in field surveys, particularly in children, in whom  >40 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.*

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)

Differential Diagnosis of Microcytic Anemia That Fails to Respond to Oral Iron

**Table 455-3**

|  |  |
| --- | --- |
| **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/mm3 or <5000/mm3 | |
| Platelet count <100,000/mm3 | |
| 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 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 |

|  |  |
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| **Table 467-1** | Differential Diagnosis of Polycythemia |
| CLONAL (PRIMARY)  Polycythemia vera | |
| NONCLONAL  Congenital  High-oxygen affinity hemoglobinopathy (e.g., hemoglobin Chesapeake, Malmo, 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 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 | |

**Chapter 455** ◆ Iron-Deficiency Anemia **2325**

**2328 Part XXI** ◆ Diseases of the Blood

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

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| **Table 458-2** | Hereditary Spherocytosis Disease Classification | | | | |
|  | | **TRAIT** | **MILD** | **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 |

**Chapter 457** ◆ Definitions and Classification of Hemolytic Anemias **2329**

|  |  |  |  |
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| **Table 457-1** Hemolytic Anemias and Their Treatment—cont’d | | | |
| **DIAGNOSIS** | **DEFECT** | **LABORATORY TESTS** | **TREATMENT** |
| EXTRACELLULAR DEFECTS  *Autoimmune*  “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 *Mycoplasma*  *pneumoniae;* anti-I 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 |
| *Fragmentation Hemolysis*  DIC, TTP, HUS, aHUS,  pneumococcal-induced HUS See Table 465-1 Extracorporeal membrane  oxygenation Prosthetic heart valve | Direct damage to RBC membrane  Direct damage to RBC membrane Direct damage to RBC membrane Direct damage to RBC membrane  Effects of sequestration, ↓ pH, lipases and other enzymes, and macrophages on RBCs  Alteration in plasma cholesterol and phospholipids  Absence of apolipoprotein β  Vitamin E deficiency and  heightened sensitivity to oxidative damage  Toxic effects on RBCs  Effect of copper on RBC membrane, usually self-limited | Fragments on blood film  Fragments on blood film Fragments on blood film | Treat underlying condition Transfusion, but transfused cells also  will have shortened life span Supportive  Transfusion until ECMO is discontinued Folic acid, 1 mg/24 hr  Iron for secondary iron deficiency Supportive  Transfusion  Treat underlying condition: cytopenias all usually mild  Splenectomy if complicating other anemia (e.g., thalassemia major)  Folic acid, 1 mg/24 hr Treat underlying condition  Transfusion, but transfused cells also will have shortened life span  Folic acid, 1 mg/24 hr Vitamin E (A, K, and D) Folic acid, 1 mg/24 hr  Dietary restriction of triglycerides  Antibiotics Supportive Penicillamine Supportive  Transfusion if acute anemia is symptomatic |
| Burns, thermal injury | Spherocytes on blood film |
| Hypersplenism | Thrombocytopenia and neutropenia |
| *Plasma Factors*  Liver disease | Target cells or spiculated RBCs on blood film  Abnormal liver function tests |
| Abetalipoproteinemia | Acanthocytes on blood film Absent chylomicrons, VLDL, and  LDL |
| Infections Wilson disease | Associated symptoms and signs Cultures  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 |

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; Vmax, 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.*

**Chapter 462** ◆ Hemoglobinopathies **2339**

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| **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 O2 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 | |

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)

Complications Associated with Sickle Cell Trait

**Table 462-5**

|  |  |  |  |  |
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| **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.*

**2350 Part XXI** ◆ Diseases of the Blood

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| **Table 462-7** | The Thalassemias | | | | |
| **THALASSEMIA** | | **GLOBIN GENOTYPE** | **FEATURES** | **EXPRESSION** | **HEMOGLOBIN ANALYSIS** |
| α-THALASSEMIA  1 Gene allele deletion  2 Gene allele deletion trait  3 Gene allele deletion hemoglobin H  2 Gene allele deletion +  Constant Spring  4 Gene allele deletion  Nondeletional | | −,α/α,α  −,α/−,α −, −/α,α  −,−/−,α  −,−/α,αConstant Spring  −,−/−,−  α,α/α,αvariant | Normal Microcytosis, mild  hypochromasia Microcytosis, hypochromic  Microcytosis, hypochromic  Anisocytosis, poikilocytosis Microcytosis, mild anemia | Normal  Normal, mild anemia  Mild anemia, transfusions not required  Moderate to severe anemia, transfusion, splenectomy.  Hydrops fetalis  Normal | Newborn: Bart 1-2%  Newborn: Bart: 5-10%  Newborn: Bart: 20-30%  2-3% Constant Spring,  10-15% HbH  Newborn: 89-90% Bart with Gower 1 and 2 and Portland  1-2% variant hemoglobin |
| β-THALASSEMIA  β0 or β+ heterozygote: trait  β0-Thalassemia | | β0/A,β+/A  β0/β0, β+/β0, E/β0 | Variable microcytosis Microcytosis, nucleated RBC | Normal  Transfusion dependent  Transfusion dependent/ thalassemia intermedia  Normal with only microcytosis A2 2-5%, F 10-30%  Moderately severe anemia, splenomegaly  Normal Mild anemia Mild anemia  Thalassemia intermedia Moderate anemia, splenomegaly,  homozygote: thalassemia intermedia  Insignificant unless homozygote | Elevated A2, variable elevation of F  F 98% and A2 2%,  E 30-40%  F 70-95%, A2 2%, trace A  A2 3.3-3.5%  Elevated F and A2  A2 absent F 5-20%  Lepore 8-20%  F 80%, Lepore 20%  Decreased F and A2 compared with  δβ-thalassemia Decreased F |
| β+-Thalassemia severe | | β+/β+ | Microcytosis nucleated RBC |
| Silent  β+/β+  Dominant (rare) | | β+/A Hypochromic,  microcytosis B0/A | Microcytosis  Mild to moderate anemia  Microcytosis, abnormal RBCs |
| δ-Thalassemia (δβ)0-Thalassemia  (δβ)+-Thalassemia Lepore  Lepore  γδβ-Thalassemia | | A/A (δβ)0/A βLepore/A  βLepore/βLepore  (γ Aδβ)0/A | Normal Hypochromic Microcytosis  Microcytic, hypochromic Microcytosis, microcytic,  hypochromic |
| γ-Thalassemia | | (γ Aγ G)0/A | Microcytosis |
| HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN  Deletional A/A Microcytic  Nondeletional A/A Normal | | | | Mild anemia Normal | F 100% homozygotes  F 20-40% |

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| **Table 463-1** | Agents Precipitating Hemolysis in Glucose-6-Phosphate Dehydrogenase Deficiency | |
| MEDICATIONS  *Antibacterials* Sulfonamides Dapsone  Trimethoprim-sulfamethoxazole Nalidixic acid  Chloramphenicol Nitrofurantoin *Antimalarials* Primaquine Pamaquine Chloroquine Quinacrine *Antihelminths*  β-Naphthol Stibophen Niridazole | | *Others* Acetanilide Vitamin K analogs Methylene blue Toluidine blue Probenecid Dimercaprol Acetylsalicylic acid Phenazopyridine Rasburicase |
| CHEMICALS  Phenylhydrazine Benzene  Naphthalene (moth balls) 2,4,6-Trinitrotoluene |
| ILLNESS  Diabetic acidosis Hepatitis  Sepsis |

|  |  |
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| **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 (*Mycoplasma pneumoniae*, 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) | |

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| **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   1. 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.*

Red cell mass

#### Normal Elevated

Low plasma volume

#### High

Smoke exposure

#### Normal

Arterial O2

#### Normal

 

**Low**

Heart Lung

Other cause Kidney CNS

#### Abnormal Normal

High O2 affinity hemoglobin

Other cause

2,3-DPG deficiency

#### Low Elevated

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

|  |  |
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| **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. | |

†No longer commonly used.

#### Normal

von Hippel–Lindau mutations Erythropoietin receptor mutations

Other causes

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)

Guidelines for Pediatric Plasma Transfusions\*

**Table 473-1**

**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.

Hemoglobin studies

CT scan head, abdomen

Erythropoietin

**COHgb**

Rule out polycythemia vera:

CBC, differential

Bone marrow with chromosomes Leukocyte alkaline phosphatase B12/B12 binding capacity

JAK2 mutation

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

|  |  |  |  |  |
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| **Table 465-1** | Thrombotic | Microangiopathies | | |
| **DISEASE\*** | | **PATHOPHYSIOLOGY** | **LAB FINDINGS** | **MANAGEMENT** |
| TTP | | Ab to AdamTS13 | AdamTS13 <10%†  Ab to AdamTS13 | PLEX with plasma |
| HUS | | *E. coli* 0157, *Shiga* toxin | *E. coli* 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

**Chapter 468** ◆ The Inherited Pancytopenias **2363**

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

Inherited Pancytopenia Syndromes

**Table 468-1**

|  |  |  |
| --- | --- | --- |
| **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 1. Quantitative analysis of telomere CT demonstrates fatty infiltration mitomycin C or diepoxybutane) length (“flow FISH”) of pancreas 2. Complementation analysis (flow cytometric 2. Gene sequencing Gene testing   analysis of G2 arrest in melphalan-exposed May evolve to myelodysplasia or  cells after transduction with retroviral leukemia  vectors expressing normal Fanconi anemia Absence of pancreatic lipomatosis,  genes) fecal fat, or dysostosis does not   1. Gene sequencing 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.*

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| **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. Fulfills both of the following | |
| FULFILLS AT LEAST 2 OF THE FOLLOWING:   1. Chronic cytopenia(s) detected on at least 2 occasions over at least 3 mo† 2. Reduced marrow progenitors or reduced clonogenic potential of hematopoietic progenitor cells or evidence of ineffective hematopoiesis‡ 3. High fetal hemoglobin for age‡ 4. Red blood cell macrocytosis (not caused by hemolysis or a nutritional deficiency) | |
| FULFILLS AT LEAST 1 OF THE FOLLOWING:   1. Family history of bone marrow failure 2. Presentation at age <1 yr 3. 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.](http://www.sickkids.ca/cimfr)

Radiation, drugs, and chemicals:

Predictable: chemotherapy, benzene

Idiosyncratic: chloramphenicol, antiepileptics, gold; 3,4-met hylenedioxymethamphetamine

Viruses:

Cytomegalovirus Epstein-Barr Hepatitis B Hepatitis C

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

Immune diseases:

Eosinophilic fasciitis Hypoimmunoglobulinemia Thymoma

Pregnancy

Paroxysmal nocturnal hemoglobinuria Marrow replacement:

Leukemia Myelodysplasia Myelofibrosis

Autoimmune Other:

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

Etiology of Acquired Aplastic Anemia

**Table 469-1**

†Cytopenia was defined as follows: neutropenia, neutrophil count of <1.5 × 109/L; thrombocytopenia, platelet count of <150 × 109/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.

|  |  |
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| **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 g/dL† in the perioperative period 3. Maintain hemoglobin >12.0 g/dL with *severe* cardiopulmonary disease 4. Maintain hemoglobin >12.0 g/dL during extracorporeal membrane oxygenation 5. Maintain hemoglobin >7.0 g/dL and *symptomatic* chronic anemia 6. Maintain hemoglobin >7.0 g/dL and *marrow failure* | |
| INFANTS ≤4 MO OLD   1. Maintain hemoglobin >12.0 g/dL and *severe* pulmonary disease 2. Maintain hemoglobin >12.0 g/dL during extracorporeal membrane oxygenation 3. Maintain hemoglobin >10.0 g/dL and *moderate* pulmonary disease 4. Maintain hemoglobin >12.0 g/dL and *severe* cardiac disease 5. Maintain hemoglobin >10.0 g/dL preoperatively and during   *major* surgery   1. Maintain hemoglobin >7.0 g/dL postoperatively 2. Maintain hemoglobin >7.0 g/dL and *symptomatic* anemia | |

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

|  |  |
| --- | --- |
| **Table 471-1** | Guidelines for Pediatric Platelet Transfusion\* |
| CHILDREN AND ADOLESCENTS   1. Maintain PLT count >50 × 109/L with bleeding 2. Maintain PLT count >50 × 109/L with *major invasive* procedure;   >25 × 109/L with minor   1. Maintain PLT count >20 × 109/L and *marrow failure* WITH hemorrhagic risk factors 2. Maintain PLT count >10 × 109/L and *marrow failure* WITHOUT hemorrhagic risk factors 3. Maintain PLT count at any level with PLT dysfunction PLUS bleeding or invasive procedure | |
| INFANTS ≤4 MO OLD   1. Maintain PLT count >100 × 109/L with bleeding or during extracorporeal membrane oxygenation 2. Maintain PLT count >50 × 109/L and an invasive procedure 3. Maintain PLT count >20 × 109/L and *clinically stable* 4. Maintain PLT count >50 × 109/L and *clinically unstable and/or bleeding or not when on indomethacin, nitric oxide, antibiotics,*   *etc. affecting PLT function*   1. Maintain PLT count at any level with PLT dysfunction PLUS bleeding invasive procedure | |

\*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.

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| **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 disease) | deficiency | is hemophilia B (sometimes referred to as Christmas |
| 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 |  |

**2382 Part XXI** ◆ Diseases of the Blood

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| **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 disease) | deficiency | is hemophilia B (sometimes referred to as Christmas |
| 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 |  |

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

**Chapter 476** ◆ Hereditary Clotting Factor Deficiencies (Bleeding Disorders) **2387**

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| **Table 476-1** | Treatment | of Hemophilia | |
| **TYPE OF HEMORRHAGE** | | **HEMOPHILIA A** | **HEMOPHILIA B** |
| Hemarthrosis\* | | 50-60 IU/kg factor VIII concentrate† 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‡; 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‡; antifibrinolytic therapy§; 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| | Apply pressure for 15-20 min; pack with petrolatum gauze; antifibrinolytic therapy; 30 IU/kg factor IX concentrate‡ 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‡, 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‡; 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; 1.5× 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; 1.5× maintenance fluids; if not controlled in 1-2 days, 40 IU/kg factor IX concentrate‡; 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 ≥1% | 30-50 IU/kg factor IX concentrate‡ every 2-3 days to  achieve a trough level ≥1% |

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

†For 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.

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

§Do 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

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **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.

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| **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†  1 spray IN (<50 kg)  2 sprays IN (>50 kg) |
| von Willebrand factor concentrates‡ | | 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§  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.

†Maximum recommended dose is 20-30 μg/day.

‡Currently 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.

**Chapter 478** ◆ Hereditary Predisposition to Thrombosis **2393**

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| **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 Heterozygote Homozygote | | 3-7  0.06-0.25 | 3.8  80-100 | DNA-based PCR assay (or screen with activated protein C resistance) |
| Prothrombin 20210 mutation Heterozygote Homozygote | | 1-3  – | 2.6  – | DNA-based PCR assay |
| 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.

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| **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 |

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| **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 |
| Mistranfusion | | 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 lymphotrophic 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 |
| *Trypanosoma cruzi* | | Unknown |
| *Leishmania* spp. | | Unknown |
| Variant Creutzfeldt-Jakob prion disease | | Unknown |

**Chapter 483** ◆ Disseminated Intravascular Coagulation **2399**

Large platelets Normal hemoglobin

and WBC

#### Consumption

Immune ITP

2° to SLE, HIV

Drug-induced

#### WELL

Small platelets Congenital anomalies

|  |  |
| --- | --- |
| **Table 483-1** | Causes of Disseminated Intravascular Coagulation |
| INFECTIOUS  Meningococcemia (purpura fulminans)  Bacterial sepsis (staphylococcal, streptococcal, *Escherichia coli*, *Salmonella*)  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 | |
| MISCELLLANEOUS  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 | |

 Mean corpuscular volume

####  Synthesis

Congenital

TAR

Wiskott-Aldrich syndrome X-linked Amegakaryocytic Fanconi anemia

Maternal ITP NATP

Non-immune

2B or platelet-type VWD

Hereditary macrothrombocytopenia

#### ILL

 Fibrinogen

 Fibrin degradation products

Acquired

Medications Toxins Radiation

Small platelets HSM

Large platelets

#### Consumption

Microangiopathy

Hemolytic-uremic syndrome TTP

*Mass*

####  Synthesis

Malignancy Storage disease

#### Sequestration

Disseminated intravascular coagulation

Necrotizing enterocolitis Respiratory distress Thrombosis

UAC

Sepsis

Viral infection

Hemangioma

Hypersplenism

|  |  |  |
| --- | --- | --- |
| **Table 487-1** | Diseases Associated with Hyposplenism or Splenic Atropy | |
| CONGENITAL FORMS  Normal and premature neonates Isolated congenital hypoplasia Ivemark syndrome  Autoimmune polyendocrinopathy- candidiasis-ectodermal dystrophy (APECED) syndrome  Hypoparathyroidism syndrome Stormorken syndrome Heterotaxia syndromes | | AUTOIMMUNE DISORDERS  Systematic lupus erythematosus Rheumatoid arthritis Glomerulonephritis  Wegener granulomatosis Goodpasture syndrome Sjögren syndrome Nodous polyarteritis Thyroiditis  Sarcoidosis |
| GASTROINTESTINAL DISORDERS  Coeliac disease Inflammatory bowel disease Whipple disease  Dermatitis herpetiformis Intestinal lymphangiectasia Idiopathic chronic ulcerative  enteritis | | INFECTIOUS DISEASES  HIV/AIDS  Pneumococcal meningitis Malaria |
| HEPATIC DISORDERS  Active chronic hepatitis Primary biliary cirrhosis Hepatic cirrhosis and portal  hypertension Alcoholism and alcoholic  hepatopathy | | IATROGENIC FORMS  Exposure to methyldopa High-dose steroids  Total parenteral nutrition Splenic irradiation |
| ONCOHEMATOLOGIC DISORDERS  Hemoglobin S diseases Bone marrow transplantation  Chronic graft-versus-host disease Acute leukemia  Chronic myeloproliferative disorders  Fanconi syndrome Splenic tumors Mastocytosis | | ALTERATION IN SPLENIC CIRCULATION  Thrombosis of splenic artery Thrombosis of splenic vein Thrombosis of coeliac artery  MISCELLANEOUS  Amyloidosis |

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 490-1** | Differential Diagnosis of Systemic Generalized Lymphadenopathy | | |
| **INFANT** | | **CHILD** | **ADOLESCENT** |
| COMMON CAUSES  Syphilis Toxoplasmosis CMV  HIV | | Viral infection EBV  CMV HIV  Toxoplasmosis | Viral infection EBV  CMV HIV  Toxoplasmosis Syphilis |
| RARE CAUSES  Chagas disease (congenital)  Leukemia Tuberculosis Reticuloendotheliosis Lymphoproliferative  disease Metabolic storage  disease  Histiocytic disorders | | Serum sickness SLE, JIA  Leukemia/ lymphoma  Tuberculosis Measles Sarcoidosis Fungal infection Plague Langerhans cell  histiocytosis Chronic  granulomatous disease  Sinus histiocytosis Drug reaction | Serum sickness SLE, JIA  Leukemia/lymphoma/ Hodgkin disease  Lymphoproliferative disease  Tuberculosis Histoplasmosis Sarcoidosis Fungal infection Plague  Drug reaction Castleman disease |

**Chapter 484** ◆ Platelet and Blood Vessel Disorders **2401**

|  |  |  |
| --- | --- | --- |
| **Table 484-1** | Differential Diagnosis of Thrombocytopenia in Children and Adolescents | |
| DESTRUCTIVE THROMBOCYTOPENIAS  Primary Platelet Consumption Syndromes  *Immune thrombocytopenias*  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  *Nonimmune thrombocytopenias*  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 | | Platelets in contact with foreign material Congenital heart disease  Drug-induced via direct platelet effects (ristocetin, protamine) Type 2B VWD or platelet-type VWD |
| Combined Platelet and Fibrinogen Consumption Syndromes  Disseminated intravascular coagulation Kasabach-Merritt syndrome  Virus-associated hemophagocytic syndrome |
| IMPAIRED PLATELET PRODUCTION  Hereditary disorders Acquired disorders  Aplastic anemia Myelodysplastic syndrome  Marrow infiltrative process—neoplasia Osteopetrosis  Nutritional deficiency states (iron, folate, vitamin B12, anorexia nervosa) Drug- or radiation-induced thrombocytopenia  Neonatal hypoxia or placental insufficiency |
| SEQUESTRATION  Hypersplenism Hypothermia Burns |

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.*

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| **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., proprionic and methylmalonic acidemia) | |
| Congenital/inherited (e.g., TAR, CAMT) | |
| 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., proprionic 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., *Escherichia coli*, GBS, herpes simplex)  DIC  Alloimmune thrombocytopenia Autoimmune condition (e.g., ITP, SLE)  Congenital infection (e.g., CMV, toxoplasma, rubella, HIV) |

\*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.

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| **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 hypertropic 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 |

**Chapter 486** ◆ Splenomegaly **2409**

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| **Table 486-1** | Differential Diagnosis of Splenomegaly by Pathophysiology | |
| ANATOMIC LESIONS  Cysts, pseudocysts Hamartomas Polysplenia syndrome  Hemangiomas and lymphangiomas Hematoma or rupture (traumatic) Peliosis | | Parasitic  Malaria  Toxoplasmosis, especially congenital  *Toxocara canis, Toxocara cati* (visceral larva migrans) Leishmaniasis (kala-azar)  Schistosomiasis (hepatic-portal involvement) Trypanosomiasis  Fascioliasis Babesiosis  IMMUNOLOGIC AND INFLAMMATORY PROCESSES\*  Systemic lupus erythematosus Rheumatoid arthritis  Mixed connective tissue disease Systemic vasculitis  Serum sickness  Drug hypersensitivity, especially to phenytoin Graft-versus-host disease  Sjögren syndrome Cryoglobulinemia Amyloidosis Sarcoidosis  Autoimmune lymphoproliferative syndrome Posttransplant lymphoproliferative disease Large granular lymphocytosis and neutropenia Histiocytosis syndromes  Hemophagocytic syndromes (nonviral, familial) |
| HYPERPLASIA CAUSED BY HEMATOLOGIC DISORDERS  Acute and Chronic Hemolysis\*  Hemoglobinopathies (sickle cell disease in infancy with or without sequestration crisis and sickle variants, thalassemia major, unstable hemoglobins)  Erythrocyte membrane disorders (hereditary spherocytosis, elliptocytosis, pyropoikilocytosis)  Erythrocyte enzyme deficiencies (severe G6PD deficiency, pyruvate kinase deficiency)  Immune hemolysis (autoimmune and isoimmune hemolysis) Paroxysmal nocturnal hemoglobinuria  Chronic Iron Deficiency Extramedullary Hematopoiesis  Myeloproliferative diseases: CML, juvenile CML, myelofibrosis with myeloid metaplasia, polycythemia vera  Osteopetrosis  Patients receiving granulocyte and granulocyte-macrophage colony- stimulating factors | |
| INFECTIONS†  Bacterial  Acute sepsis: *Salmonella typhi, Streptococcus pneumoniae, Haemophilus influenzae* type b, *Staphylococcus aureus*  Chronic infections: infective endocarditis, chronic meningococcemia, brucellosis, tularemia, cat-scratch disease  Local infections: splenic abscess (*S. aureus,* streptococci, less often *Salmonella* species, polymicrobial infection), pyogenic liver abscess (anaerobic bacteria, Gram-negative enteric bacteria), cholangitis  Viral\*  Acute viral infections, especially in children Congenital CMV, herpes simplex, rubella Hepatitides 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.

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| **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

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| **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 | |
| EPITROCHLEAR  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, *Yersinia*, group A streptococcus) | |

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| **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 | |

\*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.*

# Cancer and Benign Tumors

**2418 Part XXII** ◆ Cancer and Benign Tumors

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| **Table 491-2** Known Risk Factors for Selected Childhood Cancers | | |
| **CANCER TYPE** | **RISK FACTOR** | **COMMENTS** |
| Acute lymphoid leukemia | Ionizing radiation  Race  Genetic factors\* | Although primarily of historical significance, prenatal diagnostic x-ray exposure increases risk.  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  Race | Aniridia, Beckwith-Wiedemann syndrome, and other congenital and genetic conditions are associated with increased risk.  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.*

**2420 Part XXII** ◆ Cancer and Benign Tumors

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| **Table 492-2** Familial or Genetic | Susceptibility to Malignancy | |
| **DISORDER** | **TUMOR/CANCER** | **COMMENT** |
| CHROMOSOMAL SYNDROMES  Chromosome 11p deletion syndrome with sporadic aniridia  Chromosome 13q deletion syndrome Trisomy 21  Klinefelter syndrome (47,XXY) Trisomy 8  Noonan syndrome Monosomy 5 or 7 | Wilms tumor Retinoblastoma, sarcoma  Lymphocytic or nonlymphocytic leukemia, especially megakaryocytic leukemia; transient leukemoid reaction  Breast cancer, extragonadal germ cell tumors Preleukemia  JMML  Myelodysplastic syndrome | Associated with genitourinary anomalies, mental retardation, *WT1* gene  Associated with intellectual disability, skeletal malformations; autosomal dominant (bilateral) or sporadic new mutations, *RB1* gene  Risk of ALL is increased 20%; risk of AML is increased 400%; patients have an increased sensitivity to chemotherapy  Autosomal dominant; mutations in *PTPN11* gene Recurrent infections may precede neoplasia |
| CHROMOSOMAL INSTABILITY  Xeroderma pigmentosum Fanconi anemia  Bloom syndrome Ataxia-telangiectasia  Dysplastic nevus syndrome Rothmund-Thompson syndrome Werner syndrome (premature aging) | Basal cell and squamous cell carcinomas; melanoma  Leukemia, myelodysplastic syndrome, liver neoplasias, rare head and neck tumors, GI and GU cancers  Leukemia, lymphoma, and solid tumors  Lymphoma, leukemia, less commonly central nervous system and nonneural solid tumors  Melanoma  Osteosarcoma; skin cancers Soft tissue sarcomas | Autosomal recessive; failure to repair  UV-damaged DNA. Mutations in *XP* gene on chromosome 3p25  Autosomal recessive; chromosome fragility; positive diepoxybutane test result. Mutations in *FANCX* gene family  Autosomal recessive; increase sister chromatid exchange; mutations in *BLM* gene; member of the RecQ helicase gene  Autosomal recessive; sensitive to X-irradiation, radiomimetic drugs; mutation in *ATM* tumor- suppressor gene  Autosomal dominant; some cases associated with mutations in *CDKN2A* gene  Autosomal recessive; mutation in RecQ helicase gene family  Autosomal recessive; mutation in the *WRN* gene; member of the RecQ helicase gene family |
| IMMUNODEFICIENCY SYNDROMES  Wiskott-Aldrich syndrome  X-linked immunodeficiency (Duncan syndrome)  X-linked agammaglobulinemia (Bruton disease)  Severe combined immunodeficiency | Lymphoma, leukemia  Lymphoproliferative disorder Lymphoma, leukemia Leukemia, lymphoma | X-linked recessive; *WAS* gene mutation (Xp11.22- 23); WASP protein functions in signal transduction associated with cytoskeletal actin filament rearrangement  X-linked; Epstein-Barr viral infection can result in fatal outcome; mutation in *SH2D1A* gene locus  X-linked; mutation in *BKT* gene resulting in absence of mature B cells  X-linked; mutations in *ADA* gene |

**Chapter 492** ◆ Molecular and Cellular Biology of Cancer **2421**

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| **Table 492-2** Familial or Genetic Susceptibility to Malignancy—cont’d | | |
| **DISORDER** | **TUMOR/CANCER** | **COMMENT** |
| OTHERS  Neurofibromatosis 1  Neurofibromatosis 2 | Neurofibroma, optic glioma, acoustic neuroma, astrocytoma, meningioma, pheochromocytoma, sarcoma  Bilateral acoustic neuromas, meningiomas | Autosomal dominant; mutation in tumor- suppressor gene, *NF1*  Autosomal dominant; mutation in tumor- suppressor gene, *NF2*  Autosomal dominant  Autosomal dominant; mutation in *PTCH* gene  Mutation of *P53* tumor-suppressor gene, autosomal dominant  Autosomal recessive; increased risk of secondary malignancy 10-20 yr later; mutation in *RB* tumor-suppressor gene  *WT1* gene; 25% develop tumor, most in 1st 5 yr of life  Autosomal dominant; mutation of tumor- suppressor gene, *VHL* gene  Autosomal dominant; mutation in *PYGM*  tumor-suppressor gene  Autosomal dominant; mutations in CYS-rich regions of the *RET* gene activate this protooncogene; *RET* codes for a tyrosine kinase; monitor calcitonin and calcium levels  Autosomal dominant; mutation in catalytic site (codon 883 or 914) activates protooncogene; *RET* codes for a tyrosine kinase  Autosomal dominant; mutation in *APC* gene  Autosomal dominant; mutation in *SMAD4* gene Autosomal dominant; mutation in mismatch  repair genes; *hMSH2, hMLH1, PMS1, PMS2, hMSH6, hMSG3*  Mutation in *APC* gene  Autosomal dominant, *APC* gene Autosomal dominant, *APC* gene  Autosomal dominant, *LKB1* gene codes for a Ser/Thr kinase that regulates cell cycle, metabolism, cell polarity  Autosomal dominant; malignancy associated with cirrhotic liver  Autosomal recessive; malignancy associated with cirrhotic liver  Mutation in glucose-6-phosphatase or glucose-6- phosphatase translocase genes  Autosomal recessive; tumor associated with cirrhotic liver  DNA repair defect  Autosomal dominant; family 9 genes encoding ribosomal proteins  Autosomal recessive; *SBDS* gene; chromosome 7q11.21  Autosomal dominant; *CDH1* gene  Encoded protein is a ribonuclease required for microRNA processing  Two genes have been identified:   * Anaplastic lymphoma kinase *(ALK)* at chromosome 2p23 * Paired-like homeobox 2b *(PHOX2B)* at chromosome 4q12   Mutation in the mitochondrial enzyme succinate dehydrogenase protein (SDH)  *ELANE* mutation at 19p13.3; elastase; neutrophil expressed |
| Tuberous sclerosis  Gorlin-Goltz syndrome (nevus basal cell carcinoma syndrome)  Li-Fraumeni syndrome | Fibroangiomatous nevi, myocardial rhabdomyoma  Multiple basal cell carcinomas; medulloblastoma  Bone, soft tissue sarcoma, breast |
| Retinoblastoma | Sarcoma |
| Hemihypertrophy ± Beckwith syndrome von Hippel-Landau disease  Multiple endocrine neoplasia syndrome, type 1 (Wermer syndrome)  Multiple endocrine neoplasia syndrome, type 2A (Sipple syndrome) | Wilms tumor, hepatoblastoma, adrenal carcinoma  Hemangioblastoma of the cerebellum and retina, pheochromocytoma, renal cancer  Parathyroid, pancreatic islet, and pituitary tumors  Medullary carcinoma of the thyroid, hyperparathyroidism, pheochromocytoma |
| Multiple endocrine neoplasia type 2B (multiple mucosal neuroma syndrome)  Familial adenomatous polyposis  Familial juvenile polyposis  Hereditary nonpolyposis colon cancer (Lynch syndrome, NHPCC) | Mucosal neuroma, pheochromocytoma, medullary thyroid carcinoma, Marfan habitus; neuropathy  Colorectal, thyroid carcinoma, duodenal and periampullar carcinomas; pediatric hepatoblastoma  Colorectal carcinoma Colon cancer |
| Turcot syndrome  Familial adenomatous polyposis coli Gardner syndrome  Peutz-Jeghers syndrome | Pediatric brain tumors and increased risk of colon carcinoma and polyps  Adenocarcinoma of colon Adenocarcinoma of colon, skull and soft  tissue tumors  Gastrointestinal carcinoma, ovarian neoplasia |
| Hemochromatosis | Hepatocellular carcinoma |
| Glycogen storage disease 1 (von Gierke disease) | Hepatocellular carcinoma |
| Tyrosinemia, galactosemia | Hepatocellular carcinoma |
| *BRCA1* and *BRCA2*  Diamond-Blackfan anemia  Shwachman-Diamond syndrome | Breast, ovarian  AML, myelodysplastic syndrome, osteogenic sarcoma  AML, myelodysplasia |
| Hereditary diffuse gastric cancer Pleuropulmonary blastoma family tumor  and dysplasia syndrome (DICER1) Hereditary neuroblastoma | Gastric cancer Pulmonary blastoma  Neuroblastoma |
| Hereditary paraganglioma– pheochromocytoma syndrome  Congenital or cyclic neutropenia | Paraganglioma Pheochromocytomas Myelodysplastic syndrome AML |

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

**Chapter 493** ◆ Principles of Diagnosis **2423**

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| **Table 493-1** Common | Manifestations of Childhood Malignancies | | |
|  | **SIGNS AND SYMPTOMS** | **POTENTIAL ETIOLOGY** | **POSSIBLE ONCOLOGIC DIAGNOSIS** |
| Constitutional/Systemic | Fever, persistent or recurrent infection, neutropenia  Fever of unknown origin, weight loss, night sweats  Painless lymphadenopathy  Hypertension Soft tissue mass | Bone marrow infiltration Lymphoma  Lymphoma, metastatic solid tumor  Renal or adrenal tumor Local or metastatic tumor | Leukemia, neuroblastoma  Hodgkin and non-Hodgkin lymphoma  Leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, thyroid carcinoma  Neuroblastoma, pheochromocytoma, Wilms tumor  Ewing sarcoma, osteosarcoma, neuroblastoma, thyroid carcinoma, rhabdomyosarcoma, Langerhans cell histiocytosis |
| Neurologic/Ophthalmologic | Headache with emesis, visual disturbances, ataxia, papilledema, cranial nerve palsies  Leukokoria (white pupil) Periorbital ecchymosis Miosis, ptosis, heterochromia  Opsoclonus myoclonus, ataxia Exophthalmos, proptosis | Increased intracranial pressure  Retinal mass Metastasis  Horner syndrome: compression of cervical sympathetic nerves  Neurotransmitters? Autoimmunity?  Orbital tumor | Primary brain tumor; metastasis  Retinoblastoma Neuroblastoma Neuroblastoma  Neuroblastoma  Rhabdomyosarcoma, lymphoma, Langerhans cell histiocytosis |
| Respiratory/Thoracic | Cough, stridor, pneumonia, tracheal- bronchial compression; superior vena cava syndrome  Vertebral or nerve root compression; dysphagia | Anterior mediastinal mass  Posterior mediastinal mass | Germ cell tumor, non-Hodgkin lymphoma, Hodgkin lymphoma  Neuroblastoma, neuroenteric cyst |
| Gastrointestinal | Abdominal mass  Diarrhea | Adrenal, renal, or lymphoid tumor  Vasoactive intestinal polypeptide | Neuroblastoma, Wilms tumor, lymphoma  Neuroblastoma, ganglioneuroma |
| Hematologic | Pallor, anemia  Petechiae, thrombocytopenia | Bone marrow infiltration Bone marrow infiltration | Leukemia, neuroblastoma Leukemia, neuroblastoma |
| Musculoskeletal | 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 |

**Chapter 493** ◆ Principles of Diagnosis **2425**

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| **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

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| **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.

**Chapter 494** ◆ Principles of Treatment **2429**

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| **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

**2430 Part XXII** ◆ Cancer and Benign Tumors

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| **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 |
| Pegaspargase (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  *trans-*retinoic acid); and isotretinoin (cis-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.

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| **Table 494-3** | Infectious Complications of Malignancy | | | |
| **PREDISPOSING FACTOR** | | **ETIOLOGY** | **SITE OF INFECTION** | **INFECTIOUS AGENTS** |
| Neutropenia | | Chemotherapy, bone marrow infiltration | Sepsis, shock, pneumonia, soft tissue, proctitis, mucositis | *Streptococcus viridans, Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa, Candida, Aspergillus,* anaerobic oral and rectal bacteria |
| Immunosuppression, lymphopenia, lymphocyte- monocyte dysfunction | | Chemotherapy, corticosteroid | Pneumonia, meningitis, disseminated viral infection | *Pneumocystis jiroveci, Cryptococcus neoformans, Mycobacterium, Nocardia, Listeria monocytogenes, Candida, Aspergillus, Strongyloides, Toxoplasma,* varicella-zoster virus, cytomegalovirus, herpes simplex |
| Indwelling central venous catheter | | Nutrition, administration of chemotherapy | Line sepsis, tract of tunnel, exit site | *S. epidermidis, S. aureus, Candida albicans,*  *P. aeruginosa, Aspergillus, Corynebacterium*, *Streptococcus faecalis, Mycobacterium fortuitum, Propionibacterium acnes* |

**Chapter 494** ◆ Principles of Treatment **2433**

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| **Table 494-4** Oncologic Emergencies | | | | |
| **CONDITION** | **MANIFESTATIONS** | **ETIOLOGY** | **MALIGNANCY** | **TREATMENT** |
| METABOLIC  Hyperuricemia Hyperkalemia  Hyperphosphatemia  Hyponatremia Hypercalcemia | Uric acid nephropathy Arrhythmias, cardiac arrest  Hypocalcemic tetany; metastatic calcification, photophobia, pruritus  Seizure, lethargy (may also be asymptomatic)  Anorexia, nausea, polyuria, pancreatitis, gastric ulcers; prolonged PR, shortened QT interval | Tumor lysis syndrome Tumor lysis syndrome  Tumor lysis syndrome  SIADH; fluid, sodium losses in vomiting  Bone resorption; ectopic parathormone, vitamin D, or prostaglandins | Lymphoma, leukemia Lymphoma, leukemia  Lymphoma, leukemia  Leukemia, CNS tumor  Metastasis to bone, rhabdomyosarcoma, leukemia | Allopurinol, alkalinize urine; hydration and diuresis, rasburicase  Kayexalate, sodium bicarbonate, glucose, and insulin; check for pseudohyperkalemia from leukemic cell lysis in test tube  Hydration, forced diuresis; stop alkalinization; oral aluminum hydroxide to bind phosphate  Restrict free water for SIADH; replace sodium if depleted  Hydration and furosemide diuresis; corticosteroids; calcitonin, bisphosphonates |
| HEMATOLOGIC  Anemia  Thrombocytopenia | Pallor, weakness, heart failure Petechiae, hemorrhage | Bone marrow suppression or infiltration; blood loss Bone marrow suppression  or infiltration Sepsis, hypotension,  tumor factors  Bone marrow suppression or infiltration  Leukostasis; vascular occlusion  Immunosuppression and nonirradiated blood products; bone marrow transplantation | Any with chemotherapy Any with chemotherapy  Promyelocytic leukemia, others  Any with chemotherapy  Leukemia  Any with immunosuppression | Packed red blood cell transfusion  Platelet transfusion |
| Disseminated intravascular coagulation  Neutropenia  Hyperleukocytosis (>100,000/mm3)  Graft-versus-host disease | Shock, hemorrhage Infection  Hemorrhage, thrombosis; pulmonary infiltrates, hypoxia; tumor lysis syndrome  Dermatitis, diarrhea, hepatitis | Fresh-frozen plasma; platelets, cryoprecipitate, treat underlying disorder  If febrile, administer broad- spectrum antibiotics, and filgrastim (G-CSF) if appropriate  Leukapheresis; chemotherapy; hydroxyurea  Corticosteroids; cyclosporine; tacrolimus; antithymocyte globulin |
| SPACE-OCCUPYING LESIONS  Spinal cord Back pain ± radicular compression *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  Increased intracranial Confusion, coma, emesis, pressure headache, hypertension,  bradycardia, seizures, papilledema, hydrocephalus; cranial nerves III and VI palsies  Superior vena cava Distended neck veins syndrome plethora, edema of head  and neck, cyanosis, proptosis, Horner syndrome  Tracheal compression Respiratory distress | | Metastasis to vertebra and extramedullary space  Primary or metastatic brain tumor  Superior mediastinal mass  Mediastinal mass compressing trachea | Neuroblastoma; medulloblastoma  Neuroblastoma, astrocytoma; glioma  Lymphoma  Lymphoma | MRI or myelography for diagnosis; corticosteroids; radiotherapy; laminectomy; chemotherapy |
| CT or MRI for diagnosis; corticosteroids; phenytoin; ventriculostomy tube; radiotherapy; chemotherapy |
| Chemotherapy; radiotherapy |
| 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

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| **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:   * Executive function * Sustained attention * Memory * Processing speed * Visual-motor integration Learning deficits Diminished IQ   Behavioral change | Chemotherapy:   * Methotrexate Radiation affecting brain: * 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:   * Cisplatin * Carboplatin   Radiation affecting hearing:   * Cranial * Infratemporal * Nasopharyngeal Radiation affecting hearing: * Cranial * Infratemporal * Nasopharyngeal Chemotherapy: * Busulfan * Glucocorticoids Radiation affecting eye: * Cranial * Orbital/eye * TBI   Chemotherapy:   * Vincristine * Vinblastine * Cisplatin * Carboplatin | Higher cisplatin dose (360 mg/m2) Higher radiation dose impacting ear (>30 Gy)  Concurrent radiation and cisplatin  Higher radiation dose affecting ear (>30 Gy)  Higher radiation dose impacting eye (≥15 Gy for cataracts; >45 Gy for retinopathy and visual impairment)  Higher cisplatin dose (≥300 mg/m2) | | 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:   * 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:   * 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 |

**Chapter 494** ◆ Principles of Treatment **2435**

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| **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:   * Busulfan * Carmustine (BCNU) * Chlorambucil * Cyclophosphamide * Ifosfamide * Lomustine (CCNU) * Mechlorethamine * Melphalan * Procarbazine   Radiation affecting reproductive system:   * 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, ≥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:   * Daunorubicin * Doxorubicin * Idarubicin | Female sex  Age <5 yr at time of treatment Higher doses of chemotherapy (≥300 mg/m2)  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:   * Chest * Mantle * Mediastinum * Axilla * Spine * Upper abdomen |  |
| PULMONARY  Pulmonary fibrosis Interstitial pneumonitis Restrictive lung disease Obstructive lung disease | Chemotherapy:   * Bleomycin * Busulfan * Carmustine (BCNU) * Lomustine (CCNU) Radiation impacting lungs: * 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  HCST |
| 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:   * Ifosfamide * Cisplatin * Carboplatin   Radiation affecting kidneys:   * 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, Arnstrong GT, Cash DK, et al: Primary care management of the childhood cancer survivor,* J Pediatr *152:458–466, 2008.*

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| **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 |

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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); *MLLT3-MLL*
* AML with t(6;9)(p23;q34); *DEK-NUP214*
* AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
* AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
* *Provisional entity: AML with mutated NPM1*
* *Provisional entity: AML with mutated CEBPA*

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

WHO Classification of Acute Myeloid Neoplasms

**Table 495-3**

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

Nodular lymphocyte predominance Classical Hodgkin lymphoma Lymphocyte rich

Mixed cellularity Nodular sclerosis Lymphocyte depletion

New World Health Organization/Revised European–American Classification of Lymphoid Neoplasms Classification System for Hodgkin Lymphoma

**Table 496-1**

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| **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 | |

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| **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% |

**Chapter 496** ◆ Lymphoma **2449**

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| **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  Prognosis | *FAB/LMB 96 Group A therapy:*  Complete surgical resection followed by 2 cycles of chemotherapy  4 yr EFS:  98% (CI95 94-99.5%)  4 yr OS:  99% (CI95 96-99.9%) | *FAB/LMB 96 Group B* therapy with reduced cyclophosphamide and no maintenance therapy;  *COG ANHL01P1*: FAB/LMB  Group B therapy + rituximab  *FAB/LMB96:*  4 yr EFS: 92% (CI95 90-94%)  4 yr OS: 95% (CI95 93-96%)  \*PMB DLBCL has worse prognosis (EFS/OS: 66/73%)  *COG ANHL01P1:*  3 yr EFS 93% (CI95 79-98%)  3 yr OS 95% (CI95 83-99%) | *FAB/LMB 96:* standard-intensity Group C therapy:  Reduction, induction, intensification, and maintenance therapy  *COG ANHL01P1*: FAB/LMB Group C  therapy + rituximab  *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% (CI95 75-96%)  CNS+: 93% (CI95 61-99%) |
| Lymphoblastic lymphoma | | Treatment  Prognosis | *NHL-BFM86/90/95:*  *COG A5971:*  ALL-type therapy × 2 yr without prophylactic cranial RT  *COG A5971:*  5 yr EFS: 90 (CI95 78-96%)  5 yr OS: 96 (CI95 84-99%) | No intermediate group; disease classified as localized (stages I/II) or advanced (stages III/IV)  No intermediate group; see above | *NHL-BFM86/90/95:* ALL-type therapy ×  2 yr ± px CRT  *CCG 5941:* Intensive chemotherapy ×  1 yr + cranial RT if CNS + at diagnosis  *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  Prognosis | *EICHNL ALCL 99:* Short  intensive chemotherapy + HD MTX  Completely resected stage I disease may be treated with surgery alone  *EICHNL database:*  5 yr PFS: 89% (CI95 82-96%)  5 yr OS: 94% (CI95 89-99%) | No intermediate group; disease classified as standard risk (no skin, visceral, or mediastinal involvement) or high risk (presence of skin, mediastinal, or visceral involvement)  No intermediate group; see above | *ALCL 99, CCG 5941:*  Short intensive chemotherapy + HD MTX  *COG ANHL0131*: APO (doxorubicin, prednisone, vincristine) ± vinblastine  *ALCL99:*  2 yr EFS: 71% (CI95 75-77%)  2 yr OS: 94% (CI95 89-95%)  *COG5941:*  5 yr EFS 68% (CI95 57-78%)  5 yr OS: 80% (CI95 69-87%)  *COH ANHL0131:*  2 yr EFS 79% (CI95 71-88%)  2 yr OS 89% (CI95 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; EICHNL, 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 Burkit; 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.

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| **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 | |

Group B

All patients not in Group A or C

Group C

Bone marrow disease (≥25% L3 blasts) and/or CNS-positive

French-American-British (FAB)

Group A

Resected stage I and abdominal completely resected stage II

Berlin-Frankfurt-Munster (BFM)

R1

Stage I or II, completely resected

R2

Stage I or II, not resected Stage III with LDH <500 U/L

R3

Stage III with LDH ≥500 to

<1000 U/L or

Stage IV with LDH <1000 U/L and CNS-negative

R4

Stage III or IV with LDH

≥1000 U/L and/or CNS-positive

Low Risk

High Risk

Risk Stratification Groups for Pediatric B-Cell NHL

**Table 496-6**

*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

Ages 0-14 yr (n=14,846)

Neuronal and mixed neuronal-glial

Ages 15-19 yr (n=5,863)

Neuronal and mixed-glial

Lymphoma 0.3%

Germ cell tumors

3.6%

Tumors of the pituitary 3.4%

Craniopharyngioma 4.1%

Meningioma 1.8%

Nerve sheath tumors 4.9%

tumors

7.8% All other

8.7%

Pilocytic astrocytoma 17.7%

All other astrocytomas 9.0%

Glioblastoma 2.6%

Oligodendrogliomas

Lymphoma 0.4%

Germ cell tumors 5.1%

Tumors of the pituitary 23.2%

Craniopharyngioma 2.7%

Meningioma

tumors

8.2% All other

10.6%

Pilocytic astrocytoma 10.5%

All other astrocytomas 8.6%

Glioblastoma 3.0%

Oligodendrogliomas 2.5%

Embryonal tumors 15.1%

Glioma malignant,

1.1%

Ependymal tumors 5.7%

4.7%

Nerve sheath tumors 6.3%

Glioma malignant,

Ependymal tumors 4.7%

NOS

13.7%

Gliomas (9380-9384,9391-9460,9480)

account for 53% of all tumors and 69% of malignant tumors

Oligoastrocytic

tumors 0.6%

Embryonal tumors 4.5%

NOS 4.3%

Oligoastrocytic tumors 0.9%

**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.)*

Gliomas (9380-9384,9391-9460,9480)

account for 37% of all tumors and 73% of malignant tumors

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| **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* |
| Nevoid 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.*

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| **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 cervicomedullary 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

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| **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.*

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| **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 compres- sion, 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,

**Chapter 498** ◆ Neuroblastoma **2463**

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| **Table 498-4** | Phenotypic and Genetic Features of Neuroblastoma, Treatment, and Survival According to Prognostic Category | | | | |
| **VARIABLE** | | **PROGNOSTIC CATEGORY\*** | | | |
| **Low Risk** | **Intermediate Risk** | **High Risk** | **Tumor Stage 4S** |
| 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 Whole-chromosome gains 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.

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| **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 opsoclonus, 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 |

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| **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. | |

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| **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  Malignant fibrous histiocytoma | 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.  Most commonly arises in the trunk and extremities, deep in the subcutaneous layer. Histologically  subdivided into storiform, giant cell, myxoid, and angiomatoid variants. The angiomatoid 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. |

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| **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 |

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*

1. Having 5 of the following 8 signs or symptoms:
   1. Fever
   2. Splenomegaly
   3. 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)

* 1. Hypertriglyceridemia (≥265 mg/dL) and/or hypofibrinogenemia (≤150 mg/dL)
  2. Hemophagocytosis in the bone marrow, spleen, or lymph

nodes without evidence of malignancy

* 1. Low or absent natural killer cell cytotoxicity
  2. Hyperferritinemia (≥500 ng/mL)
  3. Elevated soluble CD25 (interleukin-2Rα chain; ≥2,400 U/mL)

Diagnostic Guidelines for Hemophagocytic Lymphohistiocytosis

**Table 507-4**

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| **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  *Babesia microti Brucella abortus*  Enteric Gram-negative rods *Haemophilus influenzae Mycoplasma pneumoniae Staphylococcus aureus Streptococcus pneumoniae* | |
| *Candida albicans Cryptococcus neoformans Histoplasma capsulatum Fusarium* | |
| MYCOBACTERIAL  *Mycobacterium tuberculosis* | |
| RICKETTSIAL  *Coxiella burnetii*  Other rickettsial diseases | |
| PARASITIC  *Leishmania donovani Plasmodium* | |

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| **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 | |

**Chapter 507** ◆ Histiocytosis Syndromes of Childhood **2485**

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|  | **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

**Chapter 509** ◆ Clinical Evaluation of the Child with Hematuria **2495**

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| **Table 509-1** | Other Causes of Red Urine | |
| HEME POSITIVE  Hemoglobin Myoglobin | | Dyes (Vegetable/Fruit)  Beets Blackberries  Food and candy coloring Rhubarb  Metabolites Homogentisic acid Melanin Methemoglobin Porphyrin Tyrosinosis  Urates |
| HEME NEGATIVE  Drugs Chloroquine Deferoxamine Ibuprofen Iron sorbitol  Metronidazole Nitrofurantoin Phenazopyridine (Pyridium) Phenolphthalein Phenothiazines  Rifampin Salicylates Sulfasalazine | |

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

Common Causes of Gross Hematuria

**Table 509-3**

**NO**

**Extraglomerular hematuria**

*Step 1*

* Urine culture

*Step 2*

* Urine calcium/creatinine
* Sickle prep (African American)
* Renal/bladder ultrasound

*Step 3*

* Urinalysis: siblings, parents
* Serum electrolytes, Cr, Ca
* If crystalluria, urolithiasis, or nephrocalcinosis:

\*24-hr urine for Ca, creatinine, uric acid, oxalate

* If hydronephrosis/pyelocaliectasis:

\*Cystogram, ± renal scan

Cola/brown urine? Proteinuria (>30 mg/dL)? RBC casts?

Acute nephritic syndrome?

**YES**

**Glomerular hematuria**

* CBC with differential
* Electrolytes, Ca
* BUN/Cr
* Serum protein/albumin
* Cholesterol
* C3/C4
* ASO/anti-DNase B
* ANA
* Antineutrophil antibody
* Throat/skin culture (if indicated)
* 24-hr urine total protein

creatinine clearance

\*Denotes glomerulonephritides presenting with hypocomplementemia.

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| **Table 509-2** | Causes of Hematuria in Children |
| UPPER URINARY TRACT DISEASE  *Isolated renal disease*  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 *Multisystem disease*  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 *Tubulointerstitial disease* Pyelonephritis  Interstitial nephritis Papillary necrosis Acute tubular necrosis *Vascular*  Arterial or venous thrombosis Malformations (aneurysms, hemangiomas) Nutcracker syndrome  Hemoglobinopathy (sickle cell trait/disease) Crystalluria  *Anatomic*  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† | |

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

**Figure 509-1** Algorithm of the general approach to the laboratory and radiologic evaluation of the patient with glomerular or extraglo- merular 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.

**2500 Part XXIII** ◆ Nephrology

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| **Table 511-1** | Summary of Primary Renal Diseases That Manifest as Acute Glomerulonephritis | | | | |
| **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.

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| **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 | |

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| **Table 514-1** | Classification of Lupus Nephritis |
| **CLASS CLINICAL FEATURES** | |
| I. Minimal mesangial LN No renal findings | |
| II. Mesangial proliferative Mild clinical renal disease; minimally LN active urinary sediment; mild to  moderate proteinuria (never nephrotic) but may have active serology | |
| III. Focal proliferative LN More active sediment changes;  <50% glomeruli involved often active serology; increased  A. Active proteinuria (approximately 25%  A/C. Active and chronic nephrotic); hypertension may be  C. Chronic present; some evolve into class IV pattern; active lesions require treatment, chronic do not | |
| IV. Diffuse proliferative Most severe renal involvement with LN (>50% glomeruli active sediment, hypertension, involved); all may be with heavy proteinuria (frequent segmental or global nephrotic syndrome), often involvement (S or G) reduced glomerular filtration rate;  A. Active serology very active. Active lesions A/C. Active and chronic require treatment  C. Chronic | |
| V. Membranous LN Significant proteinuria (often glomerulonephritis nephrotic) with less active lupus  serology | |
| VI. Advanced sclerosing LN More than 90% glomerulosclerosis;  no treatment prevents renal failure | |

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| **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 | |

LN, lupus nephritis.

**Chapter 511** ◆ Glomerulonephritis Associated with Infections **2501**

Serum complement (C3, CH 50)

**Systemic diseases**

* Lupus nephritis (focal 75%, diffuse 90%)
* Subacute bacterial endocarditis (90%)
* Shunt nephritis (90%)
* Essential mixed cryoglobulinemia (85%)
* Visceral abscess

Normal serum complement

**Systemic diseases**

* Polyarteritis nodosa
* Hypersensitivity vasculitis
* Granulomatosis with polyangiitis
* Henoch-Schönlein purpura
* Goodpasture syndrome

Renal diseases

* Acute postinfectious GN (>90%)
* Membranoproliferative GN Type I (50–80%)

Renal diseases

* IgA nephropathy
* Idiopathic rapidly progressive (crescentic) GN

Type I (anti-GBM disease) Type II (immune complex CGN) Type III (pauciimmune CGN)

Postinfectious GN (nonstreptococcal)

Serologic evidence of an antecedent streptococcal infection

(ASO, anti–DNase B, streptozyme test)

Positive and/or return of low serum Negative or failure of low serum

C3 complement to normal C3 complement to return to normal by 6–8 wk by 6–8 wk

Acute poststreptococcal GN

Lupus nephritis (anti–nuclear antibodies,

anti–double-stranded DNA antibody)

Essential mixed cryoglobulinemia (cryoglobulin, hepatitis C virus)

Shunt nephritis (history, clinical symptoms)

Visceral abscess (blood culture) Membranoproliferative GN (C3NF) Bacterial endocarditis

Post infectious GN (non streptococcal)

Clinical features of acute glomerulonephritis

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

Thrombotic Microangiopathies Overview and Classification

**Table 518-1**

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

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.

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| **Table 521-2** | Autosomal Recessive Polycystic Kidney Disease and Hepatorenal Fibrocystic Disease Phenocopies | | | | |
| **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 (ADT3) ADT1, ADT4, ADT5* | Cystic dysplasia | CHF; Caroli disease | Yes |
| Renal-hepatic-pancreatic dysplasia (Ivemark II)  Zellweger syndrome | | *NPHP3, NEK8*  *PEX1-3;5-6;10-11;13;14;16;19;26* | Cystic dysplasia  Renal cortical microcysts | Intrahepatic biliary dysgenesis  Intrahepatic biliary dysgenesis | Yes  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.*

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| **Table 521-1** Comparison of Clinical Features of Cystic Kidney Diseases | | | | | | | | |
| **DISEASE** | **INHERITANCE** | **FREQUENCY** | **GENE PRODUCT** | **AGE OF ONSET** | **CYST ORIGIN** | **RENOMEGALY** | **CAUSE OF ESRD** | **OTHER MANIFESTATIONS** |
| ADPKD | AD | 400-1,000 | Polycystin 1  Polycystin 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 | Retinal 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 hypogenitalism, 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.*

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| **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/m2/24 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.*

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| **Table 527-1** | Causes of Childhood Nephrotic Syndrome | |
| IDIOPATHIC NEPHROTIC SYNDROME  Minimal change disease  Focal segmental glomerulosclerosis Membranous nephropathy  Glomerulonephritis associated with nephrotic syndrome– membranoproliferative glomerulonephritis, crescentic glomerulonephritis, immunoglobulin A nephropathy | | SECONDARY CAUSES OF NEPHROTIC SYNDROME  Infections Endocarditis Hepatitides B, C HIV-1  Infectious mononucleosis Malaria  Syphilis (congenital and secondary) Toxoplasmosis  Schistosomiasis Filariasis  Drugs Captopril Penicillamine Gold  Nonsteroidal antiinflammatory drugs Pamidronate  Interferon Mercury Heroin Lithium  Immunologic or Allergic Disorders Vasculitis syndromes  Castleman disease Kimura disease Beesting  Food allergens Serum sickness  Associated With Malignant Disease Lymphoma  Leukemia Solid tumors  Glomerular Hyperfiltration Oligomeganephronia Morbid obesity  Adaptation to nephron reduction |
| GENETIC DISORDERS ASSOCIATED WITH PROTEINURIA OR NEPHROTIC SYNDROME  Nephrotic Syndrome (Typical)  Finnish-type congenital nephrotic syndrome (absence of nephrin) Focal segmental glomerulosclerosis (mutations in nephrin, podocin, *MYO1E*, α-actinin 4, TRPC6)  Diffuse mesangial sclerosis (mutations in laminin β2 chain)  Denys-Drash syndrome (mutations in WT1 transcription factor)  Congenital nephrotic syndrome with lung and skin involvement (integrin α-3 mutation)  Mitochondrial disorders)  Proteinuria With or Without Nephrotic Syndrome  Nail-patella syndrome (mutation in LMX1B transcription factor) Alport syndrome (mutation in collagen biosynthesis genes)  Multisystem Syndromes With or Without Nephrotic Syndrome Galloway-Mowat syndrome  Charcot-Marie-Tooth disease Jeune syndrome  Cockayne syndrome  Laurence-Moon-Biedl-Bardet syndrome  Metabolic Disorders With or Without Nephrotic Syndrome Alagille syndrome  α1-Antitrypsin deficiency Fabry disease  Glutaric acidemia Glycogen storage disease Hurler syndrome  Partial lipodystrophy Mitochondrial cytopathies Sickle cell disease | |

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

**Chapter 527** ◆ Nephrotic Syndrome **2523**

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| **Table 527-2** | | Summary of Primary Renal Diseases That Manifest as Idiopathic Nephrotic Syndrome | | | | | |
| **MINIMAL CHANGE NEPHROTIC** | | | | **FOCAL SEGMENTAL** | **MEMBRANOUS** | **MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS** | |
| **Type I** | **Type II** |
| **FEATURES** | | | **SYNDROME** | **GLOMERULOSCLEROSIS** | **NEPHROPATHY** |
| 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; hepatitides 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.*

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| **Table 526-1** | Causes of Proteinuria | |
| TRANSIENT PROTEINURIA  Fever Exercise Dehydration  Cold exposure Congestive heart failure Seizure  Stress | | GLOMERULAR DISEASES WITH PROTEINURIA AS A PROMINENT FEATURE  Acute postinfectious glomerulonephritis (streptococcal, endocarditis, hepatitis B or C virus, HIV)  Immunoglobulin A nephropathy Henoch-Schönlein purpura nephritis Lupus nephritis  Serum sickness Alport syndrome Vasculitic disorders Reflux nephropathy |
| ORTHOSTATIC (POSTURAL) PROTEINURIA | |
| GLOMERULAR DISEASES CHARACTERIZED BY ISOLATED PROTEINURIA  Idiopathic (minimal change) nephrotic syndrome Focal segmental glomerulosclerosis  Mesangial proliferative glomerulonephritis Membranous nephropathy Membranoproliferative glomerulonephritis Amyloidosis  Diabetic nephropathy Sickle cell nephropathy | |
| TUBULAR DISEASES  Cystinosis Wilson disease Lowe syndrome  Dent disease (X-linked recessive nephrolithiasis) Galactosemia  Tubulointerstitial nephritis Acute tubular necrosis Renal dysplasia  Polycystic kidney disease Reflux nephropathy  Drugs (penicillamine, lithium, NSAID) Heavy metals (lead, gold, mercury) |

NSAID, nonsteroidal antiinflammatory drug.

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| **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 | | 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 |
| HYPERKALEMIC 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 |
| 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 hypercalciuria | |

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| **Table 535-6** | | Standardized Terminology for Stages of Chronic Kidney Disease (NKF KDOQI Guidelines) | |
| **STAGE** | **DESCRIPTION** | | **GFR (mL/min/1.73 m2)** |
| 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.

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| **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 | |

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| **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 | | 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 |
| HYPERKALEMIC 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 |
| 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 hypercalciuria | |

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| **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, hypercalciuria, 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.

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| **Table 532-1** | Etiology of Interstitial Nephritis | |
| ACUTE  Drugs   * Antimicrobials   + Penicillin derivatives   + Cephalosporins   + Sulfonamides   + Trimethoprim-sulfamethoxazole   + Ciprofloxacin   + Tetracyclines   + Vancomycin   + Erythromycin derivatives   + Rifampin   + Amphotericin B   + Acyclovir * Anticonvulsants   + Carbamazepine   + Phenobarbital   + Phenytoin   + Sodium valproate * Other drugs   + 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) Infections * Adenovirus * Bacteria associated with acute pyelonephritis * BK virus * *Brucella* * Streptococcal species * Cytomegalovirus * Epstein-Barr virus * Hepatitis B virus * Histoplasmosis * Human immunodeficiency virus * Hantavirus * Leptospirosis * *Toxoplasma gondii*   Disease-associated   * Glomerulonephritis (e.g., systemic lupus erythematosus) * Acute allograft rejection * Tubulointerstitial nephritis and uveitis (TINU) syndrome Idiopathic | | CHRONIC  Drugs and toxins   * Analgesics * Cyclosporine * Lithium * Heavy metals Infections (see Acute) Disease-associated * Metabolic and hereditary * Cystinosis * Oxalosis * Fabry disease * Wilson disease * Sickle cell nephropathy * Alport syndrome * Juvenile nephronophthisis, medullary cystic disease Immunologic * Systemic lupus erythematosus * Crohn disease * Chronic allograft rejection * Tubulointerstitial nephritis and uveitis (TINU) syndrome * Antitubular basement disease Urologic * Posterior urethral valves * Eagle-Barrett syndrome * Ureteropelvic junction obstruction * Vesicoureteral reflux Miscellaneous * Balkan nephropathy * Radiation * Sarcoidosis * Neoplasm Idiopathic |

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| **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.*

**2538 Part XXIII** ◆ Nephrology

|  |  |
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| **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 |
|  |
| Amphotericin B | RENAL TUBULAR ACIDOSIS |
| Cisplatin | Amphotericin B |
| Colchicine | Lead |
| Demeclocycline | Lithium |
| Lithium | Toluene |
| Methoxyflurane |
| INTERSTITIAL NEPHRITIS  Amidopyrine  *p*-Aminosalicylate Carbon tetrachloride Cephalosporins Cimetidine  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 |
| Propoxyphene |
| Vinblastine |
| RENAL VASCULITIS |
| Hydralazine |
| Isoniazid |
| Penicillins |
| Propylthiouracil |
| Sulfonamides |
| Numerous other drugs that can cause a hypersensitivity reaction |
| THROMBOTIC MICROANGIOPATHY |
| Cyclosporine A |
| Oral contraceptive agents |
| Mitomycin C |
| NEPHROCALCINOSIS OR NEPHROLITHIASIS |
| Allopurinol |
| Bumetanide |
| Ethylene glycol |
| Furosemide |
| Melamine |
| Methoxyflurane |
| Topiramate |
| Vitamin D |
| 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 |

**Chapter 535** ◆ Renal Failure **2539**

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| --- | --- | --- | --- |
| **Table 535-1** | | Pediatric-Modified Rifle (pRIFLE) Criteria | |
| **CRITERIA** | **ESTIMATED CCL** | | **URINE OUTPUT** |
| Risk | eCCl decrease by 25% | | <0.5 mL/kg/hr for 8 hr |
| Injury | eCCl decrease by 50% | | <0.5 mL/kg/hr for 16 hr |
| Failure | eCCl decrease by 75% or  eCCl <35 mL/min/1.73 m2 | | <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) | |  |

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

|  |  |
| --- | --- |
| **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 Ureterovesicular junction obstruction Ureterocele  Tumor Urolithiasis  Hemorrhagic cystitis Neurogenic bladder | |

|  |  |  |  |  |
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| **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 | | +  –  –  +  –  +  +  –  –  +  +  +  +  – | –  +  +  +  +  –  ++  –  +  –  –  –  –  + | –  +  –  +  +/−  –  +  +  +  –  –  –  –  + |

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

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

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

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 m2 for ≥3 mo, with or without the other signs of kidney damage described above

Criteria for Definition of Chronic Kidney Disease (NKF KDOQI Guidelines)

**Table 535-5**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table 535-3** | Urinalysis, Urine Chemistries, and Osmolality in Acute Kidney Injury | | | | | |
|  | | **HYPOVOLEMIA** | **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 ×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.

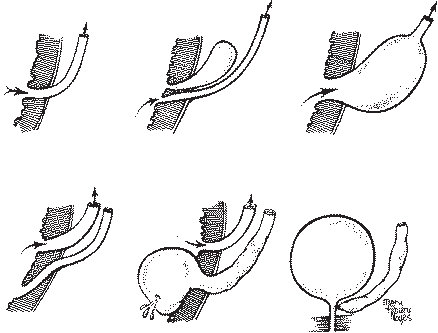
*From Singri N, Ahya SN, Levin ML: Acute renal failure,* JAMA *289:747–751, 2003.*

|  |  |  |
| --- | --- | --- |
| **Table 536-2** | Common Causes of ESRD in Pediatric Transplant Recipients (N = 9854) | |
| **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 |

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| **Table 539-1** | Classification of Vesicoureteral Reflux | |
| **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 |

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Duplication Ureterocele



Primary

A.

B.

Diverticula

|  |  |  |
| --- | --- | --- |
| **Table 535-7** | Pathophysiology of Chronic Kidney Disease | |
| **MANIFESTATION** | | **MECHANISMS** |
| 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 B12 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 |

with duplication Ureteral ectopia

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

**Chapter 538** ◆ Urinary Tract Infections **2561**

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| **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 Ultrasound scan within 6 wk of infection DMSA scan 4-6 mo after acute infection Micturating cystograms | | No Yes No  Consider if ultrasound scan abnormal | Yes Yes  No No  Yes Yes  Yes Yes |
| CHILDREN 6 MO-3 YR OLD  Ultrasound scan during acute infection Ultrasound scan within 6 wk of infection DMSA scan 4-6 mo after acute infection Micturating cystograms | | No No No No | Yes No  No Yes  Yes Yes  Not routine, consider if dilation on ultrasound, poor urine flow, non–*E. coli* infection, or family history of vesicoureteric reflux |
| CHILDREN OLDER THAN AGE 3 YR  Ultrasound scan during acute infection Ultrasound scan within 6 wk of infection DMSA scan 4-6 mo after acute infection Micturating cystograms | | No No No No | Yes No  No Yes  Yes Yes  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.*

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| --- | --- | --- |
| **Table 540-3** | The Etiology of Antenatal Hydronephrosis | |
| **ETIOLOGY** | | **INCIDENCE** |
| Transient hydronephrosis | | 41-88% |
| Ureteropelvic junction obstruction | | 10-30% |
| Vesicoureteral reflux | | 10-20% |
| Ureterovesical 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.*

*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 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 |

**Chapter 540** ◆ Obstruction of the Urinary Tract **2567**

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

Causes of Urinary Incontinence in Childhood

**Table 543-1**

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 540-2** | Definition of Antenatal Hydronephrosis by Anterior-Posterior Diameter | | |
| **DEGREE OF ANTENATAL 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 Megaureter | | | |
| **Refluxing** | | | **Obstructed**  **PRIMARY SECONDARY** | **Nonrefluxing and Nonobstructed**  **PRIMARY SECONDARY** |
| **PRIMARY** | | **SECONDARY** |
| Primary reflux | | Neuropathic bladder | Intrinsic (primary obstructed Neuropathic bladder megaureter) | Nonrefluxing, Diabetes insipidus nonobstructive |
| Megacystic-megaureter 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 |  |

|  |  |  |
| --- | --- | --- |
| **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 | |

**2582 Part XXIV** ◆ Urologic Disorders in Infants and Children

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\* | |  | | | | |
| * 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 545-3** | 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 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 | |

**Chapter 543** ◆ Enuresis and Voiding Dysfunction **2585**

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| --- | --- | --- |
| **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, | | Spermatocele\* |
| hematocele | | Testicular tumor\* |
| Inguinal hernia (incarcerated) | | Henoch-Schönlein purpura\* |
| Mumps orchitis Testicular vasculitis | | Idiopathic scrotal edema |

\*May be associated with discomfort.

|  |  |
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| **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  Adrenocorticotropic 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 | |

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| **Table 547-2** | Laboratory Tests Suggested for Evaluation of Urolithiasis | |
| SERUM  Calcium Phosphorus Uric acid  Electrolytes and anion gap Creatinine  Alkaline phosphatase | | URINE  Urinalysis Urine culture  Calcium : creatinine ratio Spot test for cystinuria 24 hr collection for:  Creatinine clearance Calcium  Phosphate Oxalate Uric acid  Dibasic amino acids (if cystine spot test result is positive) |

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| **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

**2602 Part XXIV** ◆ Urologic Disorders in Infants and C4h4il4dren

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| **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  1-<5 yr  5-12 yr  >12 yr | 0.15-0.26 mmol/mmol creat  0.11-0.12 mmol/mmol creat  0.006-0.15 mmol/mmol creat  0.002-0.083 mmol/mmol creat | ≥2 yr: <0.5 mmol/1.73 m2/24 hr | Random urine mmol/mmol highly age-dependent  Excretion rate/1.73 m2 constant through childhood and adulthood |
| Uric acid | Term infant  >3 yr | 3.3 mg/dL GFR†  <0.53 mg/dL GFR | <815 mg/1.73 m2/24 hr | Excretion rate/1.73 m2 from >1 yr age; constant through childhood |
| Magnesium | >2 yr | <0.12 mg/mg creat | <88 mg/1.73 m2/24 hr | Excretion rate/1.73 m2 constant through childhood |
| Citrate |  | >400 mg/g creat |  | Limited data available for children |
| Cystine |  | <75 mg/g creat | <60 mg/1.73 m2/24 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.*

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| **Table 547-4** | Metabolic Evaluation of Children with Hypercalciuria | | | | |
| **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.

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| **Table 547-6** Suggested Therapy for Urolithiasis Caused by Metabolic Abnormalities |  |
| **METABOLIC SECOND-LINE**  **ABNORMALITY INITIAL TREATMENT TREATMENT** | |
| Hypercalciuria Reduction of dietary Potassium citrate  Na+  Dietary calcium at RDA Neutral phosphate  Thiazides | |
| Hyperoxaluria Adjustment of dietary Neutral phosphate\*  oxalate  Potassium citrate Magnesium Pyridoxine\* | |
| Hypocitric aciduria Potassium citrate  Bicarbonate | |
| Hyperuricosuria Alkalinization Allopurinol | |
| Cystinuria Alkalinization Tiopronin (Thiola)  Reduction of dietary D-Penicillamine Na+  Captopril | |

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| **Table 547-5** | Primary Surgical Treatment Options vs Stone Size and Location | | |
| **STONES** | **SHOCK WAVE LITHOTRIPSY** | **URETEROSCOPY** | **PERCUTANEOUS NEPHROLITHOTOMY** |
| RENAL  <1 cm  1-2 cm  >2 cm | Most common Most common Optional | Optional Optional Rare | Optional Optional  Most common |
| LOWER POLE  <1 cm  >1 cm | Most common Optional | Optional Optional | Optional  Most common |
| URETERAL  Proximal Distal | Most common Optional | Optional  Most common | Occasional Rare |

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

Suggested Indications for Pelvic Examination in Adolescents

**Table 548-1**

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

\*Initial therapy in primary hyperoxaluria.

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

Recommendations for First Gynecologic Evaluation

**Table 548-2**

# Cynecologic Problems of Childhood

**2608 Part XXV** ◆ Gynecologic Problems of Childhood

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| **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  *Genital/mucocutaneous disease:*  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 (Reoccurrence): 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) |

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| **Table 552-4** | Causes of Hirsutism |
| PERIPHERAL  Idiopathic  Partial androgen insensitivity (5α-reductase deficiency)  HAIR-AN syndrome (*h*irsutism, *a*ndrogenization, *i*nsulin *r*esistance,  and *a*canthosis *n*igricans) 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 | |

**Chapter 549** ◆ Vulvovaginitis **2609**

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| **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  *Symptomatic patients:* 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 | Ultrapotent 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

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| **Table 549-2** Antibiotic | Recommendations for Specific Vulvovaginal Infections |
| **ETIOLOGY** | **TREATMENT** |
| *Streptococcus pyogenes Streptococcus pneumoniae* | 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 |
| *Staphylococcus aureus* | 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 |
| *Haemophilus influenzae* | Amoxicillin, 40 mg/kg/day divided into 3 doses daily × 7 days  Cases of treatment failure or non-encapsulated *H. influenzae*, amoxicillin–clavulanate is recommended |
| *Yersinia* | TMP-SMX 6 mg/kg (TMP component) daily for 3 days |
| *Shigella* | 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 |
| *Chlamydia trachomatis* | *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 |
| *Neisseria gonorrhoeae* | *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 |
| *Trichomonas* | 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 *(Enterobius vermicularis)* | 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*.*

**Chapter 549** ◆ Vulvovaginitis **2611**

\*HSV already ruled out with negative genital HSV culture

or PCR

First episode?

Yes

No

Associated signs/

symptoms?

H/o joint, GI, ocular or

dermatologic symptoms?

No

Yes

Non-specific

prodromal

Referral to rheumatology,

ophthalmology, gastroenterology or dermatology to rule out associated condition

Idiopathic vulvar aphthosis

Consider infectious Treatment:

workup: • Pain control: topical agents, acetaminophen

* EBV, CMV, influenza ± narcotics (parenteral if needed)
* Mycoplasma • Local care: sitz bath, whirlpool debridement
* Lesional viral cultures • Topical steroids (clobetasol ointment)

Consider specialist • Consider oral steroids

consultation based on • Bladder drainage for urinary retention symptoms Follow-up with gynecology or dermatology

None

Severe

* Persistent fever
* Lymphadenopathy
* Pharyngitis
* Persistent fatigue

AGU without history of sexual activity\*

**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 rec- ommendations.* Pediatr Dermatol *29(2);147–153, 2012.)*

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

Common Causes of Nipple Discharge

**Table 551-2**

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| **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 | |

**Chapter 553** ◆ Neoplasms and Adolescent Screening for Human Papillomavirus **2625**

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| **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  Sertoli-Leydig cell tumor  Lipoid cell tumors Gynandroblastoma | | 92%  70-90%  ~80%  90% or greater | Produce estrogen Menstrual irregularities  Isosexual precious pseudopuberty Call-Exner bodies rare  Virilization in 40% Produce testosterone  Rare heterogenous group with lipid-filled parenchyma  Rare low-grade mixed tumors that produce either estrogen or androgen |

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| **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, dehydroepiandrostenedione; E2, estradiol; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; T, testosterone, MIS, müllerian inhibiting substance; VEGF, vascular endothelial growth factor.

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| **Table 554-1** | Common Müllerian Anomalies |
| **ANOMALY DESCRIPTION** | |
| Hydrocolpos Accumulation of mucus or nonsanguineous fluid in the vagina | |
| Hemihematometra Atretic 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 cervices, 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 | |

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| **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

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

Bioinactive 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

Proposed Classification of Growth Hormone Insensitivity

**Table 557-4**

*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.*

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| **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.*

ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone;

|  |  |  |  |  |
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| **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 T4 and T3 |

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).

Pituitary

Hypothalamus

TRH

TSH

Thyroid

T4, T3

**Figure 556-1** Hypothalamic–pituitary–thyroid (HPT) axis. Thyroid- releasing hormone (TRH) from the hypothalamus stimulates the pitu- itary 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 secre- tion and thyroid hormone production through a negative feedback mechanism *(dashed lines)*. T3, triiodothyronine; T4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone (thy- rotropin); <---, inhibits; ←, stimulates.

**2642 Part XXVI** ◆ The Endocrine System

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

Clinical Features of Growth Hormone Insensitivity

**Table 557-6**

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.

|  |  |
| --- | --- |
| **Table 557-7** | Evaluation of Suspected Growth Hormone Deficiency |
| Growth-related history • Infants and children with GHD have and patient physical growth failure  exam • Short stature and growth failure may be the only clinical features present   * GHD affects ~1 in 3,500 children | |
| Imaging and other • Diagnosis is based on clinical, evaluations 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 • Measurements of GH, IGF-1, and  IGF-1–binding protein levels   * Determination of peak GH levels after stimulation test | |
| Special testing (if • Family history and genetic analyses applicable) (e.g., search for *PROP1* and *POU1F1*  mutations) | |
| Rationale for treatment • Replacement therapy with rhGH (GHT) and treatment • Predictors of greater benefit with GHT modalities 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 | |

*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.*

Diabetes insipidus (DI)

* Central DI

Genetic (autosomal dominant) Acquired

Trauma (surgical or accidental)

Congenital malformations (holoprosencephaly, septooptic dysplasia, encephalocele)

Neoplasms (craniopharyngioma, germinoma, metastasis)

Infiltrative (Langerhans cell histiocytosis), autoimmune (lymphocytic infundibuloneurohypophysitis), 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

Differential Diagnosis of Polyuria and Polydipsia

**Table 558-1**

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

|  |  |
| --- | --- |
| **Table 559-1** | Differential Diagnosis of Hyponatremia |
| **INTRAVASCULAR URINE**  **DISORDER VOLUME STATUS SODIUM** | |
| Systemic dehydration Low Low | |
| Decreased effective Low Low plasma volume | |
| Primary salt loss (nonrenal) Low Low | |
| Primary salt loss (renal) Low High | |
| SIADH High High | |
| Cerebral salt wasting Low Very high | |
| Decreased free water Normal or high Normal or high clearance | |
| Primary polydipsia Normal or high Normal | |
| Runner’s hyponatremia Low Low | |
| NSIAD High High | |
| Pseudohyponatremia Normal Normal | |
| Factitious hyponatremia Normal Normal | |

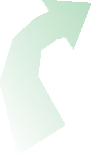
NSIAD, nephrogenic syndrome of inappropriate antidiuresis; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Nausea Hypoglycemia

**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.)*

VP secretion Renal water reabsorption

Hyperosmolality Hypotension Hypovolemia



Pain

Osmosensor Barosensor

Thirst Drinking



**Chapter 559** ◆ Other Abnormalities of Arginine Vasopressin Metabolism and Action **2647**

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| **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.

|  |  |  |  |
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| **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  *CYP11B2*—cytochrome P450, subfamily XIB, polypeptide 2 8q21 124080 | | P450c21—steroid 21-hydroxylase that converts 17 α-hydroxyprogesterone to 11-deoxycortisol and progesterone to 11-deoxycorticosterone in the adrenal zona fasciculata  P450c11B2—aldosterone synthase/corticosterone methyoxidase 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 decrease synthesis of cortisol and aldosterone, the latter resulting in the salt-losing form of classical congenital adrenal hyperplasia, AR–201910  Loss-of-function mutations associated with severe salt loss and volume depletion but not with abnormalities of genital formation or glucocorticoid synthesis AR (CMOI 203400; CMOII 610600) |
| PSEUDOHYPOALDOSTERONISM TYPE I  *NR3C2*—nuclear receptor subfamily 3, group C, member 2 (MR- mineralocorticoid receptor), 4q31.1 600983  *SCNN1A*—sodium channel, non–voltage- gated, α-subunit 12p13.31 600228  *SCNN1B*—sodium channel, non–voltage- gated, β-subunit 16p12.2 600760  *SCNN1G*—sodium channel, non–voltage-  gated, γ-subunit 16p12.2 600761 | | 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  Inactivating mutation of α-subunit of the epithelial sodium channel  Inactivating mutation of β-subunit of the epithelial sodium channel  Inactivating mutation of γ-subunit of the epithelial sodium channel | Loss-of-function mutations lead to mineralocorticoid resistance and pseudohypoaldosteronism type I, AD–177735  Pseudohypoaldosteronism type I, AR–264350 Pseudohypoaldosteronism type I, AR–264350 Pseudohypoaldosteronism type I, AR–264350 |
| PSEUDOHYPOALDOSTERONISM TYPE II  *WNK4*—protein kinase, lysine-deficient 4 17q21.31 601844  *WNK1*—protein kinase, lysine-deficient 1 12p13.33 605232  *KLH3*—Kelch-like 3 5q31.2 605775  *CUL3*—Cullin 3 2q36.2 603136 | | 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  Serine-threonine protein kinase that inactivates WNK4 by phosphorylating its kinase domain  Adaptor protein within the ubiquitination sequence that links WNK1 and WNK4 to CUL3  Scaffold protein that links to RING-box E3 ligase facilitating WNK4 ubiquitination and proteasomal destruction of WNK4 | Pseudohypoaldosteronism type IIB, AD–614491  Pseudohypoaldosteronism type IIC, AD–614492  Pseudohypoaldosteronism type IID, AD/AR–614495  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.*

**Chapter 560** ◆ Hyperpituitarism, Tall Stature, and Overgrowth Syndromes **2651**

Height SDS > +2SDS or

Height-TH > +2SDS

Height < +2SDS but

typical dysmorphic features

Dysmorphic?



No Yes

(Recent) growth acceleration? Disproportionate?

No



No

Height-TH > +2SDS? Puberty signs? No

Yes

No

Familial tall stature

Yes

Obesity

No

Pituitary gigantism Hyperthyroidism

Yes

Precocious puberty Pseudoprecocious puberty Constitutional

**Overgrowth syndromes** Sotos syndrome Weaver syndrome Nevo syndrome

Beckwith-Wiedemann syndrome Simpson-Golabi-Behmel syndrome PTEN-hamartoma syndrome

**Overgrowth syndromes** Klinefelter syndrome Marfan syndrome

Marfan type II syndrome CCA/Beals syndrome Homocystinuria

Lujan-Fryns syndrome

#### Other

Estrogen deficiency/insensitivity

advance in puberty

Estrogen deficiency or insensitivity

**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.)*

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| --- | --- |
| **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  XYY  *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) XYY  Androgen or estrogen deficiency or estrogen resistance Androgen insensitivity syndrome (testicular feminization) ACTH or cortisol deficiency or resistance  Excess GH secretion (pituitary gigantism) | |

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| **Table 564-1** | Causes of Acquired Thyroxine-Binding Globulin (TBG) Deficiency and Excess | |
| **DECREASED TBG** | | **INCREASED TBG** |
| Androgens | | Estrogens |
| Anabolic steroids | | Selective estrogen receptor modulators |
| Glucocorticoids | | Pregnancy |
| Hepatocellular disease | | Hepatitis |
| Severe illness | | Porphyria |
| Protein-losing nephropathies | | Heroin, methadone |
| Protein-losing enteropathies | | Mitotane |
| Nicotinic acid | | 5-Flurouracil |
| L-Asparaginase | | Perphenazine |

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| **Table 560-2** Genetic Overgrowth Syndromes | | | | |
| **GENETIC SYNDROMES** | **CLINICAL FEATURES** | **INCIDENCE OF MALIGNANCY (%)** | **ETIOLOGY** | **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 *NSD1* 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  *PTEN* 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 *(FBN1)* | 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 *TGFBR1* and *TGFBR2* genes | Eye examination usually normal Heart US and follow-up Monitor scoliosis |
| Beals syndrome | Congenital distal arthrogryposis Crumpled ears |  | Autosomal dominant fibrillin 2 *(FBN2)* | Eye examination and heart US usually normal |
| Homocystinuria | Marfan-like habitus Developmental delay Lens dislocation |  | Autosomal recessive Cystathionine β-synthase  (CBS) mutation | Urine metabolic screen Eye examination Monitor development |
| Lujan syndrome | Marfanoid habitus plus intellectual disability |  | X-linked recessive  *MED12* 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.*

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| **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 organification, or coupling defect: mutation in thyroid peroxidase gene * Defects in H2O2 generation: mutations in DUOXA2 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: Gsα 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 (TRBAb, measured as *thyrotropin-binding inhibitor immunoglobulin*)  Iodine deficiency (endemic goiter) Maternal medications   * Iodides, amiodarone * Propylthiouracil, methimazole * Radioiodine | |
| CENTRAL (HYPOPITUITARY) HYPOTHYROIDISM  Isolated 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 * ±Deficiency of ACTH | |

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| **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.

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| **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 123I uptake | | Variable | <5% | <5% | <5% | Normal | Low or normal |

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

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

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| **Table 565-2** Thyroid Function Tests | | |
| **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 |  |  |
| *Premature Infants (28-36 wk)* |  |  |
| 1st wk of life 0.7-27.0 mIU/L | ×1 | 0.7-27.0 mIU/L |
| *Term Infants* |  |  |
| 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 |  |  |
| *Full-Term Infants* |  |  |
| 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 |
| *Prepubertal Children* |  |  |
| 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 |
| *Pubertal Children and Adults* |  |  |
| >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 toor 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 565-4** | Autoimmune Polyglandular Syndromes 1 and 2 | | |
|  | | **APS-1** | **APS-2** |
| Incidence | | <1 in 100,000 | 1-2 in 10,000 |
|  | | population/yr | population/yr |
| Onset | | Infancy/early | Late childhood/ |
|  | | childhood | adulthood |
| Male : female ratio | | 3 : 4 | 1 : 3 |
| Inheritance | | Monogenic | Polygenic |
|  | | (*AIRE* gene) | (HLA-associated) |
| Mucocutaneous | | 73-100% | None |
| candidiasis | |  |  |
| 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.

|  |  |  |
| --- | --- | --- |
| **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 |

*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 565-5**

## DISEASE AUTOANTIGENS

Addison disease P450c21, P450c17, P450scc Hashimoto thyroiditis Thyroid peroxidase, thyroglobulin Graves disease TSH receptor

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

Etiologic Classification of Acquired Hypothyroidism

**Table 565-3**

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.*

**Chapter 567** ◆ Goiter **2679**

|  |  |
| --- | --- |
| **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) Pruritus  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 dermopathy (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  Cruciferous vegetables such as cabbage, kale, cauliflower, broccoli, turnips, rapeseed  Soy, millet | | Contain cyanogenic glucosides that are metabolized to thiocyanates that  compete with iodine for uptake by the thyroid  Contain glucosinolates; metabolites compete with iodine for uptake by the thyroid  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 Reduce thyroidal iodine uptake from coal processes)  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 Iron deficiency  Vitamin A deficiency | | Accumulated peroxides can damage the thyroid, and deiodinase deficiency impairs thyroid hormone activation  Reduces heme-dependent thyroperoxidase activity in the thyroid and might blunt the efficacy of iodine prophylaxis  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 (131I) | | 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.*

**Chapter 568** ◆ Hyperthyroidism **2683**

|  |  |  |  |
| --- | --- | --- | --- |
| **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 | |  | Common Common Very rare  Uncommon in United States and other iodine-sufficient areas |
| Toxic multinodular goiter | | Activating mutations in thyrotropin receptor or G-protein |
| Toxic solitary adenoma | | Activating mutations in thyrotropin receptor or G-protein |
| Congenital hyperthyroidism | | Activating mutations in thyrotropin receptor |
| Iodine-induced hyperthyroidism (Jod- | | Unknown; excess iodine results in unregulated thyroid |
| Basedow phenomenon) | | hormone production |
| DESTRUCTION OF THYROID FOLLICLES (THYROIDITIS)  Subacute painful thyroiditis Probable viral infection Painless sporadic thyroiditis (or postpartum Autoimmune  thyroiditis)  Amiodarone-induced thyroiditis Direct toxic drug effects  Acute (infectious) thyroiditis Thyroid infection (e.g., bacterial, fungal) and release of preformed hormone | | | Uncommon Common |
| Uncommon 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  Metastatic follicular thyroid cancer  Pituitary resistance to thyroid hormone | | Ovarian teratoma containing thyroid tissue  Large tumor mass capable of secreting thyroid hormone autonomously  Mutated thyroid hormone receptor-β | Rare Rare  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)  O2 if required  Digitalis for heart failure and to slow ventricular response; pentobarbital for sedation  Treatment of precipitating event (e.g., infection) |

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

Etiologic Classification of Solitary Thyroid Nodules

**Table 569-1**

**2690 Part XXVI** ◆ The Endocrine System

|  |  |  |
| --- | --- | --- |
| **Table 571-1** | Causes of Hypocalcemia | |
| 1. Neonatal    1. Maternal Disorders Diabetes mellitus Toxemia of pregnancy Vitamin D deficiency   High intake of alkali or magnesium sulfate Use of anticonvulsants Hyperparathyroidism   * 1. 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   1. Hypoparathyroidism    1. Congenital       1. Transient neonatal       2. Congenital hypoparathyroidism          1. Familial isolated hypoparathyroidism             1. Autosomal recessive hypoparathyroidism (GCMB, PTH)             2. Autosomal dominant hypoparathyroidism (CaSR)             3. X-linked hypoparathyroidism *(SOX3)*          2. DiGeorge syndrome *(TBX1)*          3. Sanjad-Sakati syndrome (short stature, retardation, dysmorphism; HRD); Kenny-Caffey syndrome 1 (short stature, medullary stenosis) *(TBCE)*          4. Barakat syndrome (sensorineural deafness, renal dysplasia; HDR) *(GATA3)*          5. Lymphedema-hypoparathyroidism-nephropathy, nerve deafness          6. Mitochondrial fatty acid disorders (Kearns-Sayre, Pearson, MELAS)       3. Insensitivity to PTH          1. Blomstrand chondrodysplasia *(PTHR1)*          2. Pseudohypoparathyroidism type IA *(GNAS)* Pseudohypoparathyroidism type IB Pseudohypoparathyroidism type IC Pseudohypoparathyroidism type II Pseudopseudohypoparathyroidism          3. Acrodysostosis with hormone resistance *(PRKAR1A)*          4. Hypomagnesemia | | 1. CaSR-activating mutation    1. Sporadic    2. Autosomal dominant (G protein subunit α11 mutation)   B. Acquired   1. Autoimmune polyglandular syndrome type I *(AIRE* gene mutation*)* 2. Activating antibodies to the CaSR 3. Postsurgical, radiation destruction 4. Infiltrative—excessive iron (hemochromatosis, thalassemia) or copper (Wilson disease) deposition; granulomatous inflammation, neoplastic invasion; amyloidosis, sarcoidosis 5. Maternal hyperparathyroidism 6. Hypomagnesemia/hypermagnesemia   III. Vitamin D Deficiency  IV. Other Causes of Hypocalcemia   1. Calcium Deficiency    1. Nutritional deprivation    2. Hypercalciuria 2. Disorders of Magnesium Homeostasis    1. Congenital hypomagnesemia    2. Acquired       1. Acute renal failure       2. Chronic inflammatory bowel disease, intestinal resection       3. Diuretics 3. Hyperphosphatemia    1. Renal failure    2. Phosphate administration (intravenous, oral, rectal)    3. Tumor cell lysis    4. Muscle injuries (crush, rhabdomyolysis) 4. Miscellaneous    1. Hypoproteinemia    2. Hyperventilation    3. Drugs: furosemide, aminoglycosides, bisphosphonates, calcitonin, anticonvulsants, ketoconazole, antineoplastic agents (plicamycin, asparaginase, cisplatinum, cytosine arabinoside, doxorubicin), citrated blood products    4. Hungry bone syndrome    5. Acute and critical illness: sepsis, acute pancreatitis, toxic shock       1. Organic acidemia: propionic, methylmalonic, isovaleric |

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



Confirm with repeat measurement +/— ionized Ca++

Hypocalcemia

Intact PTH level

Elevated

Low/inappropriately

normal

Vitamin D sufficiency

confirmed (25-hydroxy vitamin D >20 ng/mL)

Vitamin D

deficiency confirmed

**Evaluate for etiologies of secondary**

**hyperparathyroidism:**

·Malabsorption

·Vitamin D deficiency

·Pseudohypoparathyroidism types 1, 2

·Vitamin D–dependent rickets types 1, 2

**Evaluate for hypoparathyroidism**

mplete medical history, family history, past surgical history for prior rathyroid, thyroid, or neck surgery

ysical examination (neck scar, candidiasis, signs of tetany, cataracts, short ture, mental retardation)

mily history: mental retardation, features of autoimmune disorders

ddison disease, autoimmune thyroid disease), deafness, renal anomalies, alassemia, or iron overload

rther lab testing, genetic screening, and testing of family members as propriate (activating CaSR mutation; PTH mutation; *AIRE*, *GCMB*, or *TA3* mutational analysis)

sessment of autoantibodies (21-hydroxylase abs, antiparathyroid abs)

·Hearing test, renal imaging (as appropriate)

Evaluate for

gastrointestinal losses, low dietary intake, low sunlight exposure

Replete

vitamin D

Assess vitamin D status with 25- hydroxy vitamin D measurement

Low

Serum Mg++

**Evaluate for etiologies of**

**hypomagnesemia:** ·Co

·Gastrointestinal losses pa

(vomiting, diarrhea, ·Ph

malabsorption) sta

·Renal wasting ·Fa

·Alcoholism (A

·Malnutrition th

·Drug-induced ·Fu

·Perform 24 hr urine and ap further testing as appropriate *GA*

·As

Normal

**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

1. Neonate/Infant
   1. Maternal Disorders
      1. Excessive vitamin D ingestion, hypoparathyroidism, pseudohypoparathyroidism
   2. 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
2. Hyperparathyroidism
   1. Sporadic
      1. Parathyroid hyperplasia, adenoma, carcinoma
   2. 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)*
   3. Secondary/Tertiary
      1. Postrenal transplantation
      2. Chronic hyperphosphatemia
   4. Hypercalcemia of Malignancy
      1. Ectopic production of parathyroid hormone–related peptide
      2. Metastatic dissolution of bone
3. Familial Hypocalciuric Hypercalcemia
   1. Familial Hypocalciuric Hypercalcemia I *(CaSR)*
      1. Loss-of-function mutations in *CaSR*
         1. Monoallelic: familial benign hypercalcemia
         2. Biallelic: neonatal severe hyperparathyroidism
   2. Familial Hypocalciuric Hypercalcemia II *(GNA11)*
   3. Familial Hypocalciuric Hypercalcemia III, Oklahoma Variant *(AP2S1)*
   4. *CaSR*-blocking autoantibodies
4. Excessive Calcium or Vitamin D
   1. Milk-Alkali Syndrome
   2. Exogenous Ingestion of Calcium or Vitamin D or Topical Application of Vitamin D (calcitriol or analog)
   3. Ectopic Production of Calcitriol Associated with Granulomatous Diseases (sarcoidosis, cat-scratch fever; tuberculosis, histoplasmosis, coccidioidomycosis, leprosy; human immunodeficiency virus; cytomegalovirus; chronic inflammatory bowel disease)
   4. 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
   5. Williams-Beuren Syndrome (del7q11.23)
5. Immobilization
6. Other Causes
   1. Drugs: Thiazides, Lithium, Vitamin A and Analogs, Calcium, Alkali, Antiestrogens, Aminophylline
   2. Total Parenteral Nutrition
   3. Endocrinopathies: Hyperthyroidism, Addison disease, Pheochromocytoma
   4. Vasoactive Intestinal Polypeptide–Secreting Tumor
   5. Acute or Chronic Renal Failure/Administration of Aluminum
   6. Hypophosphatasia
   7. Juvenile Rheumatoid Arthritis: Cytokine Mediated

**Chapter 574** ◆ Physiology of the Adrenal Gland **2699**

Cholesterol

CYP11A

Pregnenolone CYP17

17-OH Pregnenolone

**Fetal Adrenal**

Progesterone

Deoxycorticosterone

Aldosterone

17-OH Progesterone

11-Deoxycortisol

Cortisol

CYP17

**Fetal Liver**

16α-OH

Dehydroepi-

Dehydroepi- androsterone

SULT2A1

Androstenedione

Testosterone

Dihydro- testosterone

androsterone sulfate

CYP3A7

Dehydroepiandrosterone sulfate

**Genital Skin**

16α-OH Dehydroepi-

androsterone

Dehydroepi- androsterone

CYP19

CYP19

HSD11B2

16α-OH-androstenedione Androstenedione

16α-OH-estrone

Estrone

Estrone

Estradiol

Cortisone

Estriol

Estradiol

**Placenta**

HSD17B1

HSD17B1

HSD17B1

CYP19

CYP19

HSD3B1

HSD3B1

ARSC1

ARSC1

SRD5A2

HSD17B5

HSD3B2

CYP11B1

CYP21

HSD3B2

CYP11B2

CYP21

HSD3B2

**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 (P450scc in older terminology); HSD3B2, 3β-hydroxysteroid dehydrogenase/Δ5,Δ4 isomerase type 2; CYP 17, 17β-hydroxylase/17,20-lyase

(P450c17); CYP 21, 21-hydroxylase (P450c21); CYP 11B1, 11β-hydroxylase (P450c11); CYP 11B2, aldosterone synthase (P450aldo; this enzyme

mediates successive 11β-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, 3β-hydroxysteroid dehydrogenase/Δ5,Δ4 isomerase type 1; HSD11B2, 11β-hydroxysteroid dehydrogenase type 2; HSD17B1 and HSD17B5 are 2 different 17-hydroxysteroid dehydrogenase enzymes; SRD5A2, steroid 5α-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 | 6% | Childhood-adolescence |
| polyendocrinopathy– |  |  |
| candidiasis–ectodermal |  |  |
| dystrophy) |  |  |
| 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.*

HYPERCALCEMIA

Normal/decreased

Increased

PTH Serum albumin

Ca2+

Increased

Normal or

increased

Decreased

Normal

Pseudohypercalcemia

PTHrP

Measure

FeCa

Increased

Normal/low

<0.01

>0.01

Malignancy 25-hydroxy

HIV vitamin D

Elevated

Elevated

FHH

*(CaSR)*

Primary

hyperparathyroidism

Vitamin D intoxication

Adenoma

Hyperplasia (MEN1) Carcinoma

Granulomatous disease

Malignancy CMV

Normal/decreased

Key clinical features

Immobilization Osteolytic malignancy Hyperthyroidism Calcium gluttony Medications

Adrenal insufficiency Vitamin A intoxication Pheochromocytoma Newborn or congenital

1,25-dihydroxy vitamin D

Maternal hypocalcemia Williams syndrome Subcutaneous fat necrosis Disaccharidase deficiency Blue diaper syndrome

**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

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

**Chapter 575** ◆ Adrenocortical Insufficiency **2705**

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| **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) Aminoglutethimide | | Cytotoxicity  Inhibition of cholesterol side chain cleavage enzyme (CYP11A1)  Inhibition of 3β-hydroxysteroid dehydrogenase type 2  Inhibition of 11β-hydroxylase (CYP11B1) Inhibition of mitochondrial cytochrome  P450 enzymes (e.g., CYP11A1, CYP11B1) | None, unless related to drug None, unless related to drug |
| Trilostane | | None, unless related to drug |
| Etomidate  Ketoconazole, fluconazole | | None, unless related to drug 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, *i*ntrauterine growth restriction (IUGR), *m*etaphyseal dysplasia, *a*drenal hypoplasia congenita (AHC), and *ge*nitourinary 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.*

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| **Table 575-2** | Causes of Secondary Adrenal Insufficiency | |
| **ETIOLOGIES** | | **CLINICAL MANIFESTATIONS IN ADDITION TO ADRENAL INSUFFICIENCY** |
| DRUG-INDUCED  Abrupt cessation of glucocorticoid Suppression of CRH and ACTH secretion leading therapy (systemic or topical) 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  Traumatic brain injury  Hypothalamic or pituitary surgery or irradiation  Infections or infiltrative processes Lymphocytic hypophysitis, hemochromatosis,  tuberculosis, meningitis, sarcoidosis, actinomycosis, histiocytosis X, Wegener granulomatosis  Pituitary apoplexy (when occurring High blood loss or hypotension in a peripartum mother, termed  Sheehan syndrome) | | Panhypopituitarism\*; primary disease-associated symptoms  Panhypopituitarism\*; primary disease-associated symptoms  Panhypopituitarism\*; primary disease-associated symptoms  Panhypopituitarism\*; primary disease-associated symptoms  Abrupt onset of severe headache, visual disturbance, nausea, vomiting; panhypopituitarism\*; primary disease-associated symptoms |
| CONGENITAL OR GENETIC CAUSES  *Abnormal Central Nervous System Development*  Anencephaly Multiple  Holoprosencephaly Multiple  *Combined Pituitary Hormone Deficiency (CPHD)†*  CPHD2 Mutations in *PROP1* (paired-like homeobox 1)  CPHD3 Mutations in *LHX3* (LIM homeobox 3)  CPHD4 Mutations in *LHX4* (LIM homeobox 4) Septooptic dysplasia, CPHD5 Mutations in *HESX1* (HESX homeobox 1)  CPHD6 Mutations in *OTX2* (orthodenticle homeobox 2)  X-linked panhypopituitarism Mutations in *SOX3* (SRY(sex-determining region Y)  box 3)  *Other Genetic Syndromes Affecting Corticotropin Secretion*  Congenital proopiomelanocortin Mutations in *POMC* (proopiomelanocortin) deficiency  Prohormone convertase 1/3 Mutations in *PC1* (prohormone convertase 1/3) deficiency  Isolated ACTH (corticotropin) Mutations in *TBX19* (T-box 19) deficiency  Prader-Willi syndrome Deletion or silencing of genes on the parental  copy of genes within the imprinted chromosome region 15q11-q13 including *SNRPN* (small nuclear ribonucleoprotein polypeptide N) and *NDN* (necdin, melanoma antigen (MAGE) family member) | | Primary disease-associated symptoms Primary disease-associated symptoms  Panhypopituitarism; corticotropin deficiency occurs in adolescence  Panhypopituitarism; deafness, short neck Panhypopituitarism; small sella, cerebellar defects Panhypopituitarism; septooptic dysplasia (blindness  owing to hypoplasic optic nerves, absence of the septum pellucidum); developmental delay  Panhypopituitarism; ectopic posterior pituitary gland Panhypopituitarism; infundibular hypoplasia,  developmental delay  Early-onset severe obesity, hyperphagia, red hair  Obesity, malabsorption or diarrhea, hypogonadotropic hypogonadism  Dysmorphic features, hypotonia, developmental delay, obesity, growth hormone deficiency, hypogonadotropic hypogonadism |

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

†CPHD1 (mutations in *POUF1*) is not associated with corticotropin deficiency.

**2716 Part XXVI** ◆ The Endocrine System

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

**Chapter 576** ◆ Congenital Adrenal Hyperplasia and Related Disorders **2717**

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| **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, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; DOC, 11-deoxycorticosterone; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone.

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| **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 Infancy Infancy (females) Childhood to adulthood,  screening) Childhood (males) or asymptomatic | | | | | |
| Virilization Severe Moderate to severe None to Mild | | | | | |
| Incidence | | 1/20,000 | 1/50,000 | 1/500 |  |

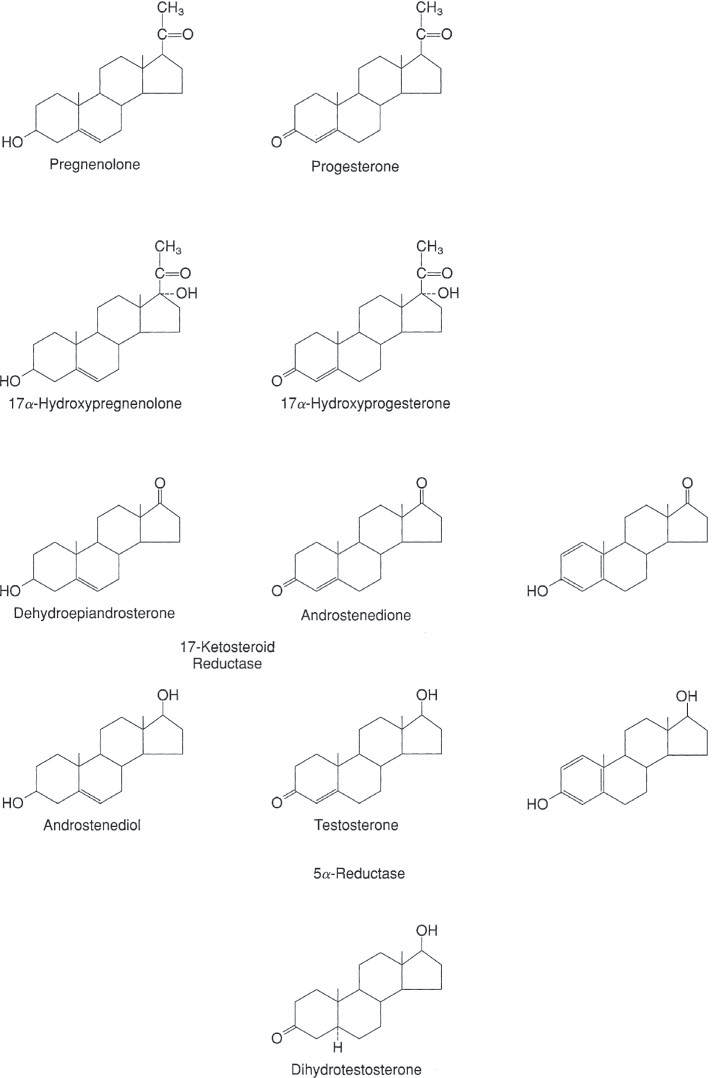
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| **Table 575-4** | Clinical Manifestations and Biochemical Findings in Adrenal Insufficiency | | |
|  | | **PATHOPHYSIOLOGIC MECHANISM** | **PREVALENCE (%)**\* |
| SYMPTOMS | |  |  |
| Fatigue | | Glucocorticoid deficiency | 90 |
| Anorexia, weight loss | | Glucocorticoid deficiency | 90 |
| Nausea, vomiting | | Glucocorticoid deficiency, mineralocorticoid deficiency | 90 |
| Salt craving (primary adrenal insufficiency only) Myalgia or joint pain | | Mineralocorticoid deficiency Glucocorticoid deficiency | 20 |
| 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 | 90 |
|  | | (leading to decreased free water excretion) |  |
| 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 | | Glucocorticoid deficiency | 100 |
| only) | |  |  |
| 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*

**Chapter 582** ◆ Development and Function of the Gonads **2733**

**Figure 582-1** Biosynthesis of sex steroids. *Dashed lines* indicate enzymatic defects associated with 46,XY disorder of sex differen- tiation. *3β-HSD2*, 3β-hydroxysteroid dehydro- genase type 2; *AKR1C2/RoDH (Ox)*, one of the



CYPIIAI + StAR

(17 CH activity) CYP17A1+POR

3βHSD2

(17,20-Lyase activity) CYP17A1+POR

ARO

3βHSD2

ARO

5αRED2

AKRIC2/RoDH

(ox)

Estradiol 17β

HSD17B3

Estrone

3βHSD2

enzymes in the recently described alternative androgen biosynthetic pathway; *ARO,* aroma- tase; *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 oxido- reductase; *StAR,* steroidogenic acute regula- tory protein.

**Chapter 583** ◆ Hypofunction of the Testes **2735**

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

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| **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 | |

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| **Table 589-2** | Diagnostic Criteria for Impaired Glucose Tolerance and Diabetes Mellitus |
| **IMPAIRED GLUCOSE**  **TOLERANCE DIABETES MELLITUS** | |
| Fasting glucose 100-125 mg/ Symptoms\* of diabetes mellitus dL (5.6-7.0 mmol/L) plus random or casual plasma  glucose ≥200 mg/dL (11.1 mmol/L) | |
| *or* | |
| 2-hr plasma glucose during Fasting (at least 8 hr) plasma  the OGTT glucose ≥126 mg/dL (7.0 mmol/L)  ≥140 mg/dL, but <200 mg/dL *or*  (11.1 mmol/L) 2 hr plasma glucose during the OGTT ≥200 mg/dL  *or*  Hemoglobin A1C ≥6.5%† | |

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

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| **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 | |

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

OGTT, oral glucose tolerance test.

**Chapter 588** ◆ Disorders of Sex Development **2751**

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| **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 |

|  |  |
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| **Table 588-4** | Sources of Maternal-Derived Androgens |
| **ENDOGENOUS EXOGENOUS** | |
| BENIGN SYNTHETIC ANDROGENS  Luteoma of pregnancy Danazol  Adrenal adenoma Progestins (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 masculinised female.* Best Pract Res Clin Endocrinol Metab *24:219–242, 2010, Table 2, p. 237.*

|  |  |
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| **Table 588-2** | Etiologic Classification of Disorders of Sex Development (DSD) |
| 46,XX DSD  *Androgen Exposure*  Fetal/Fetoplacental Source  21-Hydroxylase (P450c21 or CYP21) deficiency 11β-Hydroxylase (P450c11 or CYP11B1) deficiency  3β-Hydroxysteroid dehydrogenase II (3β-HSD II) deficiency  Cytochrome P450 oxidoreductase (POR)  Aromatase (P450arom or CYP19) deficiency Glucocorticoid receptor gene mutation Maternal Source  Virilizing ovarian tumor Virilizing adrenal tumor Androgenic drugs  *Disorder of Ovarian Development*  XX gonadal dysgenesis  Testicular DSD (SRY+, SOX9 duplication)  *Undetermined Origin*  Associated with genitourinary and gastrointestinal tract defects | |
| 46,XY DSD  *Defects in Testicular Development*  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  *Deficiency of Testicular Hormones*  Leydig cell aplasia Mutation in LH receptor  Lipoid adrenal hyperplasia (P450scc or CYP11A1) deficiency; mutation in StAR (steroidogenic acute regulatory protein) 3β-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  *Defect in Androgen Action*  Dihydrotestosterone deficiency because of 5α-reductase II mutations or *AKR1C2/AKR1C4* mutations  Androgen receptor defects:  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)  *Ovotesticular DSD*  XX XY  XX/XY chimeras  *Sex Chromosome DSD*  45,X (Turner syndrome and variants) 47,XXY (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) | |

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| **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 * 17β-hydroxysteroid dehydrogenase deficiency type 3 * 5α-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.*