**1132 Part XV** ◆ Allergic Disorders

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| **Table 149-1** | Symptoms and Signs of Anaphylaxis in Infants |
| **ANAPHYLAXIS SIGNS THAT MAY BE DIFFICULT ANAPHYLAXIS SYMPTOMS THAT TO INTERPRET/UNHELPFUL IN INFANTS,**  **INFANTS CANNOT DESCRIBE AND WHY ANAPHYLAXIS SIGNS IN INFANTS** | |
| GENERAL  Feeling of warmth, weakness, anxiety, Nonspecific behavioral changes such as persistent apprehension, impending doom crying, fussing, irritability, fright, suddenly  becoming quiet | |
| SKIN/MUCUS MEMBRANES  Itching of lips, tongue, palate, uvula, ears, Flushing (may also occur with fever, hyperthermia, or Rapid onset of hives (potentially difficult throat, nose, eyes, etc.; mouth-tingling crying spells) to discern in infants with acute atopic  or metallic taste dermatitis; scratching and excoriations  will be absent in young infants); angioedema (face, tongue, oropharynx) | |
| RESPIRATORY  Nasal congestion, throat tightness; chest Hoarseness, dysphonia (common after a crying spell); Rapid onset of coughing, choking, stridor, tightness; shortness of breath drooling or increased secretions (common in wheezing, dyspnea, apnea, cyanosis  infants) | |
| GASTROINTESTINAL  Dysphagia, nausea, abdominal pain/ Spitting up/regurgitation (common after feeds), Sudden, profuse vomiting cramping loose stools (normal in infants, especially if  breastfed); colicky abdominal pain | |
| CARDIOVASCULAR  Feeling faint, presyncope, dizziness, Hypotension (need appropriate-size blood pressure Weak pulse, arrhythmia, diaphoresis/ confusion, blurred vision, difficulty in cuff; low systolic blood pressure for children is sweating, collapse/unconsciousness hearing defined as <70 mm Hg from 1 mo to 1 yr, and less  than (70 mm Hg + [2 × age in yr]) from 1-10 yr; tachycardia, defined as >140 beats/min from 3 mo to 2 yr, inclusive; loss of bowel and bladder control (ubiquitous in infants) | |
| CENTRAL NERVOUS SYSTEM  Headache Drowsiness, somnolence (common in infants after Rapid onset of unresponsiveness, lethargy, feeds) or hypotonia; seizures | |

*Adapted from Simons FER. Anaphylaxis in infants: can recognition and management be improved?* J Allergy Clin Immunol *120:537–540, 2007.*

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| **Table 149-2** | Anaphylaxis Triggers in the Community\* |
| ALLERGEN TRIGGERS (IgE-DEPENDENT IMMUNOLOGIC MECHANISM)\*  Foods (e.g., peanut, tree nuts, shellfish, fish, milk, egg, wheat, soy, sesame, meat [galactose-α-1,3-galactose]) Food additives (e.g., spices, colorants, vegetable gums, and contaminants)  Stinging insects: Hymenoptera species (e.g., bees, yellow jackets, wasps, hornets, and fire ants) Medications (e.g., β-lactam antibiotics, ibuprofen)  Biologic agents (e.g., monoclonal antibodies [infliximab, omalizumab] and allergens [challenge tests, specific immunotherapy]) Natural rubber latex  Vaccines  Inhalants (rare) (e.g., horse or hamster dander, grass pollen)  Previously unrecognized allergens (foods, venoms, biting insect saliva, medications, biologic agents) | |
| OTHER IMMUNE MECHANISMS (IGE INDEPENDENT)  IgG mediated (infliximab, high-molecular-weight dextrans) Immune aggregates (IVIG)  Drugs (aspirin, NSAID, opiates, contrast material, ethylene oxide/dialysis tubing) Complement activation  Physical factors (e.g., exercise†, cold, heat, sunlight/ultraviolet radiation) Ethanol  Idiopathic\* | |

\*In the pediatric population, some anaphylaxis triggers, such as hormones (progesterone), seminal fluid, and occupational allergens, are uncommon, as is idiopathic anaphylaxis.

†Exercise with or without a cotrigger, such as a food or medication, cold air, or cold water. IVIG, intravenous immunoglobulin; NSAID, nonsteroidal antiinflammatory drug.

*Adapted from Leung DYM, Sampson HA, Geha RS, et al:* Pediatric allergy principles and practice*, New York, 2010, Elsevier, p. 652.*

**Chapter 149** ◆ Anaphylaxis **1133**

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| **Table 149-3** | Patient Risk Factors for Anaphylaxis |
| AGE-RELATED FACTORS  Infants: anaphylaxis can be hard to recognize, especially if the first episode; patients cannot describe symptoms  Adolescents and young adults: increased risk taking behaviors such as failure to avoid known triggers and to carry an epinephrine autoinjector consistently  Pregnancy: risk of iatrogenic anaphylaxis—for example, from β lactam antibiotics to prevent neonatal group B streptococcal infection, agents used perioperatively during caesarean sections, and natural rubber latex  Older people: increased risk of death because of concomitant disease and drugs | |
| CONCOMITANT DISEASES  Asthma and other chronic respiratory diseases Cardiovascular diseases  Mastocytosis  Allergic rhinitis and eczema\*  Depression, cognitive dysfunction, substance misuse | |
| DRUGS  β-Adrenergic blockers†  Angiotensin-converting enzyme (ACE) inhibitors†  Sedatives, antidepressants, narcotics, recreational drugs, and alcohol may decrease the patient’s ability to recognize triggers and symptoms | |
| COFACTORS THAT AMPLIFY ANAPHYLAXIS  Exercise: anaphylaxis associated with exercise may be food dependent or food independent; nonsteroidal antiinflammatory drugs and other listed cofactors may also be relevant  Acute infection such as an upper respiratory tract infection Fever  Emotional stress  Disruption of routine—for example, travel and jet lag Premenstrual status in women and girls | |

Anaphylaxis is highly likely when any *1* of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin and/or mucosal tissue (e.g., *generalized* hives, pruritus or flushing, swollen lips/tongue/uvula)

*AND AT LEAST 1 OF THE FOLLOWING:*

* 1. Respiratory compromise (e.g., dyspnea, wheeze/ bronchospasm, stridor, reduced peak PEF, hypoxemia)
  2. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

1. Two or more of the following that occur rapidly after exposure

*to a* likely *allergen for that patient* (minutes to several hours):

* 1. Involvement of the skin/mucosal tissue (e.g., *generalized*

hives, itch/flush, swollen lips/tongue/uvula)

* 1. Respiratory compromise (e.g., dyspnea, wheeze/ bronchospasm, stridor, reduced PEF, hypoxemia)
  2. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
  3. *Persistent* gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

1. Reduced BP following exposure to known *allergen for that patient* (minutes to several hours):
   1. Infants and children: low systolic BP (age-specific) or >30% drop in systolic BP
   2. Adults: systolic BP <90 mm Hg or >30% drop from patient’s baseline

Diagnosis of Anaphylaxis

**Table 149-4**

\*Atopic diseases are a risk factor for anaphylaxis triggered by food, latex, and exercise, but not for anaphylaxis triggered by most drugs or by insect stings

†Patients taking β-adrenergic blockers or ACE inhibitors seem to be at increased risk for severe anaphylaxis. In addition, those taking β-adrenergic

Isolated Raynaud phenomenon

Occupational Raynaud phenomenon:

Cold injury Vibrating tools

Polyvinyl chloride exposure

Secondary Raynaud phenomenon:

Systemic sclerosis

Mixed connective tissue disease Sjögren syndrome

Systemic lupus erythematosus Polymyositis/dermatomyositis Rheumatoid arthritis

Arteritis

Antiphospholipid antibody syndrome Primary biliary cirrhosis

Carpal tunnel syndrome Cryoglobulinemia Leukemia

Vasospastic disorders (migraine, Prinzmetal angina)

Infection:

Hepatitis B and C (cryoglobulinemia) Cytomegalovirus (?)

Obstructive vascular disease:

Thromboangiitis obliterans

Thoracic outlet syndrome (cervical rib)

Metabolic syndrome: Hypothyroid Carcinoid syndrome

Drug-induced: Antimigraine medications β-Blocker

Bleomycin Interferons

Ergotamine derivatives

Classification of Raynaud Phenomenon

**Table 160-2**

blockers may not respond optimally to epinephrine treatment and may need glucagon, a polypeptide with non–catecholamine-dependent inotropic and chronotropic cardiac effects, atropine for persistent bradycardia, or ipratropium

for persistent bronchospasm.

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Good NO

NO

YES

**Immediate intervention**

* Assess airway, breathing, circulation, mentation
* Inject epinephrine and reevaluate for repeat injection if necessary
* Supine position (if cardiovascular involvement suspected)

**Anaphylaxis preparedness**

Consider other diagnosis

**Subsequent emergency care that may be necessary depending on response to epinephrine:**

**Consider:**

* Call 911 and request assistance
* Recumbent position with elevation lower extremity
* Establish airway
* O2
* Repeat epinephrine injection if indicated
* IV fluids if hypotensive; rapid volume expansion

**Consider inhaled bronchodilators if wheezing**

* H1 and H2 antihistamines
* Corticosteroids

Initial assessment supports potential anaphylaxis?

e.g., non-localized urticaria after immunotherapy

Patient presents with possible/probable acute anaphylaxis

clinical

response?

YES NO

* Observation

Length and setting of observation must be individualized

* Autoinjectible epinephrine

YES

Good NO clinical

response?

#### Call 911 if not already done Consider:

* Epinephrine intravenous infusion
* Other intravenous vasopressors
* Consider glucagon

Consultation with allergist- immunologist

**Cardiopulmonary arrest during anaphylaxis:**

* CPR and ACLS measures
* Prolonged resucitation efforts encouraged (if necessary)
* Consider:
  + High-dose epinephrine
  + Rapid volume expansion
  + Atropine for asystole or pulseless electrical activity
  + Transport to emergency dept. or ICU

**Figure 149-1** Algorithm for the treatment of anaphylactic event in the outpatient setting. IV, Intravenous. *(From Lieberman P, Nicklas RA, Oppenheimer J, et al: The diagnosis and management of anaphylaxis practice parameter: 2010 update,* J Allergy Clin Immunol *126:477–480 e471–442, 2010 [Fig. E2].)*

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| **Table 149-5** Management of a Patient with Anaphylaxis |
| **MECHANISM(S) OF**  **TREATMENT EFFECT DOSAGE(S) COMMENTS; ADVERSE REACTIONS** |
| PATIENT EMERGENCY MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)  Epinephrine (adrenaline) α1, β1, β2 adrenergic 0.01 mg/kg up to 0.5 mg IM in Tachycardia, hypertension, nervousness, effects lateral thigh headache, nausea, irritability, and tremor  Weight 8-25 kg: Adrenaclick, Auvi-Q, EpiPen Jr (0.15 mg) IM  Weight >25 kg: Adrenaclick, Auvi-Q, EpiPen (0.3 mg) IM  Cetirizine (liquid) Antihistamine (competitive Cetirizine liquid–5 mg/5 mL Hypotension, tachycardia, and somnolence of H1 receptor) 0.25 mg/kg up to 10 mg PO  Alt: diphenhydramine Antihistamine (competitive 1.25 mg/kg up to 50 mg PO or IM Hypotension, tachycardia, somnolence, and of H1 receptor) paradoxical excitement  Transport to an Emergency Facility |
| EMERGENCY PERSONNEL MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)  Epinephrine (adrenaline) α1, β1, β2 adrenergic 0.01 mg/kg up to 0.5 mg IM in Tachycardia, hypertension, nervousness, effects lateral thigh headache, nausea, irritability, and tremor  Epinephrine autoinjector: 0.15 mg for 8-25kg,  0.3 mg for >25 kg  0.01 mL/kg/dose of 1 : 1,000 solution up to 0.5 mL IM  May repeat every 10-15 min  For severe hypotension: 0.01 mL/kg/ dose of 1 : 10,000 slow IV push  Supplemental oxygen and airway management  Volume expanders  Crystalloids (normal 30 mL/kg in 1st hr Rate titrated against blood pressure response saline or Ringer lactate) If tolerated, place patient supine with legs  raised  Colloids (hydroxyethyl 10 mL/kg rapidly followed by slow Rate titrated against blood pressure response  starch) infusion If tolerated, place patient supine with legs raised  Antihistamines  Cetirizine (liquid) Antihistamine (competitive Cetirizine liquid–5 mg/5 mL Hypotension, tachycardia, and somnolence of H1 receptor) 0.25 mg/kg up to 10 mg PO  Alt: diphenhydramine Antihistamine (competitive 1.25 mg/kg up to 50 mg PO, IM, or Hypotension, tachycardia, somnolence, and of H1 receptor) IV paradoxical excitement  Ranitidine Antihistamine (competitive 1 mg/kg up to 50 mg IV Headache, mental confusion of H2 receptor) Should be administered slowly  Alt: cimetidine Antihistamine (competitive 4 mg/kg up to 200 mg IV Headache, mental confusion of H2 receptor Should be administered slowly  Corticosteroids  Methylprednisolone Antiinflammatory Solu-Medrol (IV) 1-2 mg/kg up to Hypertension, edema, nervousness, and  125 mg IV agitation  Depo-Medrol (IM) 1 mg/kg up to 80 mg IM  Prednisone Antiinflammatory 1 mg/kg up to 75 mg PO Hypertension, edema, nervousness, and  agitation  Nebulized albuterol β-Agonist (0.83 mg/mL [3 mL]) via mask with O2 Palpitations, nervousness, central nervous  system stimulation, tachycardia; use to supplement epinephrine when bronchospasm appears unresponsive; may repeat |
| POSTEMERGENCY MANAGEMENT  Antihistamine Cetirizine (5-10 mg qd) or loratadine (5-10 mg qd) for 3 days  Corticosteroids *Optional:* Oral prednisone (1 mg/kg up to 75 mg) daily for 3 days  Preventive treatment  Prescription for epinephrine autoinjector and antihistamine  Provide written plan outlining patient emergency management (may download form from [http://www.foodallergy.org)](http://www.foodallergy.org/) Follow-up evaluation to determine/confirm etiology  Immunotherapy for insect sting allergy  Patient education  Instruction on avoidance of causative agent Information on recognizing early signs of anaphylaxis  Stress early treatment of allergic symptoms to avoid systemic anaphylaxis Encourage wearing medical identification jewelry |

IM, intramuscularly; IV, intravenously; PO, by mouth.

**1138 Part XV** ◆ Allergic Disorders

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| **Table 151-1** | Adverse Food Reactions |
| FOOD INTOLERANCE (NON–IMMUNE SYSTEM-MEDIATED, NONTOXIC, NONINFECTIOUS)  Host factors  Enzyme deficiencies—lactase (primary or secondary), sucrase/ isomaltase, hereditary fructose intolerance, galactosemia  Gastrointestinal disorders—inflammatory bowel disease, irritable bowel syndrome, pseudoobstruction, colic  Idiosyncratic reactions—caffeine in soft drinks (“hyperactivity”) Psychologic—food phobias, obsessive/compulsive disorder Migraines (rare)  Food factors (toxic or infectious or pharmacologic)  Infectious organisms—*Escherichia coli, Staphylococcus aureus, Clostridium perfringens, Shigella,* botulism*, Salmonella, Yersinia, Campylobacter*  Toxins—histamine (scombroid poisoning), saxitoxin (shellfish) Pharmacologic agents—caffeine, theobromine (chocolate, tea),  tryptamine (tomatoes), tyramine (cheese), benzoic acid in citrus fruits (perioral flare)  Contaminants—heavy metals, pesticides, antibiotics | |
| FOOD ALLERGY  IgE-mediated  Cutaneous—urticaria, angioedema, morbilliform rashes, flushing, contact urticarial  Gastrointestinal—oral allergy syndrome, gastrointestinal anaphylaxis Respiratory—acute rhinoconjunctivitis, bronchospasm Generalized—anaphylactic shock, exercise induced anaphylaxis Mixed IgE- and non–IgE-mediated  Cutaneous—atopic dermatitis, contact dermatitis Gastrointestinal—allergic eosinophilic esophagitis and  gastroenteritis Respiratory—asthma Non–IgE-mediated  Cutaneous—contact dermatitis, dermatitis herpetiformis (celiac disease)  Gastrointestinal—food protein–induced enterocolitis, proctocolitis, and enteropathy syndromes, celiac disease, food protein induced enteropathy  Respiratory—food-induced pulmonary hemosiderosis (Heiner syndrome)  Unclassified | |

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| **Table 151-2** | Differential Diagnosis of Adverse Food Reactions |
| GASTROINTESTINAL DISORDERS (WITH VOMITING AND/OR DIARRHEA)  Structural abnormalities (pyloric stenosis, Hirschsprung disease, reflux)  Enzyme deficiencies (primary or secondary):  Disaccharidase deficiency—lactase, fructase, sucrase-isomaltase Galactosemia  Malignancy with obstruction  Other: pancreatic insufficiency (cystic fibrosis), peptic disease | |
| CONTAMINANTS AND ADDITIVES  Flavorings and preservatives—rarely cause symptoms: Sodium metabisulfite, monosodium glutamate, nitrites  Dyes and colorings—very rarely cause symptoms (urticaria, eczema): Tartrazine  Toxins:  Bacterial, fungal (aflatoxin), fish-related (scombroid, ciguatera) Infectious organisms:  Bacteria (*Salmonella, Escherichia coli, Shigella*) Virus (rotavirus, enterovirus)  Parasites (*Giardia, Akis simplex* [in fish]) Accidental contaminants:  Heavy metals, pesticides Pharmacologic agents:  Caffeine, glycosidal alkaloid solanine (potato spuds), histamine (fish), serotonin (banana, tomato), tryptamine (tomato), tyramine (cheese) | |
| PSYCHOLOGIC REACTIONS  Food phobias | |

IgE, immunoglobulin E.

|  |  |  |  |
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| **Table 151-3** | Natural History of Food Allergy and Cross-Reactivity Between Common Food Allergies | | |
| **FOOD** | **USUAL AGE AT ONSET OF ALLERGY** | **CROSS REACTIVITY** | **USUAL AGE AT RESOLUTION** |
| Hen’s egg white | 0-1 yr | Other avian eggs | 7 yr (75% of cases resolve)\* |
| Cow’s milk | 0-1 yr | Goat’s milk, sheep’s milk, buffalo milk | 5 yr (76% of cases resolve)\* |
| Peanuts | 1-2 yr | Other legumes, peas, lentils; coreactivity with tree nuts | Persistent (20% of cases resolve) |
| Tree nuts | 1-2 yr; in adults, onset occurs after cross reactivity to birch pollen | Other tree nuts; coreactivity with peanuts | Persistent (9% of cases resolve) |
| Fish | Late childhood and adulthood | Other fish (low cross-reactivity with tuna and swordfish) | Persistent† |
| Shellfish | Adulthood (in 60% of patients with this allergy) | Other shellfish | Persistent |
| Wheat\* | 6-24 mo | Other grains containing gluten (rye, barley) | 5 yr (80% of cases resolve) |
| Soybeans\* | 6-24 mo | Other legumes | 2 yr (67% of cases resolve) |
| Kiwi | Any age | Banana, avocado, latex | Unknown |
| Apples, carrots, and peaches§ | Late childhood and adulthood | Birch pollen, other fruits, nuts | Unknown |

\*Recent studies suggest that resolution may occur at a later age, especially in children with multiple food allergies and lifetime peak food-specific IgE >50 kUA/L.

†Fish allergy that is acquired in childhood can resolve.

§Allergy to fresh apples, carrots, and peaches (oral allergy syndrome) is commonly caused by heat-labile proteins. Fresh fruit causes oral pruritus, but cooked fruit is tolerated. There is generally no risk of anaphylaxis, although in rare cases, allergies to cross-reactive lipid transfer protein can cause anaphylaxis after ingestion of fruits (e.g., peach) and vegetables.

*Modified from Lack G: Food allergy,* N Engl J Med *359:1252–1260, 2008, Table 1.*

**Chapter 151** ◆ Food Allergy and Adverse Reactions to Foods **1139**

Exclusive breast feeding for 4-6 mo

Introduce solid (complementary) foods after 4-6 mo of exclusive breast feeding

Introduce low-risk complementary foods 1 at a time

Introduce potentially highly allergenic foods (fish, eggs, peanut products, milk, wheat) soon after the lower-risk foods (no need to avoid or delay)

Don’t avoid allergenic foods during pregnancy or nursing Soy-based formulas do not prevent allergic disease

Prevention of Food Allergy

**Table 151-4**

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| **Table 151-5** | Symptoms of Food-Induced Allergic Reactions | | |
| **TARGET ORGAN** | | **IMMEDIATE SYMPTOMS** | **DELAYED SYMPTOMS** |
| Cutaneous | | Erythema Pruritus Urticaria  Morbilliform eruption Angioedema | Erythema Flushing Pruritus Morbilliform  eruption Angioedema Eczematous rash |
| Ocular | | Pruritus  Conjunctival erythema Tearing  Periorbital edema | Pruritus Conjunctival  erythema Tearing Periorbital edema |
| Upper respiratory Nasal congestion  Pruritus Rhinorrhea Sneezing Laryngeal edema Hoarseness  Dry staccato cough | | | |
| Lower respiratory | | Cough  Chest tightness Dyspnea Wheezing  Intercostal retractions Accessory muscle use | Cough, dyspnea, and wheezing |
| GI (oral) | | Angioedema of the lips, tongue, or palate  Oral pruritus Tongue swelling |  |
| GI (lower) | | Nausea  Colicky abdominal pain Reflux  Vomiting Diarrhea | Nausea Abdominal pain Reflux  Vomiting Diarrhea Hematochezia  Irritability and food refusal with weight loss (young children) |
| Cardiovascular | | Tachycardia (occasionally bradycardia in anaphylaxis)  Hypotension Dizziness Fainting  Loss of consciousness |  |
| Miscellaneous | | Uterine contractions Sense of “impending  doom” |  |

Note: This table is presented as Table IV in the Guidelines. GI, gastrointestinal.

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| **Table 154-1** | Multidisciplinary Treatment of Rheumatic Diseases in Childhood | |
| Accurate diagnosis and Pediatric rheumatologist education of family Pediatrician  Nurse:   * Disease-related education * Medication administration (injection teaching) * Safety monitoring Social worker: * Facilitation of school services * Resource identification (community, government, financial, advocacy groups, vocational rehabilitation) | | |
| Physical medicine and rehabilitation | | Physical therapy:   * Addressing deficits in joint or muscle mobility, limb length discrepancies, gait abnormalities, weakness   Occupational therapy:   * Splinting to reduce joint contractures/ deformities and lessen stress on joints; adaptive devices for activities of daily living |
| Consultant team | | Ophthalmology:   * Eye screening for uveitis (see Table 155-4) * Screening for medication-related ocular toxicity (hydroxychloroquine, glucocorticoids)   Nephrology Orthopedics Dermatology Gastroenterology |
| Physical and psychosocial growth and development | | Nutrition:   * Addressing undernourishment from systemic illness, obesity/   overnourishment from glucocorticoids School integration:   * Individualized Educational Plan (IEP) or 504 plan   Peer group relationships  Individual and/or family counseling |
| Coordination of care | | Involvement of patient and family as active team members  Communication among healthcare providers  Involvement of school (school nurse) and community (social worker) resources |

*From Boyce JA, Assa’ad A, Burks AW, et al: Guideline for the diagnosis and management of food allergy in the United States: report of the NIAID- sponsored expert panel,* J Allergy Clin Immunol *126(6):S1–S58, 2010 (Table IV, p. S19).*

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| **Table 151-8** | ACIP and AAP Red Book Recommendations for Administering Vaccines to Patients with Egg Allergy | |
| **VACCINE** | **ACIP** | **AAP RED BOOK** |
| MMR/MMRV | May be used | May be used |
| Influenza | Receive with some precautions\* | Receive with some precautions\* |
| Rabies | Use caution | No specific recommendation |
| Yellow fever | Contraindicated, but desensitization protocols may be followed to administer vaccine if necessary (citing PI) | Contraindicated, but desensitization protocols may be followed to administer vaccine if necessary (citing PI) |

AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices.

*From Boyce JA, Assa’ad A, Burks AW, et al: Guideline for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel,* J Allergy Clin Immunol *126(6):S1–S58, 2010 (Table V, p S31).*

\*In 2012, recommendations changed to suggest those with mild egg allergy receive the inactivated influenza vaccine in the primary care setting with a 30 minute observation and preparedness to treat anaphylaxis. Those with severe egg allergy are referred to an allergist.

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| **Table 151-6** Food Protein-Induced Gastrointestinal Syndromes | | | | |
|  | **FPIES** | **PROCTOCOLITIS** | **ENTEROPATHY** | **EOSINOPHILIC GASTROENTEROPATHIES\*** |
| Age at onset | 1 day–1 year | 1 day–6 months | Dependent of age of exposure to antigen, cow’s milk and soy up to 2 yr | Infant to adolescent |
| Food proteins implicated  Most common Less common | Cow’s milk, soy  Rice, chicken, turkey, fish, pea | Cow’s milk, soy  Egg, corn, chocolate | Cow’s milk, soy Wheat, egg | Cow’s milk, soy, egg white, wheat, peanut  Meats, corn, rice, fruits, vegetables, fish |
| Multiple food hypersensitivities | >50% both cow’s milk and soy | 40% both cow’s milk and soy | Rare | Common |
| Feeding at the time of onset | Formula | >50% exclusive breast feeding | Formula | Formula |
| Atopic background  Family history of atopy  Personal history of atopy | 40-70%  30% | 25%  22% | Unknown 22% | ~50% (often history of eosinophilic esophagitis)  ~50% |
| Symptoms Emesis Diarrhea Bloody stools Edema Shock  Failure to thrive | Prominent Severe Severe Acute, severe 15%  Moderate | No No  Moderate No  No No | Intermittent Moderate Rare Moderate No Moderate | Intermittent Moderate Moderate Moderate No Moderate |
| Laboratory findings Anemia Hypoalbuminemia Methemoglobinemia | Moderate Acute  May be present | Mild Rare No | Moderate Moderate No | Mild-moderate Mild-severe No |
| Allergy evaluation Food prick skin test  Serum food allergen IgE Total IgE  Peripheral blood eosinophilia | Negative† Negative† Normal No | Negative Negative Negative Occasional | Negative Negative Normal No | Positive in ~50% Positive in ~50% Normal to elevated Present in <50% |
| Biopsy findings  Colitis  Lymph nodular hyperplasia  Eosinophils | Prominent No  Prominent | Focal Common  Prominent | No No  Few | May be present Yes  Prominent; also neutrophilic infiltrates, papillary elongation and basal zone hyperplasia |
| Food challenge | Vomiting in 2-4 hr; diarrhea in 5-8 hr | Rectal bleeding in 6-72 hr | Vomiting, diarrhea, or both in 40-72 hr | Vomiting and diarrhea in hours to days |
| Treatment | Protein elimination, 80% respond to casein hydrolysate and symptoms clear in 3-10 days; rechallenge in 1.5-2 yr | Protein elimination, symptoms clear in 3 days with casein hydrolysate, resume/ continue breastfeeding on maternal antigen- restricted diet | Protein elimination, symptoms clear in 1-3 wk, rechallenge and biopsy in 1-2 yr | Protein elimination, good response to casein hydrolysate, excellent response to elemental diet, symptoms  clear within 2-3 wk, excellent acute response to steroids; rechallenge and biopsy in 1-2 yr |
| Natural history | Cow’s milk: 60% resolved by 2 yr  Soy: 25% resolved by 2 yr | Resolved by 9-12 months | Most cases resolve in 2-3 yr | Typically a prolonged, relapsing course |
| Reintroduction of the food | Inpatient food challenge | At home, gradually advancing from 1 oz to full feedings over 2 weeks | Home, gradually advancing | Home, gradually advancing |

\*Eosinophilic gastroenteropathies encompass esophagitis, gastritis, gastroenterocolitis.

†If positive, may be a risk factor for persistent disease. FPIES, food protein-induced enterocolitis syndrome.

*From Nowak-Wegrzyn A, Muraro A: Food protein-induced enterocolitis syndrome.* Curr Opin Allergy Immunol *9:371-377, 2009 (Table 1, p. 372).*

**1142 Part XV** ◆ Allergic Disorders

Po ive

Positive Negative

Trial elimination diet

Resolution?

Convincing history of anaphylaxis to isolated ingestion and/or diagnostic test value

Moderate/severe atopic dermatitis, eosinophilic gastroenteropathies (biopsy-proven)

Consider: confirmatory diagnostic tests (endoscopy, serology for coeliac, etc.). Consider IgE testing to verify pathophysiology.

Trial elimination diet

Resolution?

Reconsider diagnosis, foods involved

Yes

Avoid food(s)

Consider oral food challenges if unclear cause

Avoid food(s)

Periodic reassessment based on natural history of allergy in the particular disorder, the food(s) involved, and age of patient.

Consistent with cell-mediated food allergy

Avoid food(s)

Consistent with IgE-dependent disorders

Add food back

IgE antibody screening to suspected foods to establish potential triggers for elimination, otherwise devise elimination based upon epidemiological variables

Reconsider diagnosis, foods involved

Yes

History, physical

Consistent with intolerance, or other non-immune disorders

Yes

Confirm alternative diagnosis

May require additional tests (e.g., breath hydrogen, stool culture, dietary elimination and rechallenge)

|  |  |  |
| --- | --- | --- |
| Test for IgE antibody reactive with suspect foods | | |
| sitive | Negat | |
|  | |  |

No

No

No

Food tested is likely to be tolerated, but if history suspicious, consider retesting and supervised oral food challenge

P ive

Add food back

|  |  |
| --- | --- |
| Oral food challenges | |
| ositive | Negat |
|  | |

|  |  |  |  |
| --- | --- | --- | --- |
| Oral food challenges (deferred for foods with diagnostic values) | | | |
| Positive | | Negative | |
|  |  | |  |

Add food back

**Figure 151-1** General scheme for diagnosis of food allergy. *(From Sicherer SH: Food allergy,* Lancet *360:701–710, 2002.)*

|  |  |  |
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| **Table 151-7** Clinical Implications of Cross-Reactive Proteins in IgE-Mediated Allergy | | |
| **FOOD FAMILY** | **RISK OF ALLERGY TO ≥1 MEMBER (%; APPROXIMATE)** | **FEATURE(S)** |
| Legumes | 5 | Main causes of reactions are peanut, soybean, lentil, lupine, and garbanzo (chickpea) |
| Tree nuts (e.g., almond, cashew, hazelnut, walnut, brazil) | 35 | Reactions are often severe |
| Fish | 50 | Reactions can be severe |
| Shellfish | 75 | Reactions can be severe |
| Grains | 20 |  |
| Mammalian milks | 90 | Cow’s milk is highly cross reactive with goat’s or sheep’s milk (92%) but not with mare’s milk (4%) |
| Rosaceae (pitted fruits) | 55 | Risk of reactions to more than three related foods is very low (<10%), symptoms are usually mild (oral allergy syndrome) |
| Latex-food | 35 | For individuals allergic to latex, banana, kiwi, fig, chestnut, and avocado are the main causes of reactions |
| Food-latex | 11 | Individuals allergic to banana, kiwi, fig, chestnut, and avocado may be at an increased risk of reactions to latex |

*Modified from Sicherer SH: Food allergy,* Lancet *360:701–710, 2002.*

# Rheumatic Diseases of Childhood

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| **Table 153-1** | Symptoms Suggestive of Rheumatic Disease | |
| **SYMPTOM** | **RHEUMATIC DISEASE(S)** | **POSSIBLE NONRHEUMATIC DISEASES CAUSING SIMILAR SYMPTOMS** |
| Fevers | Systemic JIA, SLE, vasculitis, acute rheumatic fever, sarcoidosis, MCTD | Malignancies, infections and post-infectious syndromes, inflammatory bowel disease, periodic fever (autoinflammatory) syndromes, Kawasaki disease, HSP |
| Arthralgias | JIA, SLE, rheumatic fever, JDM, vasculitis, scleroderma, sarcoidosis | Hypothyroidism, trauma, endocarditis, other infections, pain syndromes, growing pains, malignancies, overuse syndromes |
| Weakness | JDM, myositis secondary to SLE, MCTD, and deep localized scleroderma | Muscular dystrophies, metabolic and other myopathies, hypothyroidism |
| Chest pain | Juvenile rheumatoid arthritis, SLE (with associated pericarditis or costochondritis) | Costochondritis (isolated), rib fracture, viral pericarditis, panic attack, hyperventilation |
| Back pain | Enthesitis related arthritis, juvenile ankylosing spondylitis | Vertebral compression fracture, diskitis, intraspinal tumor, spondylolysis, spondylolisthesis, bone marrow–occupying malignancy, pain syndromes, osteomyelitis, muscle spasm, injury |
| Fatigue | SLE, JDM, MCTD, vasculitis, JIA | Pain syndromes, chronic infections, chronic fatigue syndrome, depression |

HSP, Henoch-Schönlein purpura; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus.

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| **Table 153-2** | Signs Suggestive of Rheumatic Disease | | | |
| **SIGN** | | **RHEUMATIC DISEASES** | **COMMENTS** | **NONRHEUMATIC CAUSES** |
| Malar rash | | SLE, JDM | SLE classically spares nasolabial folds | Sunburn, parvovirus B19 (fifth disease), Kawasaki disease |
| Oral ulcers | | SLE, Behçet disease | Behçet disease also associated with genital ulcers | HSV infection, PFAPA syndrome |
| Purpuric rash | | Vasculitis, e.g., ANCA-associated vasculitis, HSP | HSP typically starts as small lesions on lower extremities and buttocks that coalesce | Meningococcemia, thrombocytopenia, clotting disorders |
| Gottron papules | | JDM | Look for associated heliotrope rash, periungual telangiectasias | Psoriasis, eczema |
| Arthritis | | Juvenile idiopathic arthritis, SLE, vasculitis, HSP, MCTD, scleroderma, acute rheumatic fever, reactive arthritis | Chronic joint swelling (>6 wk) required for diagnosis of chronic arthritis of childhood; MCTD associated with diffuse puffiness of hands | Postviral arthritis, reactive arthritis, trauma, infection, Lyme disease, Kawasaki disease, malignancy, overuse syndromes |

ANCA, antineutrophilic cytoplasmic antibody; HSP, Henoch-Schönlein purpura; HSV, herpes simplex virus; JDM, juvenile dermatomyositis; MCTD, mixed connective tissue disease; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis; SLE, systemic lupus erythematosus.

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| **Table 153-3** | Autoantibody Specificity and Disease Associations | | | |
| **ANTIBODY** | | **DISEASE** | **PREVALENCE (%)** | **SPECIFICITY** |
| Antinuclear antibody (ANA) | | SLE, juvenile rheumatoid arthritis, dermatomyositis, scleroderma, psoriatic arthritis, MCTD | — | Associated with increased risk of uveitis in JIA and psoriatic arthritis  Up to 30% of children testing positive for ANAs have no underlying rheumatic disease |
| Double-stranded DNA (dsDNA) | | SLE | 60-70 | High specificity for SLE; associated with lupus nephritis |
| Smith (Sm) | | SLE | 20-30 | Highly specific for SLE; associated with lupus nephritis |
| Smooth muscle (Sm) | | Autoimmune hepatitis | — | — |
| Pm-Scl (polymyositis-scleroderma) | | Sclerodermatomyositis | — | — |
| SSA (Ro) | | SLE, Sjögren syndrome | 25-30 | Associated with neonatal lupus syndrome, subacute cutaneous lupus, thrombocytopenia |
| SSB (La) | | SLE, Sjögren syndrome | 25-30 | Usually coexists with anti-SSA antibody |
| Ribonuclease protein (RNP) | | MCTD, SLE | 30-40 | Suggestive of MCTD unless meets criteria for SLE |
| Histone | | Drug-induced lupus, SLE | — | — |
| Centromere | | Limited cutaneous systemic sclerosis | 70 | Nonspecific for systemic sclerosis |
| Topoisomerase I (Scl-70) | | Systemic sclerosis | — | Rare in childhood |
| Antineutrophil cytoplasmic antibodies (ANCAs) | | Vasculitis | — | — |
| Cytoplasmic (cANCAs)/ PR3-ANCA | |  | — | cANCAs associated with granulomatosis with polyangiitis (Wegener), cystic fibrosis |
| Perinuclear (pANCAs)/ MPO-ANCA | |  | — | pANCAs associated with microscopic polyangiitis, polyarteritis nodosa, SLE, inflammatory bowel disease, cystic fibrosis, primary sclerosing cholangitis, Henoch-Schönlein purpura, Kawasaki disease, Churg-Strauss syndrome |
| Anticitrullinated protein (ACPA) also called anti-cyclic citrullinated protein (anti-CCP) | | RF positive JIA | 50-90 | Specific for JIA (RF+), may be positive before RF |

MCTD, mixed connective tissue disease; MPO-ANCA, antimyeloperoxidase; PR3-ANCA, antiproteinase 3; RF, rheumatoid factor; SLE, systemic lupus erythematosus.

*Modified from Aggerwal A: Clinical application of tests used in rheumatology,* Indian J Pediatr *69:889–892, 2002.*

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| **Table 153-4** | Evaluation Based on Suspected Diagnosis | | | |
| **SUSPECTED RHEUMATIC DISEASE(S)** | | **INITIAL EVALUATION** | **FURTHER EVALUATION** | **SUBSPECIALTY EVALUATION** |
| SLE, MCTD | | CBC, ESR, ANA, ALT, AST, CPK,  creatinine, albumin, total protein, urinalysis, BP, thyroid profile | If ANA test result is positive: anti–SSA (Ro), anti–SSB (La), anti-Smith, and anti-RNP Abs; anti-dsDNA Ab, C3, C4, Coombs, spot urine protein/ creatinine ratio, CXR | Antiphospholipid Abs, lupus anticoagulant, anti–β2-glycoprotein, echocardiogram; consider renal biopsy, PFTs, bronchoscopy with lavage, HRCT of chest; consider lung biopsy |
| JDM | | CBC, CPK, ALT, AST, LDH, aldolase,  ANA; check gag reflex | Consider MRI of muscle | Consider electromyography and possible muscle biopsy, PFTs, swallowing study, serum neopterin |
| JIA | | CBC, ESR, creatinine, ALT,  AST, consider anti–streptolysin O/anti–DNAase B for streptococcus- induced arthritis, Epstein-Barr virus titers, Lyme titer, parvovirus B19 titer, plain radiograph of joints | Consider Ab titers to unusual infectious agents, purified protein derivative, RF, ANA, HLA-B27, anti-CCP | MRI |
| Granulomatosis with polyangiitis (Wegener granulomatosis) | | CBC, ANCA, AST, ALT, albumin,  creatinine, ESR, urinalysis, CXR, BP | Spot urine protein/creatinine ratio, anti–myeloperoxidase and anti–proteinase-3 Abs, PFTs | Bronchoscopy with lavage, HRCT chest; consider lung and kidney biopsies |
| Sarcoidosis | | CBC, electrolytes, AST, ALT, albumin, creatinine, calcium, phosphorous, ACE, BP | CXR, PFTs | Consider testing for Blau syndrome in infants (see Chapter 159); HRCT of chest; consider renal and lung biopsy |
| Localized scleroderma | | Skin biopsy, CBC, ESR |  | Serum immunoglobulin G, ANA, RF, single-stranded DNA Ab, antihistone Ab, CPK |
| Systemic scleroderma | | ANA, CBC, ESR, BP, AST, ALT, CPK,  creatinine, CXR | Anti-Scl70, PFTs | HRCT of chest, echocardiogram, upper gastrointestinal radiography series |

Ab, antibody; ACE, angiotensin-converting enzyme (normally elevated in childhood; interpret with caution); ALT, alanine aminotransferase; ANA, antinuclear antibody; anti-dsDNA Ab, anti−double stranded DNA antibody; AST, aspartate aminotransferase; BP, blood pressure; CBCD, complete blood count with differential; CCP, cyclic citrullinated protein; CPK, creatine phosphokinase; CXR, chest radiograph; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HRCT, high-resolution CT; LDH, lactate dehydrogenase; PFTs, pulmonary function tests; RF, rheumatoid factor.

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| **Table 155-5** | Frequency of Ophthalmologic Examination in Patients with Juvenile Idiopathic Arthritis | | | | |
| **TYPE** | | **ANTINUCLEAR AGE AT ANTIBODY TEST RESULT ONSET (Yr)** | **DURATION OF DISEASE (Yr)** | **RISK CATEGORY** | **EYE EXAMINATION FREQUENCY (Mo)** |
| Oligoarthritis or polyarthritis | | + ≤6  + ≤6  + ≤6  + >6  + >6  – ≤6  – ≤6  – >6 | ≤4  >4  >7  ≤4  >4  ≤4  >4  NA | High Moderate Low Moderate Low Moderate Low  Low | 3  6  12  6  12  6  12  12 |
| Systemic disease | | NA NA | NA | Low | 12 |

*From Cassidy J, Kivlin J, Lindsley C, et al: Section on Rheumatology; Section on Ophthalmology: Ophthalmologic examinations in children with juvenile rheumatoid arthritis,* Pediatrics *117:1843–1845, 2006.*

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| **Table 154-2** Therapeutics for Childhood Rheumatic Diseases\* | | | | | |
| **CLASSIFICATION** | **THERAPEUTIC†** | **DOSE** | **INDICATION†** | **ADVERSE REACTIONS** | **MONITORING** |
| Nonsteroidal antiinflammatory drugs (NSAIDs)‡ | Etodolaca  Ibuprofena | PO once-daily dose: 20-30 kg: 400 mg  31-45 kg: 600 mg  46-60 kg: 800 mg  >60 kg: 1,000 mg  40 mg/kg/day PO divided 3 times daily  Max 2400 mg per day 15 mg/kg/day PO in 2  divided doses Maximum 1,000 mg  per day  10-25 kg: 50 mg PO  twice daily  >25 kg: 100 mg PO twice daily  0.125 mg/kg,  maximum 7.5 mg, PO once daily | JIA  Spondyloarthropathy Pain  Serositis  Cutaneous vasculitis Uveitis | GI intolerance (abdominal pain, nausea),  gastritis, hepatitis, tinnitus, anemia, pseudoporphyria, aseptic meningitis, headache, renal disease | CBC, LFTs, BUN/  creatinine, urinalysis at baseline, then every 6-12 mo |
|  | Naproxena |  |
|  | Celecoxiba |  |
|  | Meloxicama |  |
| Disease modifying antirheumatic drugs (DMARDs) | Methotrexatea | 10-20 mg/m2/wk (0.35-  0.65 mg/kg/wk) PO  20-30 mg/m2/wk  (0.65-1 mg/kg/wk) SC; higher doses better absorbed by SC injection | JIA  Uveitis | GI intolerance (nausea, vomiting), hepatitis, myelosuppression, mucositis, teratogenesis, lymphoma, interstitial pneumonitis  hepatitis, hepatic necrosis, cytopenias, mucositis, teratogenesis, peripheral neuropathy  Retinal toxicity, GI intolerance, rash, skin discoloration, anemia, cytopenias, myopathy, CNS stimulation, death (overdose)  GI intolerance, rash, hypersensitivity reactions, Stevens- Johnson syndrome, cytopenias, hepatitis, headache | CBC, LFTs at baseline, monthly × 3, then every  8-12 wk |
|  | Leflunomide | PO once daily:  10 to <20 kg: 10 mg  20-40 kg: 15 mg  >40 kg: 20 mg | JIA | CBC, LFTs, at  baseline, monthly × 6, then every  8-12 wk |
|  | Hydroxychloroquine | 5-6 mg/kg PO once daily; do not exceed  6.5 mg/kg/daily Maximum dose  400 mg daily | SLE JDMS  Antiphospholipid antibody syndrome | Ophthalmologic screening every 6-12 mo |
|  | Sulfasalazinea | 30-50 mg/kg/day divided in twice- daily doses  Adult maximum 3 g/ day | Spondyloarthropathy, JIA | CBC, LFTs, BUN/  creatinine, urinalysis at baseline, every other wk × 3 mo, monthly × 3, then every 3 mo |
| Tumor necrosis factor α (TNF-α) antagonists | Adalimumaba | SC once every other wk:  15 to <30 kg: 20 mg  ≥30 kg: 40 mg | JIA,  spondyloarthropathy, psoriatic arthritis, uveitis | Injection site reaction, infection, rash, cytopenias,  lupus-like syndrome, potential increased malignancy risk  Injection site reactions, infections, rash, demyelinating disorders, cytopenias, potential increased malignancy risk  Infusion reactions, hepatitis, potential increased malignancy risk | TB test; anti- dsDNA, CBC  TB test; CBC  TB test; anti- dsDNA, LFTs |
|  | Etanercepta | 0.8 mg/kg SC once weekly (maximum 50 mg/dose) or  0.4 mg/kg SC twice weekly (maximum 25 mg/dose) | JIA |
|  | Infliximab | 5-10 mg/kg IV q4-8wk | JIA  Spondyloarthropathy Uveitis  Sarcoidosis |

\*Consult a clinical pharmacology reference for current dosing and monitoring guidelines, and complete list of known adverse effects.

##### Continued

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| **Table 154-2** Therapeutics for Childhood Rheumatic Diseases—cont’d | | | | | |
| **CLASSIFICATION** | **THERAPEUTIC†** | **DOSE** | **INDICATION†** | **ADVERSE REACTIONS** | **MONITORING** |
| Modulate T-cell activation | Abatacepta | IV every 2 wk × 3 doses, then monthly for ≥6 yr of age:  <75 kg: 10 mg/kg  75-100 kg: 750 mg  >100 kg: 1,000 mg | JIA | Infection, headache, potential increased malignancy risk |  |
| Anti-CD20 (B cell) antibody | Rituximab | 575 mg/m2, maximum 1,000 mg, IV on days 1 and 15 | SLE | Infusion reactions, lymphopenia, reactivation hepatitis B, rash, serum sickness, arthritis, PML | CBC, BMP;  consider monitoring quantitative IgG |
| Anti-BLyS antibody | Belimumabe | 10 mg/kg IV every  2 wk × 3 doses, then  every 4 wk | SLE | Infusion reactions, infection, depression |  |
| Interleukin 1 antagonist | Anakinra Canakinumabb | 1-2 mg/kg/daily Adult maximum  100 mg  Given SC every 8 wk (CAPS) every 4 wk (Systemic JIA):  15-40 kg: 2 mg/kg (up to 3 mg/kg if needed)  >40 kg: 150 mg | Systemic JIA CAPS  CAPS  Systemic JIA | Injection site reactions, infection  Injection site reaction, infection, diarrhea, nausea, vertigo, headache | CBC |
| Interleukin-6 antagonist | Tocilizumaba | ≥2 yr and ≥30 kg,  8 mg/kg/dose every 2 wk; ≥2 yr and  ≤30 kg, 12 mg/kg/ dose every 2 wk | Systemic JIA | Infusion reactions, elevated LFTs, elevated lipids, thrombocytopenia, infections | CBC, LFTs,  platelet count, serum lipid profile |
| Intravenous immunoglobulin | IVIGc | 1,000-2,000 mg/kg IV  infusion  For JDMS, give monthly | Kawasaki disease JDMS  SLE | Infusion reaction, aseptic meningitis, renal failure | Serum creatinine, BUN, IgG level |
| Cytotoxic | Cyclophosphamide | 0.5-1 g/m2 IV  (maximum 1.5 g) monthly for 6-mo induction, then every 2-3 mo  Oral regimen: 1-2 mg/ kg/daily; maximum 150 mg/daily | SLE  Vasculitis JDMS  Pulmonary hemorrhage | Nausea, vomiting, myelosuppression, mucositis, hyponatremia, alopecia, hemorrhagic cystitis, gonadal failure, teratogenesis, secondary malignancy | CBC |
| Immunosuppressive | Mycophenolate mofetil | Oral suspension: maximum 1,200 mg/ m2/day PO (up to  2 g/day) divided twice daily  Capsules: maximum 1,500 mg/day PO for BSA 1.25-1.5 m2,  2 g/day PO for BSA  >1.5 m2 divided twice daily | SLE  Uveitis | GI intolerance (diarrhea, nausea, vomiting), renal impairment, neutropenia, teratogenesis, secondary malignancy, PML | CBC, BMP |

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| **Table 154-2** | Therapeutics for Childhood Rheumatic Diseases—cont’d | | | | | |
| **CLASSIFICATION** | | **THERAPEUTIC†** | **DOSE** | **INDICATION†** | **ADVERSE REACTIONS** | **MONITORING** |
| Glucocorticoids | | Prednisonea,d-f  Methylprednisolonea,d-g  Intraarticular  Prednisolone ophthalmic suspension | 0.05-2 mg/kg/day PO given in 1-4 divided doses; maximum varies by individual (80 mg/daily)  Adverse effects are dose dependent; lowest effective dose should be used  0.5-1.7 mg/kg/day or  5-25 mg/m2/day IM/ IV in divided doses q6-12h  For severe manifestations: 30 mg/kg/dose  (maximum 1 g) daily for 1-5 days  Dose varies by joint and formulation  1-2 drops into eye up to every hr while awake  Needs monitoring by ophthalmologist | SLE JDMS  Vasculitis JIA  Uveitis Sarcoidosis  SLE JDMS  Vasculitis Sarcoidosis  Localized scleroderma  JIA  Uveitis | Cushing syndrome, osteoporosis, increased appetite, weight gain, striae, hypertension, adrenal suppression, hyperglycemia, infection, avascular necrosis  Subcutaneous atrophy, skin hypopigmentation, calcification, infection  Ocular hypertension, glaucoma, nerve damage, cataract, infection | Blood glucose, potassium  Blood pressure  Ophthalmologic exam |

Blys, B-lymphocyte stimulator; BMP, basic metabolic panel; BSA, body surface area; BUN, blood urea nitrogen; CAPS, cryopyrin-associated periodic syndrome; CBC, complete blood count; CNS, central nervous system; dsDNA, double-stranded DNA; GI, gastrointestinal; Ig, immunoglobulin; IM, intramuscular(ly);

IV, intravenous(ly); IVIG, intravenous immunoglobulin; JDMS, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; LFTs, liver function tests; PML, progressive multifocal leukoencephalopathy; PO, by mouth; SC, subcutaneous(ly); SLE, systemic lupus erythematosus; TB, tuberculosis.

†Therapeutics used in practice may not have a FDA-approved indication. Individual therapeutics annotated with FDA-approved indication as follows: a, JIA; b, CAPS; c, Kawasaki disease; d, sarcoidosis; e, SLE; f, uveitis; g, dermatomyositis.

‡Many more products available in this class.

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| **Table 154-3** | | Summary of Biologic Therapies Studied in Juvenile Idiopathic Arthritis and Their Method of Action |
| **DRUG** | **METHOD OF ACTION** | |
| Etanercept | Soluble TNF p75 receptor fusion protein that binds to and inactivates TNF-α | |
| Infliximab | Chimeric human/mouse monoclonal antibody that binds to soluble TNF-α and its membrane-bound precursor, neutralizing its action | |
| Adalimumab A humanized IgG1 monoclonal antibody that binds to TNF-α | | |
| Abatacept | Soluble, fully human fusion protein of the extracellular domain of (CTLA-4, linked to a modified Fc portion of the human IgG1. It acts as a costimulatory signal inhibitor by binding  competitively to CD80 or CD86, where it selectively inhibits T-cell activation | |
| Tocilizumab A humanized anti–human IL-6 receptor monoclonal antibody | | |
| Anakinra | An IL-1 receptor antagonist (IL-1RA) | |

*Modified from Cassidy JT, Levison JE, Bass JC, et al: A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis,* Arthritis Rheum *29:174–181, 1986.*

Age at onset: <16 yr

Arthritis (swelling or effusion, or the presence of 2 or more of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat) in ≥1 joint

Duration of disease: ≥6 wk

Onset type defined by type of articular involvement in the 1st 6 mo after onset:

Polyarthritis: ≥5 inflamed joints Oligoarthritis: ≤4 inflamed joints

Systemic-onset disease: arthritis with rash and a characteristic quotidian fever

Exclusion of other forms of juvenile arthritis

Criteria for the Classification of Juvenile Rheumatoid Arthritis

**Table 155-1**

CTLA, cytotoxic T lymphocyte–associated antigen; Ig, immunoglobulin; IL, interleukin; TNF, tumor necrosis factor.

*From Beresford MW, Baildam EM: New advances in the management of juvenile idiopathic arthritis—2: the era of biologicals,* Arch Dis Child Educ Pract Ed *94:151–156, 2009.*

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| **Table 155-2** | International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis (JIA) | | |
| **CATEGORY** | | **DEFINITION** | **EXCLUSIONS** |
| Systemic | | Arthritis in ≥1 joint with, or preceded by, fever of at least 2 wk in duration that is documented to be daily (“quotidian”\*) for at least 3 days and accompanied by  ≥1 of the following:   1. Evanescent (nonfixed) erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly or splenomegaly or both 4. Serositis† | 1. Psoriasis or a history of psoriasis in the patient or a 1st-degree relative 2. Arthritis in an HLA-B27–positive boy beginning after the 6th birthday 3. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis, or a history of one of these disorders in a 1st-degree relative 4. Presence of immunoglobulin M RF on at least 2 occasions at least 3 mo apart |
| Oligoarthritis | | Arthritis affecting 1-4 joints during the 1st 6 mo of disease. Two subcategories are recognized:   1. Persistent oligoarthritis—affecting ≤4 joints throughout the disease course 2. Extended oligoarthritis—affecting >4 joints after the 1st 6 mo of disease | a, b, c, d (above) plus  e. Presence of systemic JIA in the patient |
| Polyarthritis (RF-negative) | | Arthritis affecting ≥5 joints during the 1st 6 mo of disease; a test for RF is negative | a, b, c, d, e |
| Polyarthritis (RF-positive) | | Arthritis affecting ≥5 joints during the 1st 6 mo of disease; ≥2 tests for RF at least 3 mo apart during the 1st 6 mo of disease are positive | a, b, c, e |
| Psoriatic arthritis | | Arthritis and psoriasis, or arthritis and at least 2 of the following:   1. Dactylitis‡ 2. Nail pitting§ and onycholysis 3. Psoriasis in a 1st-degree relative | b, c, d, e |
| Enthesitis-related arthritis | | Arthritis and enthesitis,|| or arthritis or enthesitis with at least 2 of the following:   1. Presence of or a history of sacroiliac joint tenderness or inflammatory lumbosacral pain or both¶ 2. Presence of HLA-B27 antigen 3. Onset of arthritis in a male >6 yr old 4. Acute (symptomatic) anterior uveitis 5. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis in a   1st-degree relative | a, d, e |
| Undifferentiated arthritis | | Arthritis that fulfills criteria in no category or in ≥2 of the above categories. |  |

RF, rheumatoid factor.

\**Quotidian fever* is defined as a fever that rises to 39°C (102.2°F) once a day and returns to 37°C (98.6°F) between fever peaks.

†*Serositis* refers to pericarditis, pleuritis, or peritonitis, or some combination of the 3.

‡*Dactylitis* is swelling of ≥1 digits, usually in an asymmetric distribution, that extends beyond the joint margin.

§A minimum of 2 pits on any 1 or more nails at any time.

||*Enthesitis* is defined as tenderness at the insertion of a tendon, ligament, joint capsule, or fascia to bone.

¶*Inflammatory lumbosacral pain* refers to lumbosacral pain at rest with morning stiffness that improves on movement.

*From Firestein GS, Budd RC, Harris ED Jr, et al, editors:* Kelley’s textbook of rheumatology, *ed 8, Philadelphia, 2009, Saunders.*

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| **Table 155-3** | Characteristics of the American College of Rheumatology (ACR) and International League of Associations for Rheumatology (ILAR) Classifications of Childhood Chronic Arthritis | | |
| **PARAMETER** | | **ACR (1977)** | **ILAR (1997)** |
| Term | | Juvenile rheumatoid arthritis (JRA) | Juvenile idiopathic arthritis (JIA) |
| Minimum duration | | ≥6 wk | ≥6 wk |
| Age at onset | | <16 yr | <16 yr |
| ≤4 joints in 1st 6 mo after presentation | | * Pauciarticular | * Oligoarthritis:   1. Persistent: <4 joints for course of disease   2. Extended: >4 joints after 6 mo |
| >4 joints in 1st 6 mo after presentation | | * Polyarticular | * Polyarthritis rheumatoid factor–negative * Polyarthritis rheumatoid factor–positive |
| Fever, rash, arthritis | | * Systemic-onset | * Systemic |
| Other categories included | | Exclusion of other forms | * Psoriatic arthritis * Enthesitis-related arthritis * Undifferentiated:   1. Fits no other category   2. Fits more than 1 category |
| Inclusion of psoriatic arthritis, inflammatory bowel disease, ankylosing spondylitis | | No (see Chapter 156) | Yes |

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| **Table 155-4** Overview of the Main Features of the Subtypes of Juvenile Idiopathic Arthritis | | | | | | |
| **INTERNATIONAL** |  |  |  |  |  |  |
| **LEAGUE OF** |  |  |  |  |  |  |
| **ASSOCIATIONS FOR** |  | **PERCENTAGE** |  |  |  |  |
| **RHEUMATOLOGY** | **PEAK AGE OF FEMALE : MALE** | **OF ALL JIA** |  | **EXTRAARTICULAR** | **LABORATORY** |  |
| **SUBTYPE** | **ONSET (Yr) RATIO** | **CASES** | **ARTHRITIS PATTERN** | **FEATURES** | **INVESTIGATIONS** | **NOTES ON THERAPY** |
| Systemic arthritis | 1-5 1 : 1 | 5-15 | Polyarticular, often affecting knees, wrists, and ankles; also fingers, neck, and hips | Daily fever; evanescent rash; pericarditis; pleuritis | Anemia; WBC ↑↑; ESR ↑↑; CRP ↑↑; ferritin ↑; platelets  ↑↑ (normal or ↓ in MAS) | Less responsive to standard treatment with MTX and anti-TNF agents; consider IL-1 or IL-6 inhibitors in resistant cases or as  first-line therapy |
| Oligoarthritis | 2-4 3 : 1 | 40-50 (but ethnic variation) | Knees ++; ankles, fingers + | Uveitis in ≈30% of cases | ANA positive in  ≈60%; other test results usually normal; may have mildly ↑ ESR/CRP | NSAIDs and intraarticular steroids; MTX occasionally required |
| Polyarthritis: RF-negative | 2-4 and 10-14 3 : 1 and 10 : 1 | 20-35 | Symmetric or asymmetric; small and large joints; cervical spine; temporomandibular joint | Uveitis in ≈10%  Rheumatoid nodules in 10%; low-grade fever | ANA positive in 40%; RF negative;  ESR ↑ or ↑↑; CRP ↑/normal; mild anemia | Standard therapy with MTX and NSAIDs; then, if nonresponsive, anti-TNF agents or other biologics, including abatacept, indicated as first-line therapy  Long-term remission unlikely; early aggressive therapy is warranted |
| RF-positive | 9-12 9 : 1 | <10 | Aggressive symmetric polyarthritis | RF positive; ESR ↑↑; CRP ↑/normal; mild anemia |
| Psoriatic arthritis | 2-4 and 9-11 2 : 1 | 5-10 | Asymmetric arthritis of small or medium-sized joints | Uveitis in 10%;  psoriasis in 50% | ANA positive in 50%; ESR ↑;  CRP ↑/normal; mild anemia | NSAIDs and intraarticular steroids; MTX, anti-TNF agents |
| Enthesitis-related arthritis | 9-12 1 : 7 | 5-10 | Predominantly lower limb joints affected; sometimes axial skeleton (but less than in adult, ankylosing spondylitis) | Acute anterior uveitis; association with reactive arthritis and inflammatory bowel disease | 80% of patients positive for HLA-B27 | NSAIDs and intra-articular steroids; consider sulfasalazine as alternative to MTX; anti-TNF agents |

ANA, antinuclear antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; MAS, macrophage activation syndrome; MTX, methotrexate; NSAID, nonsteroidal antiinflammatory drug; RF, rheumatoid factor; TNF, tumor necrosis factor; WBC, white blood cell count.

*From Firestein GS, Budd RC, Harris ED Jr, et al, editors:* Kelley’s textbook of rheumatology, *ed 8, Philadelphia, 2009, Saunders.*

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| **Table 155-6** | Main Clinical, Laboratory, and Pathologic Features of Macrophage Activation Syndrome |
| LABORATORY CRITERIA   1. Cytopenias 2. Abnormal liver function tests 3. Coagulopathy (hypofibrinogenemia) 4. Decreased erythrocyte sedimentation rate 5. Hypertriglyceridemia 6. Hyponatremia 7. Hypoalbuminemia 8. Hyperferritinemia 9. Elevated sCD25 and sCD163 | |
| CLINICAL CRITERIA   1. Nonremitting fever 2. Hepatomegaly 3. Splenomegaly 4. Lymphadenopathy 5. Hemorrhages 6. Central nervous system dysfunction (headache, seizures, lethargy, coma, disorientation) | |
| HISTOPATHOLOGIC CRITERIA   1. Macrophage hemophagocytosis in the bone marrow aspirate 2. Increased CD163 staining of the bone marrow | |

**Chapter 155** ◆ Juvenile Idiopathic Arthritis **1167**

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| **Table 155-7** | Conditions Causing Arthritis or Extremity Pain | |
| RHEUMATIC AND INFLAMMATORY DISEASES | | BONE AND CARTILAGE DISORDERS |
| Juvenile idiopathic arthritis | | Trauma |
| Systemic lupus erythematosus | | Patellofemoral syndrome |
| Juvenile dermatomyositis | | Hypermobility syndrome |
| Polyarteritis nodosa | | Osteochondritis dissecans |
| Scleroderma | | Avascular necrosis (including Legg-Calvé-Perthes disease) |
| Sjögren syndrome | | Hypertrophic osteoarthropathy |
| Behçet disease | | Slipped capital femoral epiphysis |
| Overlap syndromes | | Osteolysis |
| Antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis | | Benign bone tumors (including osteoid osteoma) |
| Sarcoidosis | | Histiocytosis |
| Kawasaki syndrome | | Rickets |
| Henoch-Schönlein purpura  Chronic recurrent multifocal osteomyelitis | |
| NEUROPATHIC DISORDERS  Peripheral neuropathies |
|  | |
| SERONEGATIVE SPONDYLOARTHROPATHIES | | Carpal tunnel syndrome |
| Juvenile ankylosing spondylitis | | Charcot joints |
| Inflammatory bowel disease | |
| NEOPLASTIC DISORDERS  Leukemia Neuroblastoma Lymphoma  Bone tumors (osteosarcoma, Ewing sarcoma) Histiocytic syndromes  Synovial tumors |
| Psoriatic arthritis | |
| Reactive arthritis associated with urethritis, iridocyclitis, and | |
| mucocutaneous lesions | |
| INFECTIOUS ILLNESSES | |
| Bacterial arthritis (septic arthritis, *Staphylococcus aureus, Kingella* | |
| *kingae,* pneumococcus, gonococcus, *Haemophilus influenzae*) | |
| Lyme disease  Viral illness (parvovirus, rubella, mumps, Epstein-Barr virus, hepatitis B, Chikungunya virus)  Fungal arthritis | |
| HEMATOLOGIC DISORDERS  Hemophilia  Hemoglobinopathies (including sickle cell disease) |
| MISCELLANEOUS DISORDERS  Autoinflammatory diseases Recurrent multifocal osteomyelitis Pigmented villonodular synovitis  Plant-thorn synovitis (foreign-body arthritis) Myositis ossificans  Eosinophilic fasciitis Tendinitis (overuse injury) Raynaud phenomenon |
| Mycobacterial infection | |
| Spirochetal infection | |
| Endocarditis | |
| REACTIVE ARTHRITIS | |
| Acute rheumatic fever | |
| Reactive arthritis (postinfectious caused by *Shigella, Salmonella,* | |
| *Yersinia, Chlamydia,* or meningococcus) | |
| Serum sickness | |
| Toxic synovitis of the hip | |
| PAIN SYNDROMES  Fibromyalgia Growing pains  Depression (with somatization) Reflex sympathetic dystrophy Regional myofascial pain syndromes |
| Postimmunization | |
| IMMUNODEFICIENCIES | |
| Hypogammaglobulinemia | |
| Immunoglobulin A deficiency | |
| Human immunodeficiency virus | |
| CONGENITAL AND METABOLIC DISORDERS | |
| Gout | |
| Pseudogout | |
| Mucopolysaccharidoses | |
| Thyroid disease (hypothyroidism, hyperthyroidism) | |
| Hyperparathyroidism | |
| Vitamin C deficiency (scurvy) | |
| Hereditary connective tissue disease (Marfan syndrome, Ehlers-Danlos | |
| syndrome) | |
| Fabry disease | |
| Farber disease | |
| Amyloidosis (familial Mediterranean fever) | |

POSSIBLE

*Neisseria gonorrhoeae Mycoplasma fermentans Mycoplasma genitalium Ureaplasma urealyticum Escherichia coli Cryptosporidium Entamoeba histolytica Giardia lamblia*

*Brucella abortus Clostridium difficile Streptococcus pyogenes Chlamydia pneumoniae Chlamydia psittaci*

PROBABLE

*Chlamydia trachomatis Shigella flexneri Salmonella enteritidis Salmonella typhimurium Yersinia enterocolitica*

*Yersinia pseudotuberculosis Campylobacter jejuni*

Etiologic Microorganisms of Reactive Arthritis

**Table 156-2**

*From Kim PS, Klausmeier TL, Orr DP: Reactive arthritis: a review.* J Adolesc Health *44:309–315, 2009, Table 2, p. 311.*

**Chapter 155** ◆ Juvenile Idiopathic Arthritis **1169**

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| **Table 155-8** | Pharmacologic Treatment of Juvenile Idiopathic Arthritis (JIA) | | |
| **TYPICAL**  **MEDICATIONS TYPICAL DOSES** | | **JIA SUBTYPE** | **SIDE EFFECT(S)** |
| NONSTEROIDAL ANTIINFLAMMATORY DRUGS  Naproxen 15 mg/kg/day PO divided bid (maximum dose 500 mg bid)  Ibuprofen 40 mg/kg/day PO divided tid (maximum dose 800 mg tid)  Meloxicam 0.125 mg/kg PO once daily (maximum dose 15 mg daily) | | Polyarthritis Systemic Oligoarthritis Same as above  Same as above | Gastritis, renal and hepatic toxicity, pseudoporphyria  Same as above Same as above |
| DISEASE-MODIFYING ANTIRHEUMATIC DRUGS  Methotrexate 0.5-1 mg/kg PO or SC weekly  (maximum dose 25 mg/wk)  Sulfasalazine Initial 12.5 mg/kg PO daily; increase by 10 mg/kg/day  Maintenance: 40-50 mg/kg divided bid (maximum dose 2 g/day)  Leflunomide\* 10-20 mg PO daily | | Polyarthritis Systemic  Persistent or extended oligoarthritis Polyarthritis  Polyarthritis | Nausea, vomiting, oral ulcerations, hepatic toxicity, blood count dyscrasias, immunosuppression, teratogenicity  GI upset, allergic reaction, pancytopenia, renal and hepatic toxicity, Stevens- Johnson syndrome  GI upset, hepatic toxicity, allergic rash, alopecia (reversible), teratogenicity (needs washout with cholestyramine) |
| BIOLOGIC AGENTS  *Anti–Tumor Necrosis Factor-****α***  Etanercept 0.8 mg/kg SC weekly or 0.4 mg/kg Polyarthritis SC twice weekly (maximum dose Systemic  50 mg/wk) Persistent or extended oligoarthritis  Infliximab\* 3-10 mg/kg IV q4-8wk Same as above Adalimumab <30 kg: 20 mg SC every other week Same as above  >30 kg: 40 mg SC every other week  *Anticytotoxic T-Lymphocyte–Associated Antigen-4 Immunoglobulin*  Abatacept <75 kg: 10 mg/kg/dose IV q4wk Polyarthritis 75-100 kg: 750 mg/dose IV q4wk  >100 kg: 1,000 mg/dose IV q4wk  *Anti-CD20*  Rituximab\* 750 mg/m2 IV 2 wk × 2 (maximum Polyarthritis dose 1,000 mg)  *Interleukin-1 Inhibitors*  Anakinra\* 1-2 mg/kg SC daily (maximum dose Systemic  100 mg/day)  Canakinumab 15-40 kg: 2 mg/kg/dose SC q8wk Systemic  >40 kg: 150 mg SC q8wk  Rilonacept\* 2.2 mg/kg/dose SC weekly (maximum Systemic  dose 160 mg)  *Interleukin-6 Receptor Antagonist*  Tocilizumab <30 kg: 12 mg/kg/dose q2wk Systemic  >30 kg: 8 mg/kg/dose q2wk (maximum Polyarthritis dose 800 mg) | | | Immunosuppressant, concern for malignancy, demyelinating disease, lupus-like reaction, injection site reaction  Same as above, infusion reaction Same as above  Immunosuppressant, concern for malignancy, infusion reaction  Immunosuppressant, infusion reaction, progressive multifocal encephalopathy  Immunosuppressant, GI upset, injection site reaction  Immunosuppressant, headache, GI upset, injection site reaction  Immunosuppressant, allergic reaction, dyslipidemia, injection site reaction  Immunosuppressant, hepatic toxicity, dyslipidemia, cytopenias, GI upset, infusion reaction |

bid, Twice daily; GI, gastrointestinal; IV, intravenous; PO, oral; SC, subcutaneous; tid, 3 times daily.

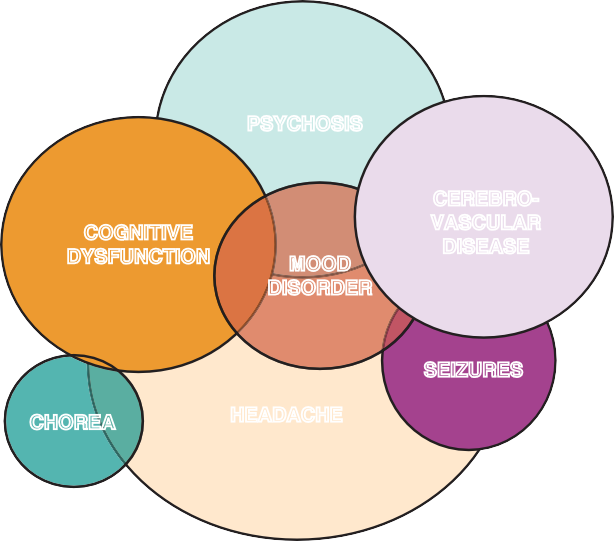
\*Not indicated by the U.S. Food and Drug Administration for use in JIA.

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| **Table 156-1** | Overlapping Characteristics of the Spondyloarthritides | | | | |
| **CHARACTERISTIC** | | **JUVENILE ANKYLOSING SPONDYLITIS** | **JUVENILE PSORIATIC ARTHRITIS** | **INFLAMMATORY BOWEL DISEASE** | **REACTIVE ARTHRITIS** |
| Enthesitis | | +++ | + | + | ++ |
| Axial arthritis | | +++ | ++ | ++ | + |
| Peripheral arthritis | | +++ | +++ | +++ | +++ |
| HLA-B27 positive | | +++ | + | +++ | +++ |
| Antinuclear antibody positive | | – | ++ | – | – |
| Rheumatoid factor positive | | – | – | – | – |
| Systemic disease: Eyes  Skin  Mucous membranes Gastrointestinal tract | | +  –  –  – | +  +++  –  – | +  +  +  ++++ | +  +  +  +++ |

Frequency of characteristics: −, absent; +, <25%; ++, 25-50%; +++, 50-75%, ++++, 75% or more.

*From Cassidy JT, Petty RE:* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Elsevier/Saunders.*

**1178 Part XVI** ◆ Rheumatic Diseases of Childhood



**PSYCHOSIS**

**COGNITIVE**

**DYSFUNCTION**

**CEREBRO-**

**VASCULAR DISEASE**

**MOOD**

**DISORDER**

**SEIZURES**

**CHOREA**

**HEADACHE**

**Figure 158-2** Overlapping neuropsychiatric symptoms in pediatric SLE. Patients with pediatric SLE most commonly have more than 1 neuropsychiatric symptom—in particular for seizures. *(From Silverman E, Eddy A: Systemic lupus erythematosus. In Cassidy JT, Petty RE, Laxer RM, et al, editors,* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders/Elsevier,* Fig. 21-17*, p. 329.)*

\*The presence of 4 of 11 criteria establishes the diagnosis of SLE. These criteria were developed for classification in clinical trials and not for clinical diagnosis.

Malar rash Discoid rash Photosensitivity

Oral or nasal ulcers Arthritis

Nonerosive, ≥2 joints

Serositis

Pleuritis, pericarditis or peritonitis

Renal manifestations†

Consistent renal biopsy

Persistent proteinuria or renal casts

Seizure or psychosis Hematologic manifestations†

Hemolytic anemia

Leukopenia (<4,000 leukocytes/mm3)

Lymphopenia (<1,500 leukocytes/mm3)

Thrombocytopenia (<100,000 thrombocytes/mm3)

Immunologic abnormalities†

Positive anti–double-stranded or anti-Smith antibody

False-positive rapid plasma regain test result, positive lupus anticoagulant test result, or elevated anticardiolipin immunoglobulin (Ig) G or IgM antibody

Positive antinuclear antibody test result

American College of Rheumatology 1997 Revised Classification Criteria for Systemic Lupus Erythematosus\*

**Table 158-2**

†Each of these criteria counts as a single criterion whether 1 or more definitions are satisfied.

*Adapted from Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus,* Arthritis Rheum *40:1725, 1997.*

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| **Table 158-3** | Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus\* |
| **CLINICAL CRITERIA IMMUNOLOGIC CRITERIA** | |
| Acute cutaneous lupus Positive antinuclear antibody  Malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, Positive double-stranded DNA antibody  maculopapular lupus rash, photosensitive lupus rash, or subacute Positive anti-Smith antibody  cutaneous lupus Antiphospholipid antibody positivity  Chronic cutaneous lupus Positive lupus anticoagulant, false-positive test for rapid plasma Classic discoid rash, lupus panniculitis, mucosal lupus, lupus regain, medium to high titer anticardiolipin antibody level (IgA, IgG,  erythematous tumidus, chilblains lupus, discoid lupus/lichen IgM), or positive anti–B2-glycoprotein I antibody (IgA, IgG, IgM) planus overlap Low complement  Oral or nasal ulcers Low C3, C4, or Ch50 level  Nonscarring alopecia Positive direct Coombs test (in the absence of hemolytic anemia)  Synovitis (≥2 joints)  Serositis  Pleurisy or pericardial pain ≥1 day, pleural effusion or rub, pericardial effusion or rub, ECG evidence of pericarditis  Renal  Presence of red blood cell casts or urine protein/creatinine ratio representing >500 mg protein/24 hours  Neurologic  Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, or acute confusional state  Hemolytic anemia  Leukopenia (<4,000/mm3) or lymphopenia (<1,000/mm3)  Thrombocytopenia (<100,000/mm3) | |

\*The presence of 4 criteria (including at least 1 clinical and 1 immunologic criterion) establishes the diagnosis of SLE. Biopsy-proven lupus nephritis with positive ANA or anti–double-stranded DNA also satisfies the diagnosis of SLE. These criteria were developed for classification in clinical trials and not for clinical diagnosis.

*Adapted from Petri M: Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus,*

Arthritis Rheum *64(8):2677–2686, 2012.*

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| **Table 158-4** | Medications Associated with Drug- Induced Lupus |
| DEFINITE ASSOCIATION  Minocycline, procainamide, hydralazine, isoniazid, penicillamine, diltiazem, interferon-α, methyldopa, chlorpromazine, etanercept, infliximab, adalimumab | |
| PROBABLE ASSOCIATION  Phenytoin, ethosuximide, carbamazepine, sulfasalazine, amiodarone, quinidine, rifampin, nitrofurantoin, beta blockers, lithium, captopril, interferon-γ, hydrochlorothiazide, glyburide, docetaxel, penicillin, tetracycline, statins, gold, valproate, griseofulvin, gemfibrozil, propylthiouracil | |

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| **Table 158-5** | Autoantibodies Commonly Associated with Systemic Lupus Erythematosus (SLE) | |
| **ANTIBODY** | | **CLINICAL ASSOCIATION** |
| Anti–double-stranded Correlates with disease activity, especially DNA nephritis, in some with SLE | | |
| Anti-Smith antibody | | Specific for the diagnosis of SLE |
| Antiribonucleoprotein Increased risk for Raynaud phenomenon antibody and pulmonary hypertension  High titer may suggest diagnosis of mixed connective tissue disorder | | |
| Anti-Ro antibody (anti-SSA antibody)  Anti-La antibody (anti-SSB antibody) | | Associated with sicca syndrome May suggest diagnosis of Sjögren  syndrome  Increased risk of neonatal lupus in offspring (congenital heart block)  May be associated with cutaneous and pulmonary manifestations of SLE  May be associated with isolated discoid lupus |
| Antiphospholipid antibodies (including anticardiolipin antibodies) | | Increased risk for venous and arterial thrombotic events |
| Antihistone antibodies | | Present in a majority of patients with drug-induced lupus  May be present in SLE |

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| **Table 158-6** | Morbidity in Childhood Lupus |
| Renal | Hypertension, dialysis, transplantation |
| Central nervous system | Organic brain syndrome, seizures, psychosis, neurocognitive dysfunction |
| Cardiovascular | Atherosclerosis, myocardial infarction, cardiomyopathy, valvular disease |
| Immune | Recurrent infection, functional asplenia, malignancy |
| Musculoskeletal | Osteopenia, compression fractures, avascular necrosis |
| Ocular | Cataracts, glaucoma, retinal detachment, blindness |
| Endocrine | Diabetes, obesity, growth failure, infertility, fetal wastage |

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| **Table 158-1** | Potential Clinical Manifestations of Systemic Lupus Erythematosus | |
| **TARGET ORGAN** | | **POTENTIAL CLINICAL MANIFESTATIONS** |
| Constitutional | | Fatigue, anorexia, weight loss, fever, lymphadenopathy |
| Musculoskeletal | | Arthritis, myositis, tendonitis, arthralgias, myalgias, avascular necrosis, osteoporosis |
| Skin | | Malar rash, discoid (annular) rash, photosensitive rash, cutaneous vasculitis (petechiae, palpable purpura, digit ulcers, gangrene, urticaria), livedo reticularis, periungual capillary abnormalities, Raynaud phenomenon, alopecia, oral and nasal ulcers, panniculitis, chilblains, alopecia |
| Renal | | Hypertension, proteinuria, hematuria, edema, nephrotic syndrome, renal failure |
| Cardiovascular | | Pericarditis, myocarditis, conduction system abnormalities, Libman-Sacks endocarditis |
| Neurologic | | Seizures, psychosis, cerebritis, stroke, transverse myelitis, depression, cognitive impairment, headaches, migraines, pseudotumor, peripheral neuropathy (mononeuritis multiplex) , chorea, optic neuritis, cranial nerve palsies, acute confusional states, dural sinus thrombosis |
| Pulmonary | | Pleuritis, interstitial lung disease, pulmonary hemorrhage, pulmonary hypertension, pulmonary embolism |
| Hematologic | | Immune-mediated cytopenias (hemolytic anemia, thrombocytopenia or leukopenia), anemia of chronic inflammation, hypercoagulability, thrombocytopenic thrombotic microangiopathy |
| Gastroenterology Hepatosplenomegaly, pancreatitis, vasculitis  affecting bowel, protein-losing enteropathy, peritonitis | | |
| Ocular | | Retinal vasculitis, scleritis, episcleritis, papilledema, dry eyes, optic neuritis |

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| **Table 159-2** | Clinical Features of Juvenile Dermatomyositis During the Course of the Disease | |
| **FEATURE** | | **%** |
| Muscle weakness | | 90-100 |
| Dysphagia or dysphonia | | 13-40 |
| Muscle atrophy | | 10 |
| Muscle pain and tenderness | | 30-83 |
| Skin lesions | | 85-100 |
| Heliotrope rash of eyelids | | 66-83 |
| Gottron papules | | 57-91 |
| Erythematous rash of malar/facial area | | 42-100 |
| Periungual capillary changes | | 80 |
| Photosensitive rash | | 5-42 |
| Ulcerations | | 22-30 |
| Calcinosis | | 12-30 |
| Lipodystrophy | | 11-14 |
| Raynaud phenomenon | | 2-15 |
| Arthritis and arthralgia | | 22-58 |
| Joint contractures | | 26-27 |
| Fever | | 16-46 |
| Gastrointestinal signs and symptoms | | 8-22 |
| Restrictive pulmonary disease | | 4-32 |
| Interstitial lung disease | | 1-7 |
| Cardiac involvement | | 0-3 |

**Chapter 158** ◆ Systemic Lupus Erythematosus **1179**

**Chapter 159** ◆ Juvenile Dermatomyositis **1185**

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| **Table 159-3** | Phenotypic Characteristics of the Clinical Subgroups of Juvenile Myositis\* | | | |
| **CHARACTERISTIC** | | **JDM** | **JPM** | **JCTM** |
| *Demographics* | | | | |
| Median age at diagnosis (yr) | | Youngest (7.4 yr) | Oldest (12.1 yr) | Intermediate (10.2 yr) |
| Race | | Predominantly white (71.2%) | Black (39.4%) | Black or other (49.0%) |
| Severity at onset | | Mild or moderate severity | Severe or very severe onset | Mild or moderate severity |
| Median delay to diagnosis (mo) | | 4 mo | 3.5 mo | Longer delay (7 mo) |
| *Clinical features* | | Gottron papules Heliotrope rash  Periungual capillary abnormalities Malar rash  *Photosensitivity*  *Linear extensor erythema*†  Cuticular overgrowth  Mucous membrane involvement “V-sign” and “shawl-sign” rashes Skin ulcerations  Dyspnea on exertion | *Weight loss*  Falling episodes Raynaud phenomenon Abnormal PFT Dyspnea on exertion  Cardiac abnormalities on EKG or ECHO | Gottron papules Heliotrope rash  Malar rash  Raynaud phenomenon Interstitial lung disease Arthralgia  *Linear extensor erythema*† *Mucous membrane involvement Arthritis*  *Photosensitivity Sclerodactyly*  *Periungual capillary abnormalities*†  Cuticular overgrowth Abdominal pain, GI bleeding Dyspnea on exertion  Weight loss |
| *Autoantibodies* | | Intermediate ANA titer (median, 1:320)  *Anti-p155/140*†  Anti-MJ Anti-Mi-2 | Intermediate ANA titer (median, 1:320) Anti-SRP  Anti-aminoacyl-tRNA synthetase (anti–Jo-1) | Highest ANA titer (median, 1:1280)  Anti-U1-RNP  Anti-PM-Sc1 Anti-Ro  Anti-SM Anti-La  All other U-RNP autoantibodies |
| *Laboratory features* | | *Lowest CK level (median, 829 U/L)* | Highest CK level (median, 5027 U/L)  Highest levels of aldolase and ALT | Intermediate CK level (median 1208 U/L) |
| Outcome | | Low mortality (2.4%)  Calcinosis (34.0%) | Medium mortality (6.3%)  Frequently hospitalized (71.9%)  Wheelchair use | Highest mortality (14.6%) |

ALT, alanine aminotransferase; ANA, antinuclear antibody; CK, creatine kinase; ECHO, echocardiogram; EKG, electrocardiogram; GI, gastrointestinal; JCTM, juvenile myositis overlapping with another autoimmune or connective tissue disease; JDM, juvenile dermatomyositis; JPM, juvenile polymyositis; PFT, pulmonary function test; tRNA, transfer RNA.

\*Bold indicates significant in logistic regression; *italics* indicates top variables entered in pruned-down random forest models. Other variables included in this table were significant in univariable analysis to p ≤0.01.

†Removed from logistic regression analyses because variable was either 100% or 0% in 1 of the compared subgroups. Gottron papules and heliotrope rash, which were part of the definition of cases of dermatomyositis, were not entered into multivariable analyses.

*Modified from Shah M, Mamyrova G, Targoff IN, et al: The clinical phenotypes of the juvenile idiopathic inflammatory myopathies.* Medicine (Baltimore) *92:25–41, 2013, Table 9, p. 36.*

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| **Table 160-3** | Provisional Criteria for the Classification of Juvenile Systemic Sclerosis (SSc) |
| MAJOR CRITERION (REQUIRED)\*  Proximal skin sclerosis/induration of the skin proximal to metacarpophalangeal or metatarsophalangeal joints | |
| MINOR CRITERIA (AT LEAST 2 REQUIRED)  Cutaneous: sclerodactyly  Peripheral vascular: Raynaud phenomenon, nailfold capillary abnormalities (telangiectasias), digital tip ulcers  Gastrointestinal: dysphagia, gastroesophageal reflux Cardiac: Arrhythmias, heart failure  Renal: Renal crisis, new-onset arterial hypertension Respiratory: pulmonary fibrosis (high-resolution computed  tomography/radiography), decreased diffusing capacity for carbon monoxide, pulmonary arterial hypertension  Neurologic: neuropathy, carpal tunnel syndrome Musculoskeletal: tendon friction rubs, arthritis, myositis Serologic: antinuclear antibodies—SSc-selective autoantibodies  (anticentromere, antitopoisomerase I [Scl-70], antifibrillarin, anti-PM/Scl, antifibrillin or anti-RNA polymerase I or III | |

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| **Table 159-1** | Diagnostic Criteria for Juvenile Dermatomyositis |
| Classic rash Heliotrope rash of the eyelids Gottron papules | |
| *Plus* 3 of the following:  Weakness Symmetric Proximal  Muscle enzyme Creatine kinase  elevation (≥1) Aspartate aminotransferase  Lactate dehydrogenase Aldolase  Electromyographic Short, small polyphasic motor unit potentials changes Fibrillations  Positive sharp waves Insertional irritability  Bizarre, high-frequency repetitive discharges  Muscle biopsy Necrosis Inflammation | |

\*Diagnosis requires at least 1 major and at least 2 minor criteria.

**Chapter 160** ◆ Scleroderma and Raynaud Phenomenon **1187**

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| **Table 160-1** | Classification of Pediatric Scleroderma (Morphea) |
| LOCALIZED SCLERODERMA  *Plaque Morphea*  Confined to dermis, occasionally superficial panniculus  Well-circumscribed circular area of induration, often a central waxy, ivory-colored area surrounded by a violaceous halo; unilateral  *Generalized Morphea*  Involves dermis primarily, occasionally panniculus  Defined as confluence of individual morphea plaques or lesions in 3 or more anatomic sites; more likely to be bilateral  *Bullous Morphea*  Bullous lesions that can occur with any of the subtypes of morphea  *Linear Scleroderma*  Linear lesions can extend through the dermis, subcutaneous tissue, and muscle to underlying bone; more likely unilateral  Limbs/trunk:  One or more linear streaks of the extremities or trunk  Flexion contracture occurs when lesion extends over a joint; limb length discrepancies  En coup de sabre:  Involves the scalp and/or face; lesions can extend into the central nervous system, resulting in neurologic sequelae, most commonly seizures and headaches  Parry Romberg syndrome:  Hemifacial atrophy without a clearly definable en coup de sabre lesion; can also have neurologic involvement  *Deep Morphea*  Involves deeper layers, including panniculus, fascia, and muscle; more likely to be bilateral  Subcutaneous morphea:  Primarily involves the panniculus or subcutaneous tissue Plaques are hyperpigmented and symmetric  Eosinophilic fasciitis:  Fasciitis with marked blood eosinophilia  Fascia is the primary site of involvement; typically involves extremities  Classic description is “peau d’orange” or orange peel texture, but early disease manifests as edema (see Fig. 160-2)  Morphea profunda:  Deep lesion extending to fascia and sometimes muscle, but may be limited to a single plaque, often on trunk  Disabling pansclerotic morphea of childhood:  Generalized full-thickness involvement of skin on the trunk, face and extremities, sparing finger tips and toes | |
| SYSTEMIC SCLEROSIS  *Diffuse*  Most common type in childhood  Symmetric thickening and hardening of the skin (sclerosis) with fibrous and degenerative changes of viscera  *Limited*  Rare in childhood  Previously known as CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome | |

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| **Table 160-1** | Classification of Pediatric Scleroderma (Morphea) |
| LOCALIZED SCLERODERMA  *Plaque Morphea*  Confined to dermis, occasionally superficial panniculus  Well-circumscribed circular area of induration, often a central waxy, ivory-colored area surrounded by a violaceous halo; unilateral  *Generalized Morphea*  Involves dermis primarily, occasionally panniculus  Defined as confluence of individual morphea plaques or lesions in 3 or more anatomic sites; more likely to be bilateral  *Bullous Morphea*  Bullous lesions that can occur with any of the subtypes of morphea  *Linear Scleroderma*  Linear lesions can extend through the dermis, subcutaneous tissue, and muscle to underlying bone; more likely unilateral  Limbs/trunk:  One or more linear streaks of the extremities or trunk  Flexion contracture occurs when lesion extends over a joint; limb length discrepancies  En coup de sabre:  Involves the scalp and/or face; lesions can extend into the central nervous system, resulting in neurologic sequelae, most commonly seizures and headaches  Parry Romberg syndrome:  Hemifacial atrophy without a clearly definable en coup de sabre lesion; can also have neurologic involvement  *Deep Morphea*  Involves deeper layers, including panniculus, fascia, and muscle; more likely to be bilateral  Subcutaneous morphea:  Primarily involves the panniculus or subcutaneous tissue Plaques are hyperpigmented and symmetric  Eosinophilic fasciitis:  Fasciitis with marked blood eosinophilia  Fascia is the primary site of involvement; typically involves extremities  Classic description is “peau d’orange” or orange peel texture, but early disease manifests as edema (see Fig. 160-2)  Morphea profunda:  Deep lesion extending to fascia and sometimes muscle, but may be limited to a single plaque, often on trunk  Disabling pansclerotic morphea of childhood:  Generalized full-thickness involvement of skin on the trunk, face and extremities, sparing finger tips and toes | |
| SYSTEMIC SCLEROSIS  *Diffuse*  Most common type in childhood  Symmetric thickening and hardening of the skin (sclerosis) with fibrous and degenerative changes of viscera  *Limited*  Rare in childhood  Previously known as CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome | |

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| **Table 161-1** | Criteria of the International Study Group for the Diagnosis of Behçet disease |
| **CRITERION DESCRIPTION** | |
| Recurrent oral ulceration Minor aphthous, major aphthous, or  herpetiform ulceration recurring at least 3 times in one 12 mo period, observed by physician or patient | |
| *Plus* 2 of the following:  Recurrent genital ulcers Aphthous ulceration or scarring  observed by physician or patient  Eye lesions Anterior uveitis, posterior uveitis, cells in vitreous on slit-lamp examination, or retinal vasculitis observed by an ophthalmologist  Skin lesions Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions, or acneiform nodules observed by physician in postadolescent patient not on corticosteroid treatment  Pathergy Skin reaction to a needle prick observed by physician at 24-48 hr | |

1. CLINICAL SYMPTOMS
   1. Oral: recurrent parotitis or enlargement of parotid gland, dry mouth (xerostomia)
   2. Ocular: dry eyes (xerophthalmia) recurrent conjunctivitis without obvious allergic or infectious etiology, keratoconjunctivitis sicca
   3. Other mucosal: recurrent vaginitis
   4. Systemic: fever, non-inflammatory arthralgias, hypokalemic paralysis, abdominal pain
2. IMMUNOLOGIC ABNORMALITIES: presence of at least 1 of the following antibodies: anti-SSA, anti-SSB, high titer antinuclear antibody, rheumatoid factor
3. OTHER ABNORMALITIES OR INVESTIGATIONS
   1. Biochemical: elevated serum amylase
   2. Hematologic: leukopenia, high sedimentation rate
   3. Immunologic: polyclonal hyperimmunoglobulinemia
   4. Renal: renal tubular acidosis
   5. Histologic proof of lymphocytic infiltration of salivary glands or other organs (i.e., liver)
   6. Objective documentation of ocular dryness (Bengal red staining or Schirmer test)
   7. Positive findings of parotid gland scintigraphy
4. Exclusion of all other autoimmune diseases

Proposed Criteria for Pediatric Sjögren Syndrome

**Table 162-1**

Diagnosis requires ≥4 criteria.

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| **Table 163-1** Differential Diagnosis of Familial Autoinflammatory Syndromes | | | | |
|  |  | **TUMOR** | **Cryopyrin-Associated Periodic Syndrome (CAPS)** |  |
|  |  | **NECROSIS** | **CHRONIC** |  |
|  |  | **FACTOR** | **INFANTILE** |  |
|  |  | **RECEPTOR–** | **NEUROLOGIC** | **DEFICIENCY** |
|  | **Mevalonate Kinase Deficiency (MKD)** | **ASSOCIATED** | **MUCKLE- CUTANEOUS AND** | **OF IL-1** |
|  | **FAMILIAL** | **PERIODIC** | **FAMILIAL COLD WELLS ARTICULAR** | **RECEPTOR** |
|  | **MEDITERRANEAN HYPERIMMUNOGLOBULIN MEVALONIC** | **SYNDROME** | **AUTOINFLAMMATORY SYNDROME SYNDROME** | **ANTAGONIST** |
|  | **FEVER (FMF) D SYNDROME (HIDS) ACIDURIA** | **(TRAPS)** | **SYNDROME (FCAS) (MWS) (CINCA)** | **(DIRA)** |
| Mode of Inheritance | Autosomal Autosomal recessive Autosomal recessive recessive | Autosomal dominant | Autosomal dominant Autosomal Autosomal dominant  dominant | Autosomal recessive |
| Age at Onset (yr) | <20 <1 <1 | <20 | <1 <20 <1 | Birth, <4 wk |
| Duration of attack (days)\* | <2 4-6 4-5 | >14 | <2 1-2 ? | Continuous |
| Cutaneous Involvement | Erysipelas-like Maculopapular rash Morbilliform erythema rash | Migratory rash, overlying area of myalgia | Cold-induced urticaria- Urticaria-like Urticaria-like lesions like lesions rash | Generalized pustulosis |
| Musculoskeletal Involvement | Monoarthritis Arthralgia, occasional Arthralgia common oligoarthritis common | Severe myalgia common; occasional frank monoarthritis | Arthralgia common; Lancing limb Epiphyseal bone occasional mild pain, formation  myalgia arthralgia  common; arthritis can occur | Sterile pustulous osteomyelitis |
| Abdominal Involvement | Sterile peritonitis Splenomegaly, severe pain Splenomegaly, common common pain may  occur | Severe pain common | None May occur Hepatosplenomegaly |  |
| Eye Involvement | Uncommon Uncommon Uncommon | Conjunctivitis and periorbital edema common | Conjunctivitis Conjunctivitis; Papilledema with sometimes possible loss of optic nerve vision, uveitis elevation |  |
| Distinguishing Clinical Symptoms | Erysipelas-like Prominent cervical Dysmorphic  erythema lymphadenopathy features, neurologic symptoms | Migratory nature of myalgia and rash, periorbital edema | Cold-induced urticaria- Sensorineural Chronic aseptic like lesions hearing loss meningitis,  sensorineural hearing loss, arthropathy |  |
| Gene Involved | *MEFV MVK MVK* | *TNFRSF1A* | *CIAS1 = NLRP3 CIAS1 = CIAS1 = NRLP3 NLRP3* | *IL-1RN* |
| Protein Involved | Pyrin (marenostrin) Mevalonate kinase Mevalonate  kinase | Type 1 tumor necrosis factor receptor | Cryopyrin Cryopyrin Cryopyrin | IL-1RA |

Note: For details on Blau syndrome, DIRA, and pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome, see text.

\*Duration may vary; this is a typical duration.

*Modified from Hull KM, Shoham N, Chae JJ, et al: The expanding spectrum of systemic autoinflammatory disorders and their rheumatic manifestations,* Curr Opin Rheumatol *15:61–69, 2003.*

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| --- | --- | --- | --- | --- |
| **Table 163-1** Differential Diagnosis of Familial Autoinflammatory Syndromes | | | | |
|  |  | **TUMOR** | **Cryopyrin-Associated Periodic Syndrome (CAPS)** |  |
|  |  | **NECROSIS** | **CHRONIC** |  |
|  |  | **FACTOR** | **INFANTILE** |  |
|  |  | **RECEPTOR–** | **NEUROLOGIC** | **DEFICIENCY** |
|  | **Mevalonate Kinase Deficiency (MKD)** | **ASSOCIATED** | **MUCKLE- CUTANEOUS AND** | **OF IL-1** |
|  | **FAMILIAL** | **PERIODIC** | **FAMILIAL COLD WELLS ARTICULAR** | **RECEPTOR** |
|  | **MEDITERRANEAN HYPERIMMUNOGLOBULIN MEVALONIC** | **SYNDROME** | **AUTOINFLAMMATORY SYNDROME SYNDROME** | **ANTAGONIST** |
|  | **FEVER (FMF) D SYNDROME (HIDS) ACIDURIA** | **(TRAPS)** | **SYNDROME (FCAS) (MWS) (CINCA)** | **(DIRA)** |
| Mode of Inheritance | Autosomal Autosomal recessive Autosomal recessive recessive | Autosomal dominant | Autosomal dominant Autosomal Autosomal dominant  dominant | Autosomal recessive |
| Age at Onset (yr) | <20 <1 <1 | <20 | <1 <20 <1 | Birth, <4 wk |
| Duration of attack (days)\* | <2 4-6 4-5 | >14 | <2 1-2 ? | Continuous |
| Cutaneous Involvement | Erysipelas-like Maculopapular rash Morbilliform erythema rash | Migratory rash, overlying area of myalgia | Cold-induced urticaria- Urticaria-like Urticaria-like lesions like lesions rash | Generalized pustulosis |
| Musculoskeletal Involvement | Monoarthritis Arthralgia, occasional Arthralgia common oligoarthritis common | Severe myalgia common; occasional frank monoarthritis | Arthralgia common; Lancing limb Epiphyseal bone occasional mild pain, formation  myalgia arthralgia  common; arthritis can occur | Sterile pustulous osteomyelitis |
| Abdominal Involvement | Sterile peritonitis Splenomegaly, severe pain Splenomegaly, common common pain may  occur | Severe pain common | None May occur Hepatosplenomegaly |  |
| Eye Involvement | Uncommon Uncommon Uncommon | Conjunctivitis and periorbital edema common | Conjunctivitis Conjunctivitis; Papilledema with sometimes possible loss of optic nerve vision, uveitis elevation |  |
| Distinguishing Clinical Symptoms | Erysipelas-like Prominent cervical Dysmorphic  erythema lymphadenopathy features, neurologic symptoms | Migratory nature of myalgia and rash, periorbital edema | Cold-induced urticaria- Sensorineural Chronic aseptic like lesions hearing loss meningitis,  sensorineural hearing loss, arthropathy |  |
| Gene Involved | *MEFV MVK MVK* | *TNFRSF1A* | *CIAS1 = NLRP3 CIAS1 = CIAS1 = NRLP3 NLRP3* | *IL-1RN* |
| Protein Involved | Pyrin (marenostrin) Mevalonate kinase Mevalonate  kinase | Type 1 tumor necrosis factor receptor | Cryopyrin Cryopyrin Cryopyrin | IL-1RA |

Note: For details on Blau syndrome, DIRA, and pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome, see text.

\*Duration may vary; this is a typical duration.

*Modified from Hull KM, Shoham N, Chae JJ, et al: The expanding spectrum of systemic autoinflammatory disorders and their rheumatic manifestations,* Curr Opin Rheumatol *15:61–69, 2003.*

**Chapter 163** ◆ Hereditary Periodic Fever Syndromes and Other Systemic Autoinflammatory Diseases **1195**

1. Nonspecific maculopapular rashes with recurrent episodic fever and abdominal pain (the classic “periodic fever syndromes”)

Recurrent fever attacks of short duration (typically **<**7 days)

* + FMF: familial Mediterranean fever
  + HIDS: mevalonate kinase deficiency/hyperimmunoglobulinemia D with periodic fever syndrome

Recurrent fever attacks of longer duration (typically **>**7 days)

* + TRAPS: TNF receptor-associated periodic fever syndrome

1. Neutrophilic urticaria (the cryopyrinopathies)

Recurrent fever attacks of short duration (typically **<**24 hr)

* + CAPS/FCAS: familial cold autoinflammatory syndrome
  + CAPS/MWS: Muckle-Wells syndrome

Continuous low-grade fever

* + CAPS/NOMID: neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular syndrome (CINCA)

1. Granulomatous skin lesions and minimal or low-grade fever attacks
   * Blau syndrome/early-onset sarcoidosis (pediatric granulomatous arthritis)
2. Pustular skin rashes and episodic fever

With inflammatory bone disease

* + DIRA: deficiency of interleukin-1 receptor agonist
  + Majeed syndrome

With pyogenic arthritis

* + PAPA: pyogenic arthritis, pyoderma gangrenosum, and acne syndrome

With inflammatory bowel disease

* + Early-onset inflammatory bowel disease

Without other organ involvement

* + DITRA: deficiency of interleukin-36-receptor antagonist
  + CAMPS: CARD14-mediated psoriasis

1. Atypical neutrophilic dermatosis with histiocytic-like infiltrate
   * PRAAS: proteasome associated autoinflammatory syndromes
2. Syndromes with autoinflammation and immunodeficiency
   * PLAID: PLCγ2-associated antibody deficiency and immune dysregulation
   * APLAID: autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation
   * HOIL-1 deficiency

Clinical Grouping of Autoinflammatory Diseases by Fever and Skin Manifestations

**Table 163-2**

*From Almeida de Jesus A, Goldbach-Mansky R: Monogenic autoinflammatory diseases: concept and clinical manifestations.* Clin Immunol *147:155-174, 2013, Table 1.*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table 163-3** | Autoinflammatory Bone Disorders | | | | | |
|  | | **CRMO** | **Majeed Syndrome** | **DIRA** | **Cherubism** | **cmo and lupo Mice** |
| Ethnicity | | Worldwide, but mostly European | Arabic | European, Puerto Rican, Arabic | Worldwide | Occurs in various backgrounds |
| Fever | | Uncommon | Common | Uncommon | No | Not assessed |
| Sites of osseous involvement | | Metaphyses of long bones > vertebrae, clavicle, sternum, pelvis, others | Similar to CRMO | Anterior rib ends, metaphyses of long bones, vertebrae, others | Mandible > maxilla Rarely ribs | Vertebrae hind > forefeet |
| Extraosseous manifestations | | PPP, psoriasis, IBD, others | Dyserythropoietic anemia, Sweet syndrome, HSM, growth failure | Generalized pustulosis, nail changes, lung disease, vasculitis | Cervical lymphadenopathy | Dermatitis, extramedullary hematopoiesis, splenomegaly |
| Family history of inflammatory disorders | | Psoriasis, PPP, arthritis, IBD, others | Psoriasis in some obligate carriers | No known associations | No known associations | Heterozygotes normal |
| Inheritance | | Not clear | Autosomal recessive | Autosomal recessive | Autosomal dominant; incomplete penetrance | Autosomal recessive |
| Gene defect | | Unknown | *LPIN2* | *IL1RN* | *SH3BP2* ≫ *PTPN11* | *Pstpip2* |
| Protein name | | ? | Lipin2 | IL-1Ra | SH3BP2 | PSTPIP2 (a.k.a. MAYP) |
| Protein function | | ? | Fat metabolism: (PAP enzyme  activity), ↑ message to oxidative stress,  ? role in mitosis | Antagonist of IL-1 receptor | ↑ Myeloid cell response to M-CSF and RANKL,  ↑ TNF-α expression in macrophages | Macrophage proliferation, macrophage recruitment to sites of inflammation, cytoskeletal function |
| Cytokine abnormalities | | ↑ serum TNF-α | Not tested | ↑ IL-1α, IL-1β, MIP-1α, TNF-α, IL-8, IL-6 ex  vivo monocyte assay; skin reveals ↑ IL-17 staining | ↑ serum TNF-α in mouse model | cmo: ↑serum IL-6, MIP-1α, TNF-α, CSF-1, IP-10  Lupo: ↑ serum MIP-1α, IL-4, RANTES, TGF-β |

CRMO, chronic recurrent multifocal osteomyelitis; CSF, colony-stimulating factor; DIRA, deficiency of interleukin-1 receptor antagonist; HSM, hepatosplenomegaly; IBD, inflammatory bowel disease; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; IP-10, interferon-inducible protein-10; M-CSF, macrophage–colony- stimulating factor; MIP-1α, macrophage inflammatory protein-1α; PAP, phosphatidate phosphatase; PPP, palmer-plantar pustulosis; PSTPIP2, proline-serine-threonine phosphatase interacting protein; RANKL, receptor activator of nuclear factor-κB ligand; RANTES, regulated upon activation, normal T-cell expressed and secreted; SH3BP2, SH3 binding protein 2; TGF, transforming growth factor; TNF-α, tumor necrosis factor α.

*From Ferguson PJ, Laxer RM: Autoinflammatory bone disorders. In Cassidy JT, Petty RE, Laxer RM, et al, editors:* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2010, Saunders, Table 44-2.*

**Chapter 163** ◆ Hereditary Periodic Fever Syndromes and Other Systemic Autoinflammatory Diseases **1197**

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| --- | --- | --- |
| **Table 163-4** | Clues That May Assist in the Diagnosis of Autoinflammatory Syndromes | |
| AGE OF ONSET  At birth  Infancy and 1st yr of life Toddler  Late childhood  Most common of autoinflammatory syndromes to have onset in adulthood  Variable (mostly in childhood) | | NOMID, DIRA, FCAS HIDS, FCAS, NLRP12 PFAPA  PAPA  TRAPS, DITRA  All others |
| ETHNICITY AND GEOGRAPHY  Armenians, Turks, Italian, Sephardic Jews  Arabs  Dutch, French, German, Western Europe  United States  Can occur in blacks (West Africa origin)  Eastern Canada, Puerto Rico Worldwide | | FMF  FMF, DITRA (Arab Tunisian) HIDS, MWS, NLRP12  FCAS TRAPS  DIRA  All others |
| TRIGGERS  Vaccines  Cold exposure Stress, menses  Minor trauma Exercise Pregnancy Infections | | HIDS  FCAS, NLRP12  FMF, TRAPS, MWS, PAPA, DITRA  PAPA, MWS, TRAPS, HIDS FMF, TRAPS  DITRA  All, especially DITRA |
| ATTACK DURATION  <24 h  1–3 d  3–7 d  >7 d  Almost always “in attack” | | FCAS, FMF  FMF, MWS, DITRA (fever) HIDS, PFAPA  TRAPS, PAPA NOMID, DIRA |
| INTERVAL BETWEEN ATTACKS  3–6 wk  >6 wk  Mostly unpredictable Truly periodic | | PFAPA, HIDS TRAPS  All others  PFAPA, cyclic neutropenia |
| USEFUL LABORATORY TESTS  Acute-phase reactants must be normal between attacks  Urine mevalonic acid in attack IgD > 100 mg/dL  Proteinuria (amyloidosis) | | PFAPA  HIDS HIDS  FMF, TRAPS, MWS, NOMID |
| RESPONSE TO THERAPY  Corticosteroid dramatic Corticosteroid partial  Colchicine Cimetidine Etanercept Anti–IL-1 dramatic  Anti–IL-1 mostly Anti–IL-1 partial | | PFAPA  TRAPS, FCAS, MWS, NOMID, PAPA\*  FMF, PFAPA (30% effective) PFAPA (30% effective) TRAPS, FMF arthritis  DIRA (anakinra), FCAS, MWS, NOMID, PFAPA  TRAPS, FMF HIDS, PAPA |

1. Hereditary (see Table 163-1)
2. Nonhereditary a Infectious
   1. Hidden infectious focus (e.g., aortoenteric fistula, Caroli disease)
   2. Recurrent reinfection (e.g., chronic meningococcemia, host defense defect)
   3. Specific infection (e.g., Whipple disease, malaria) b Noninfectious inflammatory disorder, e.g.:
3. Adult-onset Still disease
4. Juvenile chronic rheumatoid arthritis
5. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis
6. Schnitzler syndrome
7. Behçet syndrome
8. Crohn disease
9. Sarcoidosis
10. Extrinsic alveolitis
11. Humidifier lung, polymer fume fever c Neoplastic
12. Lymphoma (e.g., Hodgkin disease, angioimmunoblastic lymphoma)
13. Solid tumor (e.g., pheochromocytoma, myxoma, colon carcinoma)
14. Vascular (e.g., recurrent pulmonary embolism)
15. Hypothalamic
16. Psychogenic periodic fever
17. Factitious or fraudulent

Differential Diagnosis of Periodic Fever

**Table 163-5**

DIRA, deficiency of the IL-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor antagonist (generalized pustular psoriasis); FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D syndrome; IL, interleukin; MWS, Muckle-Wells syndrome; NLRP, nucleotide oligomerization domain–like receptor family, pyrin domain; NOMID, neonatal-onset multisystem inflammatory disorder; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis; TRAPS, tumor necrosis factor receptor–associated periodic syndrome.

\*For intraarticular steroids.

*From Hashkes PJ, Toker O: Autoinflammatory syndromes.* Pediatr Clin North Am *59:447–470, 2012, Table 2.*

**1210 Part XVI** ◆ Rheumatic Diseases of Childhood

Fever Strawberry tongue Conjunctivitis Desquamation Polymorphous skin rashes

Induration

Pyuria BCG LAP

Diarrhea

CAD

Arthritis

0

### Figure 166-1

10 20 30 40 50 60 70 80 90 100

Percentage of Cases

|  |  |
| --- | --- |
| **Table 166-1** | Clinical and Laboratory Features of Kawasaki Disease |
| EPIDEMIOLOGIC CASE DEFINITION (CLASSIC CLINICAL CRITERIA)\*  Fever persisting at least 5 days† Presence of at least 4 principal features:  Changes in extremities:  Acute: Erythema of palms, soles; edema of hands, feet Subacute: Periungual peeling of fingers, toes in weeks 2 and 3  Polymorphous exanthem  Bilateral bulbar conjunctival injection without exudate  Changes in lips and oral cavity: erythema, lip cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosa  Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral Exclusion of other diseases with similar findings‡ | |
| OTHER CLINICAL AND LABORATORY FINDINGS  Cardiovascular findings:  Congestive heart failure, myocarditis, pericarditis, valvular regurgitation  Coronary artery abnormalities  Aneurysms of medium-size noncoronary arteries Raynaud phenomenon  Peripheral gangrene Musculoskeletal system:  Arthritis, arthralgias Gastrointestinal tract:  Diarrhea, vomiting, abdominal pain Hepatic dysfunction  Hydrops of gallbladder Central nervous system:  Extreme irritability Aseptic meningitis Sensorineural hearing loss  Genitourinary system:  Urethritis/meatitis Other findings:  Erythema, induration at bacille Calmette-Guérin inoculation site Anterior uveitis (mild)  Desquamating rash in groin | |
| LABORATORY FINDINGS IN ACUTE KAWASAKI DISEASE  Leukocytosis with neutrophilia and immature forms Elevated erythrocyte sedimentation rate  Elevated C-reactive protein Anemia  Abnormal plasma lipids Hypoalbuminemia Hyponatremia Thrombocytosis after week 1§ Sterile pyuria  Elevated serum transaminases  Elevated serum gamma glutamyl transpeptidase Pleocytosis of cerebrospinal fluid  Leukocytosis in synovial fluid | |

Clinical symptoms and signs of Kawasaki disease. A summary of the clinical features from 110 cases of Kawasaki disease seen in Kaohsiung, Taiwan. LAP, lymphadenopathy in head and neck area; BCG, reactivation of bacille Calmette-Guérin inoculation site; CAD, coronary artery dilation, defined by an internal diameter >3 mm. *(From Wang CL, Wu YT, Liu CA, et al: Kawasaki disease: infection, immunity and genetics,* Pediatr Infect Dis J *24:998–1004, 2005.)*

|  |  |
| --- | --- |
| **Table 166-2** | Differential Diagnosis of Kawasaki Disease |
| VIRAL INFECTIONS   * Adenovirus * Enterovirus * Measles * Epstein-Barr virus * Cytomegalovirus | |
| BACTERIAL INFECTIONS   * Scarlet fever * Rocky Mountain spotted fever * Leptospirosis * Bacterial cervical lymphadenitis * Meningococcemia | |
| RHEUMATOLOGIC DISEASE   * Systemic-onset juvenile idiopathic arthritis * Behçet disease | |
| OTHER   * Toxic shock syndromes * Staphylococcal scalded skin syndrome * Drug hypersensitivity reactions * Stevens-Johnson syndrome | |

|  |  |
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| **Table 167-5** | Classification Criteria for Henoch- Schönlein Purpura\* |
| AMERICAN COLLEGE OF RHEUMATOLOGY CLASSIFICATION CRITERIA†  Two of the following criteria must be present:   * Palpable purpura * Age at onset ≤20 yr * Bowel angina (postprandial abdominal pain, bloody diarrhea) * Biopsy demonstrating intramural granulocytes in small arterioles and/or venules | |
| EUROPEAN LEAGUE AGAINST RHEUMATISM/PEDIATRIC RHEUMATOLOGY EUROPEAN SOCIETY CRITERIA‡  Palpable purpura (in absence of coagulopathy or thrombocytopenia) and 1 or more of the following criteria must be present:   * Abdominal pain (acute, diffuse, colicky pain) * Arthritis or arthralgia * Biopsy of affected tissue demonstrating predominant immunoglobulin A deposition * Renal involvement (proteinuria >3 grams/24 hr), hematuria or red cell casts | |

\*Classification criteria are developed for use in research and not validated for clinical diagnosis.

†Developed for use in adult and pediatric populations. Adapted from MillsJA, Michel BA, Bloch DA, et al: The American College of Rheumatology 1990 criteria

for classification of Henoch-Schönlein purpura,*Arthritis Rheum*

33:1114–1121, 1990.

\*Patients with fever at least 5 days and <4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities are detected by

2-dimensional echocardiography or angiography.

†In the presence of ≥4 principal criteria, Kawasaki disease diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many patients with Kawasaki disease may establish diagnosis before day 4.

‡See differential diagnosis (Table 166-2).

§Some infants present with thrombocytopenia and disseminated intravascular coagulation.

**Chapter 167** ◆ Vasculitis Syndromes **1215**

|  |  |
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| **Table 166-3** | Treatment of Kawasaki Disease |
| ACUTE STAGE   * Intravenous immunoglobulin 2 g/kg over 10-12 hr   *and*   * Aspirin 80-100 mg/kg/day divided every 6 hr orally until patient is afebrile for at least 48 hr | |
| CONVALESCENT STAGE   * Aspirin 3-5 mg/kg once daily orally until 6-8 wk after illness onset if normal coronary findings throughout course | |
| LONG-TERM THERAPY FOR PATIENTS WITH CORONARY ABNORMALITIES   * Aspirin 3-5 mg/kg once daily orally * Clopidogrel 1 mg/kg/day (maximum: 75 mg/day) * Most experts add warfarin or low-molecular-weight heparin for those patients at particularly high risk of thrombosis | |
| ACUTE CORONARY THROMBOSIS   * Prompt fibrinolytic therapy with tissue plasminogen activator or other thrombolytic agent under supervision of a pediatric cardiologist | |

1. Predominantly Large Vessel Vasculitis
   * Takayasu arteritis
2. Predominantly Medium Vessel Vasculitis
   * Childhood polyarteritis nodosa
   * Cutaneous polyarteritis nodosa
   * Kawasaki disease
3. Predominantly Small Vessel Vasculitis
4. Granulomatous:
   * Granulomatosis with polyangiitis (Wegener granulomatosis)\*
   * Eosinophilic granulomatosis with polyangiitis (Churg- Strauss syndrome)\*
5. Nongranulomatous:
   * Microscopic polyangiitis\*
   * Henoch-Schönlein purpura
   * Isolated cutaneous leukocytoclastic vasculitis
   * Hypocomplementemic urticarial vasculitis

IV. Other Vasculitides

* Behçet disease
* Vasculitis secondary to infection (including hepatitis B–associated polyarteritis nodosa), malignancies, and drugs, including hypersensitivity vasculitis
* Vasculitis associated with connective tissue disease
* Isolated vasculitis of the central nervous system
* Cogan syndrome
* Unclassified

Classification of Childhood Vasculitis

**Table 167-2**

ANCA, Antibodies directed at neutrophil cytoplasmic antigen; BPI, Bactericidal permeability increasing protein. cANCA, cytoplasmic ANCA; pANCA, perinuclear ANCA.

|  |  |
| --- | --- |
| **Table 167-1** | Common Disease Associations with Antibodies to Neutrophil Cytoplasmic Antigens |
| **ANCA FREQUENCY**  **ANTIGEN PATTERN DISEASE ASSOCIATION (%)** | |
| PR3 cANCA Wegener granulomatosis 30 to 90  Churg-Strauss 25 to 50 | |
| MPO pANCA Microscopic polyarteritis 25 to 75  Ulcerative colitis 40 to 80  Sclerosing cholangitis 65 to 85  Crohn disease 10 to 40 | |
| BPI ANCA Cystic fibrosis 80 to 90 | |
| Actin pANCA Autoimmune hepatitis 70 to 75  type 1 | |

*From Cabral D, Benseler S: Granulomatous vasculitis, microscopic polyangiitis and primary angiitis of the central nervous system. In Cassidy JT, Petty RE, Laxer RM, Lindsley CB, editors,* Textbook of pediatric rheumatology*, ed 6, Philadelphia, 2011, Elsevier/Saunders, Table 34-3, p. 526.*

\*Associated with antineutrophil cytoplasmic antibody.

*Adapted from Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria.* Ann Rheum Dis *69:798-806; 2010.*

|  |  |
| --- | --- |
| **Table 167-3** | Features That Suggest a Vasculitic Syndrome |
| CLINICAL FEATURES  Fever, weight loss, fatigue of unknown origin  Skin lesions (palpable purpura, vasculitic urticaria, livedo reticularis, nodules, ulcers)  Neurologic lesions (headache, mononeuritis multiplex, focal central nervous system lesions)  Arthralgia or arthritis, myalgia, or myositis Serositis  Hypertension  Pulmonary infiltrates or hemorrhage | |
| LABORATORY FEATURES  Increased erythrocytes sedimentation rate or C-reactive protein level  Leukocytosis, anemia Eosinophilia  Antineutrophil cytoplasmic antibodies  Elevated factor VIII–related antigen (von Willebrand factor) Cryoglobulins  Circulating immune complexes  Hematuria, proteinuria, elevated serum creatinine | |

*From Cassidy JT, Petty RE:* Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Elsevier/Saunders.*

###### Occiput:

Suboccipital

Angiographic abnormalities (conventional, CT, or magnetic resonance angiography) of the aorta or its main branches and at least one of the following criteria:

* Decreased peripheral artery pulse(s) and/or claudication of extremities
* Blood pressure difference between arms or legs of >10 mm Hg
* Bruits over the aorta and/or its major branches
* Hypertension (defined by childhood normative data)
* Elevated acute phase reactant (erythrocyte sedimentation rate or C-reactive protein)

Proposed Classification Criteria for Pediatric-Onset Takayasu Arteritis

**Table 167-6**

muscle insertions

**Trapezius:** Midpoint of the upper border

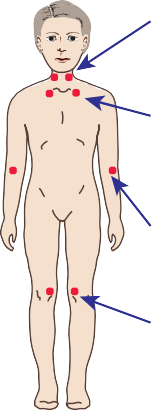
**Supraspinatus:** Above the medial border of the scapular spine

**Gluteal:** Upper outer quadrants of buttocks

###### Greater trochanter:

Posterior to the trochanteric prominence

###### Low cervical:

Anterior aspects

of the intertransverse spaces at C5-C7

**Second rib:** Second costochondral junctions

**Lateral epicondyle:** 2 cm distal to

the epicondyles

###### Knee:

Medial fat pad proximal to the joint line

**Figure 168-1** Fibromyalgia tender points.

**1216 Part XVI** ◆ Rheumatic Diseases of Childhood

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table 167-4** | Clinical and Pathologic Characteristics of Some Vasculitides in Childhood | | | |
| **SYNDROME** | | **FREQUENCY** | **VESSELS AFFECTED** | **CHARACTERISTIC PATHOLOGY** |
| POLYARTERITIS  Polyarteritis nodosa  Kawasaki disease | | Rare  Common | Medium-size and small muscular arteries and sometimes arterioles  Coronary and other muscular arteries | Focal segmental (often near bifurcations); fibrinoid necrosis; gastrointestinal, renal microaneurysms; lesions at various stages of evolution  Thrombosis, fibrosis, aneurysms, especially of coronary vessels |
| LEUKOCYTOCLASTIC VASCULITIS  Henoch-Schönlein purpura Hypersensitivity angitis | | Common Rare | Arterioles and venules, often small arteries and veins  Arterioles and venules | Leukocytoclasis; mixed cells, eosinophils, immunoglobulin A deposits in affected vessels  Leukocytoclastic or lymphocytic, varying eosinophils, occasionally granulomatous; widespread lesions at same stage of evolution |
| GRANULOMATOUS VASCULITIS  Granulomatosis with polyangiitis  Eosinophilic granulomatosis with polyangiitis (Churg- Strauss syndrome) | | Rare Rare | Small arteries and veins, occasionally larger vessels  Small arteries and veins, often arterioles and venules | Upper and lower respiratory tract, necrotizing granulomata glomerulonephritis  Necrotizing extravascular granulomata; lung involvement; eosinophilia |
| GIANT CELL ARTERITIS  Takayasu arteries  Temporal arteritis | | Uncommon Rare | Large arteries  Medium-size and large arteries | Granulomatous inflammation, giant cells; aneurysms, dissection  Granulomatous inflammation, giant cell arteries |

Histopathology showing granulomatous inflammation Upper airway involvement

Laryngeal, tracheal or bronchial involvement ANCA positivity

Renal involvement

Proteinuria, hematuria, red blood cell casts, necrotizing pauci- immune glomerulonephritis

EULAR/PReS Classification Criteria for Pediatric-Onset Granulomatosis with Polyangiitis\*

**Table 167-8**

\*Diagnosis requires 3 of 6 criteria.

\*The presence of all 5 criteria provides 89.6% sensitivity and 99.6% specificity for the diagnosis of childhood onset polyarteritis nodosa.

|  |  |
| --- | --- |
| **Table 167-7** | Proposed Classification Criteria for Pediatric-Onset Polyarteritis Nodosa\* |
| Histopathology Necrotizing vasculitis in medium or small  arteries | |
| Angiographic Angiography showing aneurysm, stenosis, abnormalities or occlusion of a medium or small size  artery not from a noninflammatory cause | |
| Cutaneous findings Livedo reticularis, tender subcutaneous  nodules, superficial skin ulcers, deep skin ulcers, digital necrosis, nail bed infarctions or splinter hemorrhages | |
| Muscle involvement Myalgia or muscle tenderness | |
| Hypertension Systolic or diastolic blood pressure >95th  percentile for height | |
| Peripheral neuropathy Sensory peripheral neuropathy, motor  mononeuritis multiplex | |
| Renal involvement Proteinuria (>300 mg/24 hr equivalent),  hematuria or red blood cell casts, impaired renal function (glomerular filtration rate <50% normal) | |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 167-9** | Differential Diagnostic Features of Small Vessel Vasculitis | | | | |
| **FEATURE** | | **HENOCH-SCHÖNLEIN PURPURA** | **GRANULOMATOSIS WITH POLYANGIITIS** | **CHURG-STRAUSS SYNDROME** | **MICROSCOPIC POLYANGIITIS** |
| Signs and symptoms of small vessel vasculitis\* | | + | + | + | + |
| Immunoglobulin A–dominant immune deposits | | + | – | – | – |
| Circulating antineutrophil cytoplasmic antibodies | | – | + (PR3) | + (MPO > PR3) | + (MPO) |
| Necrotizing vasculitis | | – | + | + | + |
| Granulomatous inflammation | | – | + | + | – |
| Asthma and eosinophilia | | – | – | + | – |

MPO, myeloperoxidase-reactive antibodies; PR3, proteinase 3–reactive antibodies; +, presence; −, absent.

\*Signs and symptoms of small vessel vasculitis include purpura, other rash, arthralgias, arthritis, and constitutional symptoms.

**1226 Part XVI** ◆ Rheumatic Diseases of Childhood

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| --- | --- | --- | --- |
| **Table 168-2** | Common Musculoskeletal Pain Syndromes in Children by Anatomic Region | | |
| **ANATOMICAL REGION** | | **PAIN SYNDROMES** |  |
| Shoulder | | Impingement syndrome |  |
| Elbow | | Little League elbow Avulsion fractures Osteochondritis dissecans | Tennis elbow Panner disease |
| Arm | | Localized hypermobility syndrome Complex regional pain syndrome |  |
| Pelvis and hip | | Avulsion injuries  Legg-Calvé-Perthes syndrome | Slipped capital femoral epiphysis Congenital hip dysplasia |
| Knee | | Osteochondritis dissecans Osgood-Schlatter disease Sinding-Larsen syndrome | Patellofemoral syndrome Malalignment syndromes |
| Leg | | Growing pains  Complex regional pain syndrome Localized hypermobility syndrome | Shin splints Stress fractures  Compartment syndromes |
| Foot | | Plantar fasciitis Tarsal coalition Stress fractures | Achilles tendonitis Juvenile bunion |
| Spine | | Musculoskeletal strain Spondylolisthesis Spondylolysis | Scoliosis  Scheuermann disease (kyphosis) Low back pain |
| Generalized | | Hypermobility syndrome Juvenile fibromyalgia Generalized pain syndrome |  |

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 168-1** | Potential Indicators of Benign Versus Serious Causes of Musculoskeletal Pain | | |
| **CLINICAL FINDING** | | **BENIGN CAUSE OF MUSCULOSKELETAL PAIN** | **SERIOUS CAUSE OF MUSCULOSKELETAL PAIN** |
| Effects of rest versus activity on pain | | Relieved by rest and worsened by activity | Relieved by activity and present at rest |
| Time of day pain occurs | | End of the day and nights | Morning\* |
| Objective joint swelling | | No | Yes |
| Joint characteristics | | Hypermobile/normal | Stiffness, limited range of motion |
| Bony tenderness | | No | Yes |
| Muscle strength | | Normal | Muscle weakness |
| Growth | | Normal growth pattern or weight gain | Poor growth and/or weight loss |
| Constitutional symptoms (e.g., fever, malaise) | | Fatigue without other constitutional symptoms | Yes |
| Lab findings | | Normal CBC, ESR, CRP | Abnormal CBC, raised ESR and CRP |
| Radiographic findings | | Normal | Effusion, osteopenia, radiolucent metaphyseal lines, joint space loss, bony destruction |

CBC, complete blood count; CRP, C-reactive protein level; ESR, erythrocyte sedimentation rate.

\*Cancer pain is often severe and worst at night.

*Adapted from Malleson PN, Beauchamp RD: Diagnosing musculoskeletal pain in children.* CMAJ *165:183–188, 2001.*

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 168-3** | Definition of “Growing Pains” | | |
|  | | **INCLUSIONS** | **EXCLUSIONS** |
| Nature of pain | | Intermittent; some pain-free days and nights, deep aching, cramping | Persistent; increasing intensity, pain during the day |
| Unilateral or bilateral | | Bilateral | Unilateral |
| Location of pain | | Anterior thigh, calf, posterior knee—in muscles | Articular, back, or groin pain |
| Onset of pain | | Late afternoon or evening | Pain still present next morning |
| Physical findings | | Normal | Swelling, erythema, tenderness; local trauma or infection; reduced joint range of motion; limping, fever, weight loss, mass |
| Laboratory findings | | Normal | Objective evidence of abnormalities; increased erythrocyte sedimentation rate, C-reactive protein, abnormal complete blood count, radiography, bone scan or MRI |

# lnfectious Diseases

**1246 Part XVII** ◆ Infectious Diseases

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 172-3** Currently\* Available Vaccines in the United States by Type | | | |
| **PRODUCT** | **TYPE** | **PRODUCT** | **TYPE** |
| Anthrax vaccine adsorbed | Cell-free filtrate of components including protective antigen | Japanese encephalitis vaccine | Inactivated whole virus that is purified |
| Bacille Calmette-Guérin (BCG) vaccine | Live-attenuated mycobacterial strain used to prevent tuberculosis in very limited circumstances | Measles, mumps, rubella (MMR) vaccine | Live-attenuated viruses |
| Measles, mumps, rubella, varicella (MMRV) vaccine | Live-attenuated viruses |
| Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine | Toxoids of diphtheria and tetanus and purified and detoxified components from *Bordetella pertussis* |
| Meningococcal conjugate vaccine against serogroups A, C, W135, and Y (MCV4) | Polysaccharide from each serogroup conjugated to diphtheria toxoid or CRM 197 |
| DTaP–hepatitis B–inactivated polio vaccine (DTaP-HepB-IPV) | DTaP with hepatitis B surface antigen (HBsAg) produced through recombinant techniques in yeast with inactivated whole polioviruses | Meningococcal conjugate vaccine against serogroups C and Y and Hib conjugate vaccine | Polysaccharide from each serogroup conjugated to diphtheria toxoid and Hib polysaccharide conjugated to tetanus toxoid |
| DTaP with IPV and Hib (DTaP-IPV/Hib) | DTaP with inactivated whole polioviruses and Hib polysaccharide conjugated to tetanus toxoid | Meningococcal polysaccharide vaccine against serogroups A, C, W135, and Y (MPSV4) | Polysaccharides from each of the serogroups |
| Pneumococcal conjugate vaccine (13 valent) (PCV13) | Pneumococcal polysaccharides conjugated to a nontoxic form of diphtheria toxin CRM197  Contains 13 serotypes that accounted for >80% of invasive disease in young children prior to vaccine licensure |
| DTaP and inactivated polio vaccine (DTaP-IPV) | DTaP with inactivated whole polioviruses |
| Hib conjugate vaccine (Hib) | Polysaccharide conjugated to either tetanus toxoid or meningococcal group B outer membrane protein |
| Pneumococcal polysaccharide vaccine (23 valent) (PPSV23) | Pneumococcal polysaccharides of 23 serotypes responsible for  85-90% of bacteremic disease in the United States |
| Hepatitis A vaccine (HAV) | Inactivated whole virus |
| Hepatitis A–hepatitis B vaccine (HAV-HBV) | Combined hepatitis A and B vaccine |
| Poliomyelitis (inactivated, enhanced potency) (IPV) | Inactivated whole virus |
| Hepatitis B vaccine (HBV) | HBsAg produced through recombinant techniques in yeast |
| Rabies vaccines (human diploid and purified chick embryo cell) | Inactivated whole virus |
| Hepatitis B–Hib vaccine (Hib-HBV) | Combined hepatitis B–Hib vaccine; the Hib component is polysaccharide conjugated to meningococcal group B outer membrane protein |
| Rotavirus vaccines (RV5 and RV1) | Bovine rotavirus pentavalent vaccine (RV5) live reassortment attenuated virus, and human live-attenuated virus (RV1) |
| Human papillomavirus vaccine (bivalent) (HPV2), (quadrivalent) (HPV4), and 9-valent (HPV9) | The L1 capsid proteins of HPV types 6, 11, 16, and 18 to prevent cervical cancer and genital warts (HPV4) and types 16 and 18 to prevent cervical cancer (HPV2); HPV9 also contains types 31, 33,  45, 52, and 58. |
| Smallpox vaccine | Vaccinia virus, an attenuated poxvirus that provides cross- protection against smallpox |
| Tetanus and diphtheria toxoids, adsorbed (Td, adult use) | Tetanus toxoid plus a reduced quantity of diphtheria toxoid compared to diphtheria toxoid used for children <7 yr of age |
| Influenzavirus vaccine inactivated (IIV) | Available either as trivalent (A/H3N2, A/H1N1, and B) split and purified inactivated vaccines containing the hemagglutinin  (H) and neuraminidase (N) of each type or as quadrivalent preparations (which include representative strains from 2  B-lymphocyte clades in addition to the 2 influenza A strains in trivalent inactivated influenza vaccine) |
| Tetanus and diphtheria toxoids adsorbed plus acellular pertussis (Tdap) vaccine | Tetanus toxoid plus a reduced quantity of diphtheria toxoid plus acellular pertussis vaccine to be used in adolescents and adults and in children 7 through 9 yr  of age who have not been appropriately immunized with DTaP |
| Typhoid vaccine (polysaccharide) | Vi capsular polysaccharide of  *Salmonella typhi* |
| Influenzavirus vaccine live, intranasal (LAIV) | Live-attenuated, temperature- sensitive, cold-adapted trivalent vaccine containing the H and  N genes from the wild strains reassorted to have the 6 other genes from the cold-adapted parent, only available as quadrivalent preparation | Typhoid vaccine (oral) | Live-attenuated Ty21a strain of  *S. typhi* |
| Varicella vaccine | Live-attenuated Oka strain |
| Yellow fever vaccine | Live-attenuated 17D strain |

\*As of January 2015.

*Data from Centers for Disease Control and Prevention: U.S. vaccine names.* [*http://www.cdc.gov/vaccines/about/terms/USvaccines.html*](http://www.cdc.gov/vaccines/about/terms/USvaccines.html)

**1244 Part XVII** ◆ Infectious Diseases

|  |  |
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| **Table 172-2** Immunoglobulin and Animal Antisera Preparations | |
| **PRODUCT** | **MAJOR INDICATIONS** |
| Immunoglobulin for intramuscular injection | Replacement therapy in primary immunodeficiency disorders  Hepatitis A prophylaxis Measles prophylaxis |
| Intravenous immunoglobulin (IVIG) | Replacement therapy in primary immune-deficiency disorders  Kawasaki disease Pediatric HIV infection  Hypogammaglobulinemia in chronic B-lymphocyte lymphocytic leukemia  Immune-mediated thrombocytopenia  Hematopoietic cell transplantation in adults to prevent graft-versus- host disease and infection  May be useful in a variety of other conditions |
| Hepatitis B immunoglobulin (IM) | Postexposure prophylaxis Prevention of perinatal infection in  infants born to hepatitis B surface antigen–positive mothers |
| Rabies immunoglobulin (IM) | Postexposure prophylaxis |
| Tetanus immunoglobulin (IM) | Wound prophylaxis Treatment of tetanus |
| Varicella-zoster immunoglobulin (IM) or IVIG | Postexposure prophylaxis of susceptible people at high risk for complications from varicella |
| Cytomegalovirus IVIG | Prophylaxis of disease in seronegative transplant recipients |
| Subcutaneous immunoglobulin Treatment of patients with primary  immunodeficiencies | |
| Vaccinia immunoglobulin (IV) | Prevent or modify serious adverse events following smallpox vaccination caused by vaccinia replication |
| Botulism IVIG human | Treatment of infant botulism |
| Diphtheria antitoxin, equine | Treatment of diphtheria |
| Heptavalent botulinum antitoxin against all 7 (A-G) botulinum toxin types | Treatment of food and wound botulism |
| Palivizumab (monoclonal antibody) (IM) | Prophylaxis for infants against respiratory syncytial virus (see Chapter 260) |



**Chapter 172** ◆ Immunization Practices **1251**

**Figure 172-2 Recommended immunization schedule for persons aged 0 through 18 years – United States, 2015. (FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE [FIGURE 172-3]).**

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 172-2. To determine minimum intervals between doses, see the catch-up schedule (Figure 172-3). School entry and adolescent vaccine age groups are shaded.



Vaccine

Birth

1 mo

2 mos

4 mos

6 mos

9 mos

12 mos 15 mos 18 mos

19–23

mos

2-3 yrs

4-6 yrs 7-10 yrs 11-12 yrs 13–15 yrs 16–18 yrs

Hepatitis B*1* (HepB)

1st dose

2nd dose

3rd dose

Rotavirus*2* (RV) RV1 (2-dose series); RV5 (3-dose series)

Diphtheria, tetanus, & acellular pertussis*3* (DTaP: <7 yrs)

Tetanus, diphtheria, & acellular pertussis*4* (Tdap: >7 yrs)

*Haemophilus influenzae* type b*5* (Hib)

Pneumococcal conjugate*6* (PCV13)

Pneumococcal polysaccharide*6* (PPSV23)

Inactivated poliovirus*7* (IPV: <18 yrs)

Influenza*8* (IIV; LAIV) 2 doses for some: See footnote 8

1st dose 2nd dose

See footnote 2

1st dose 2nd dose 3rd dose

4th dose

5th dose

(Tdap)

1st dose 2nd dose

See footnote 5

3rd or 4th dose, See footnote 5

1st dose 2nd dose 3rd dose

4th dose

1st dose 2nd dose

3rd dose

4th dose

Annual vaccination (IIV only) 1 or 2 doses

Annual vaccination (LAIV or IIV) 1 or 2 doses

Annual vaccination (LAIV or IIV) 1 dose only

Measles, mumps, rubella*9* (MMR)

See footnote 9

1st dose

2nd dose

Varicella*10* (VAR)

1st dose

2nd dose

Hepatitis A*11* (HepA)

Human papillomavirus*12* (HPV2: females only; HPV4: males and females)

Meningococcal*13* (Hib-MenCY

> 6 weeks; MenACWY-D >9 mos; MenACWY-CRM ≥ 2 mos)

2-dose series, See footnote 11

(3-dose series)

See footnote 13

1st dose

Booster

Range of recommended ages for all children

Range of recommended ages for catch-up immunization

Range of recommended ages for certain high-risk groups

Range of recommended ages during which catch-up is encouraged and for certain high-risk groups

Not routinely recommended

This schedule includes recommendations in effect as of January 1, 2015. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at [http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.](http://www.cdc.gov/vaccines/hcp/acip-recs/index.html) Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online ([http://www.vaers.hhs.gov)](http://www.vaers.hhs.gov/) or by telephone (800-822-7967). Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (<http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm)> or by telephone (800-CDC-INFO [800-232-4636]).

This schedule is approved by the Advisory Committee on Immunization Practices (http//[www.cdc.gov/vaccines/acip),](http://www.cdc.gov/vaccines/acip)) the American Academy of Pediatrics ([http://www.aap.org),](http://www.aap.org/) the American Academy of Family Physicians ([http://www.aafp.org),](http://www.aafp.org/) and the American College of Obstetricians and Gynecologists ([http://www.acog.org).](http://www.acog.org/)

**NOTE: The above recommendations must be read along with the footnotes of this schedule.**

## Footnotes — Recommended immunization schedule for persons aged 0 through 18 years—United States, 2015

For further guidance on the use of the vaccines mentioned below, see: [http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.](http://www.cdc.gov/vaccines/hcp/acip-recs/index.html) For vaccine recommendations for persons 19 years of age and older, see the Adult Immunization Schedule.

**Additional information**

* For contraindications and precautions to use of a vaccine and for additional information regarding that vaccine, vaccination providers should consult the relevant ACIP statement available online at [http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.](http://www.cdc.gov/vaccines/hcp/acip-recs/index.html)
* For purposes of calculating intervals between doses, 4 weeks = 28 days. Intervals of 4 months or greater are determined by calendar months.
* Vaccine doses administered 4 days or less before the minimum interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum interval or minimum age should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see *MMWR, General Recommendations on Immunization and Reports* / Vol. 60 / No. 2; Table 1. *Recommended and minimum ages and intervals between vaccine doses* available online at [http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.](http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf)
* Information on travel vaccine requirements and recommendations is available at [http://wwwnc.cdc.gov/travel/destinations/list.](http://wwwnc.cdc.gov/travel/destinations/list)
* For vaccination of persons with primary and secondary immunodeficiencies, see Table 13, *“Vaccination of persons with primary and secondary immunodeficiencies,”* in *General Recommendations on Immunization* (ACIP), available at [http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.;](http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.%3B) and American Academy of Pediatrics. “Immunization in Special Clinical Circumstances,” in Pickering LK, Baker CJ, Kimberlin DW, Long SS eds. *Red Book: 2012 report of the Committee on Infectious Diseases. 29th ed.* Elk Grove Village, IL: American Academy of Pediatrics.

1. **Hepatitis B (HepB) vaccine. (Minimum age: birth)**

**Routine vaccination:**

**At birth:**

* + Administer monovalent HepB vaccine to all newborns before hospital discharge.
  + For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer HepB vaccine and

0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of the HepB series at age 9 through 18 months (preferably at the next well-child visit).

* + If mother’s HBsAg status is unknown, within 12 hours of birth administer HepB vaccine regardless of birth weight. For infants weighing less than 2,000 grams, administer HBIG in addition to HepB vaccine within 12 hours of birth. Determine mother’s HBsAg status as soon as possible and, if mother is HBsAg-positive, also administer HBIG for infants weighing 2,000 grams or more as soon as possible, but no later than age 7 days.

**Doses following the birth dose:**

* + The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
  + Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months starting as soon as feasible. See Figure 2.
  + Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks), administer the third dose at least 8 weeks after the second dose AND at least 16 weeks after the **first** dose. The final (third or fourth) dose in the HepB vaccine series should be administered **no earlier than age 24 weeks**.
  + Administration of a total of 4 doses of HepB vaccine is permitted when a combination vaccine containing HepB is administered after the birth dose.

**Catch-up vaccination:**

* + Unvaccinated persons should complete a 3-dose series.
  + A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
  + For other catch-up guidance, see Figure 172-3.

1. **Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV1 [Rotarix] and RV5 [RotaTeq])**

**Routine vaccination:**

Administer a series of RV vaccine to all infants as follows:

1. If Rotarix is used, administer a 2-dose series at 2 and 4 months of age.
2. If RotaTeq is used, administer a 3-dose series at ages 2, 4, and 6 months.
3. If any dose in the series was RotaTeq or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

**Catch-up vaccination:**

* The maximum age for the first dose in the series is 14 weeks, 6 days; vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
* The maximum age for the final dose in the series is 8 months, 0 days.
* For other catch-up guidance, see Figure 172-3.

1. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: 6 weeks. Exception: DTaP-IPV [Kinrix]: 4 years)**

**Routine vaccination:**

* + Administer a 5-dose series of DTaP vaccine at ages 2, 4, 6, 15 through 18 months, and 4 through 6 years. The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose. However, the fourth dose of DTaP need not be repeated if it was administered at least 4 months after the third dose of DTaP.

**Figure 172-2** Recommended immunization schedule for persons aged 0 through 18 yr—United States, 2015. *(From Centers for Disease Control and Prevention. Available at:* [*http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html)*](http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html))

##### Continued

**1252 Part XVII** ◆ Infectious Diseases

1. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine (cont’d)**

**Catch-up vaccination:**

* + The fifth dose of DTaP vaccine is not necessary if the fourth dose was administered at age 4 years or older.
  + For other catch-up guidance, see Figure 172-3.

1. **Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine. (Minimum age: 10 years for both Boostrix and Adacel)**

**Routine vaccination:**

* + Administer 1 dose of Tdap vaccine to all adolescents aged 11 through 12 years.
  + Tdap may be administered regardless of the interval since the last tetanus and diphtheria toxoid- containing vaccine.
  + Administer 1 dose of Tdap vaccine to pregnant adolescents during each pregnancy (preferred during 27 through 36 weeks’ gestation) regardless of time since prior Td or Tdap vaccination.

**Catch-up vaccination:**

* + Persons aged 7 years and older who are not fully immunized with DTaP vaccine should receive Tdap vaccine as 1 dose (preferably the first) in the catch-up series; if additional doses are needed, use Td vaccine. For children 7 through 10 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap vaccine dose at age 11 through 12 years should NOT be administered. Td should be administered instead 10 years after the Tdap dose.
  + Persons aged 11 through 18 years who have not received Tdap vaccine should receive a dose followed by tetanus and diphtheria toxoid (Td) booster doses every 10 years thereafter.
  + Inadvertent doses of DTaP vaccine:
    - If administered inadvertently to a child aged 7 through 10 years may count as part of the catch-up series. This dose may count as the adolescent Tdap dose, or the child can later receive a Tdap booster dose at age 11 through 12 years.
    - If administered inadvertently to an adolescent aged 11 through 18 years, the dose should be counted as the adolescent Tdap booster.
  + For other catch-up guidance, see Figure 172-3.

1. ***Haemophilus influenzae* type b (Hib) conjugate vaccine. (Minimum age: 6 weeks for PRP-T [ACTHIB, DTaP-IPV/Hib (Pentacel) and Hib-MenCY (MenHibrix)], PRP-OMP [PedvaxHIB or COMVAX], 12 months for PRP-T [Hiberix])**

**Routine vaccination:**

* + Administer a 2- or 3-dose Hib vaccine primary series and a booster dose (dose 3 or 4 depending on vaccine used in primary series) at age 12 through 15 months to complete a full Hib vaccine series.
  + The primary series with ActHIB, MenHibrix, or Pentacel consists of 3 doses and should be administered at 2, 4, and 6 months of age. The primary series with PedvaxHib or COMVAX consists of 2 doses and should be administered at 2 and 4 months of age; a dose at age 6 months is not indicated.
  + One booster dose (dose 3 or 4 depending on vaccine used in primary series) of any Hib vaccine should be administered at age 12 through 15 months. An exception is Hiberix vaccine. Hiberix should only be used for the booster (final) dose in children aged 12 months through 4 years who have received at least 1 prior dose of Hib-containing vaccine.
  + For recommendations on the use of MenHibrix in patients at increased risk for meningococcal disease, please refer to the meningococcal vaccine footnotes and also to *MMWR* February 28, 2014 / 63(RR01);1- 13, available at [http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.](http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf)

**Catch-up vaccination:**

* + If dose 1 was administered at ages 12 through 14 months, administer a second (final) dose at least 8 weeks after dose 1, regardless of Hib vaccine used in the primary series.
  + If both doses were PRP-OMP (PedvaxHIB or COMVAX), and were administered before the first birthday, the third (and final) dose should be administered at age 12 through 59 months and at least 8 weeks after the second dose.
  + If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a third (and final) dose at age 12 through 15 months or 8 weeks after second dose, whichever is later.
  + If first dose is administered before the first birthday and second dose administered at younger than 15 months, a third (and final) dose should be given 8 weeks later.
  + For unvaccinated children aged 15 months or older, administer only 1 dose.
  + For other catch-up guidance, see Figure 172-3. For catch-up guidance related to MenHibrix, please see the meningococcal vaccine footnotes and also *MMWR* February 28, 2014 / 63(RR01);1-13, available at [http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.](http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf)

**Vaccination of persons with high-risk conditions:**

* + Children aged 12 through 59 months who are at increased risk for Hib disease, including chemotherapy recipients and those with anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV ) infection, immunoglobulin deficiency, or early component complement deficiency, who have received either no doses or only 1 dose of Hib vaccine before 12 months of age, should receive 2 additional doses of Hib vaccine 8 weeks apart; children who received 2 or more doses of Hib vaccine before 12 months of age should receive 1 additional dose.
  + For patients younger than 5 years of age undergoing chemotherapy or radiation treatment who received a Hib vaccine dose(s) within 14 days of starting therapy or during therapy, repeat the dose(s) at least 3 months following therapy completion.
  + Recipients of hematopoietic stem cell transplant (HSCT) should be revaccinated with a 3-dose regimen of Hib vaccine starting 6 to 12 months after successful transplant, regardless of vaccination history; doses should be administered at least 4 weeks apart.
  + A single dose of any Hib-containing vaccine should be administered to unimmunized\* children and adolescents 15 months of age and older undergoing an elective splenectomy; if possible, vaccine should be administered at least 14 days before procedure.
  + Hib vaccine is not routinely recommended for patients 5 years or older. However, 1 dose of Hib vaccine should be administered to unimmunized\* persons aged 5 years or older who have anatomic or functional asplenia (including sickle cell disease) and unvaccinated persons 5 through 18 years of age with human immunodeficiency virus (HIV) infection.

*\* Patients who have not received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months of age are considered unimmunized.*

1. **Pneumococcal vaccines. (Minimum age: 6 weeks for PCV13, 2 years for PPSV23)**

**Routine vaccination with PCV13:**

* + Administer a 4-dose series of PCV13 vaccine at ages 2, 4, and 6 months and at age 12 through 15 months.
  + For children aged 14 through 59 months who have received an age-appropriate series of 7-valent PCV (PCV7), administer a single supplemental dose of 13-valent PCV (PCV13).

**Catch-up vaccination with PCV13:**

* + Administer 1 dose of PCV13 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
  + For other catch-up guidance, see Figure 172-3.

**Vaccination of persons with high-risk conditions with PCV13 and PPSV23:**

* + All recommended PCV13 doses should be administered prior to PPSV23 vaccination if possible.
  + For children 2 through 5 years of age with any of the following conditions: chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin’s disease; solid organ transplantation; or congenital immunodeficiency:

1. Administer 1 dose of PCV13 if any incomplete schedule of 3 doses of PCV (PCV7 and/or PCV13) were received previously.
2. Administer 2 doses of PCV13 at least 8 weeks apart if unvaccinated or any incomplete schedule of fewer than 3 doses of PCV (PCV7 and/or PCV13) were received previously.
3. Administer 1 supplemental dose of PCV13 if 4 doses of PCV7 or other age-appropriate complete PCV7 series was received previously.
4. The minimum interval between doses of PCV (PCV7 or PCV13) is 8 weeks.
5. For children with no history of PPSV23 vaccination, administer PPSV23 at least 8 weeks after the most recent dose of PCV13.
   * For children aged 6 through 18 years who have cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms,

leukemias, lymphomas, and Hodgkin’s disease; generalized malignancy; solid organ transplantation; or multiple myeloma:

1. If neither PCV13 nor PPSV23 has been received previously, administer 1 dose of PCV13 now and 1 dose of PPSV23 at least 8 weeks later.
2. If PCV13 has been received previously but PPSV23 has not, administer 1 dose of PPSV23 at least 8 weeks after the most recent dose of PCV13.
3. If PPSV23 has been received but PCV13 has not, administer 1 dose of PCV13 at least 8 weeks after the most recent dose of PPSV23.
   * For children aged 6 through 18 years with chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), diabetes mellitus, alcoholism, or chronic liver disease, who have not received PPSV23, administer 1 dose of PPSV23. If PCV13 has been received previously, then PPSV23 should be administered at least 8 weeks after any prior PCV13 dose.
   * A single revaccination with PPSV23 should be administered 5 years after the first dose to children with sickle cell disease or other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated

with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin’s disease; generalized malignancy; solid organ transplantation; or multiple myeloma.

1. **Inactivated poliovirus vaccine (IPV). (Minimum age: 6 weeks)**

**Routine vaccination:**

* + Administer a 4-dose series of IPV at ages 2, 4, 6 through 18 months, and 4 through 6 years. The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.

**Catch-up vaccination:**

* + In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk of imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).
  + If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years and at least 6 months after the previous dose.
  + A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.
  + If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child’s current age. IPV is not routinely recommended for U.S. residents aged 18 years or older.
  + For other catch-up guidance, see Figure 172-3.

1. **Influenza vaccines. (Minimum age: 6 months for inactivated influenza vaccine [IIV], 2 years for live, attenuated influenza vaccine [LAIV])**

**Routine vaccination:**

* + Administer influenza vaccine annually to all children beginning at age 6 months. For most healthy, nonpregnant persons aged 2 through 49 years, either LAIV or IIV may be used. However, LAIV should NOT be administered to some persons, including 1) persons who have experienced severe allergic reactions to LAIV, any of its components, or to a previous dose of any other influenza vaccine; 2) children 2 through 17 years receiving aspirin or aspirin-containing products; 3) persons who are allergic to eggs; 4) pregnant women; 5) immunosuppressed persons; 6) children 2 through 4 years of age with asthma or who had wheezing in the past 12 months; or 7) persons who have taken influenza antiviral medications in the previous 48 hours. For all other contraindications and precautions to use of LAIV, see *MMWR* August 15, 2014 / 63(32);691-697 [40 pages] available at

[http://www.cdc.gov/mmwr/pdf/wk/mm6332.pdf.](http://www.cdc.gov/mmwr/pdf/wk/mm6332.pdf)

### Figure 172-2, cont’d



**Chapter 172** ◆ Immunization Practices **1251**

**Figure 172-2 Recommended immunization schedule for persons aged 0 through 18 years – United States, 2015. (FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE [FIGURE 172-3]).**

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 172-2. To determine minimum intervals between doses, see the catch-up schedule (Figure 172-3). School entry and adolescent vaccine age groups are shaded.



Vaccine

Birth

1 mo

2 mos

4 mos

6 mos

9 mos

12 mos 15 mos 18 mos

19–23

mos

2-3 yrs

4-6 yrs 7-10 yrs 11-12 yrs 13–15 yrs 16–18 yrs

Hepatitis B*1* (HepB)

1st dose

2nd dose

3rd dose

Rotavirus*2* (RV) RV1 (2-dose series); RV5 (3-dose series)

Diphtheria, tetanus, & acellular pertussis*3* (DTaP: <7 yrs)

Tetanus, diphtheria, & acellular pertussis*4* (Tdap: >7 yrs)

*Haemophilus influenzae* type b*5* (Hib)

Pneumococcal conjugate*6* (PCV13)

Pneumococcal polysaccharide*6* (PPSV23)

Inactivated poliovirus*7* (IPV: <18 yrs)

Influenza*8* (IIV; LAIV) 2 doses for some: See footnote 8

1st dose 2nd dose

See footnote 2

1st dose 2nd dose 3rd dose

4th dose

5th dose

(Tdap)

1st dose 2nd dose

See footnote 5

3rd or 4th dose, See footnote 5

1st dose 2nd dose 3rd dose

4th dose

1st dose 2nd dose

3rd dose

4th dose

Annual vaccination (IIV only) 1 or 2 doses

Annual vaccination (LAIV or IIV) 1 or 2 doses

Annual vaccination (LAIV or IIV) 1 dose only

Measles, mumps, rubella*9* (MMR)

See footnote 9

1st dose

2nd dose

Varicella*10* (VAR)

1st dose

2nd dose

Hepatitis A*11* (HepA)

Human papillomavirus*12* (HPV2: females only; HPV4: males and females)

Meningococcal*13* (Hib-MenCY

> 6 weeks; MenACWY-D >9 mos; MenACWY-CRM ≥ 2 mos)

2-dose series, See footnote 11

(3-dose series)

See footnote 13

1st dose

Booster

Range of recommended ages for all children

Range of recommended ages for catch-up immunization

Range of recommended ages for certain high-risk groups

Range of recommended ages during which catch-up is encouraged and for certain high-risk groups

Not routinely recommended

This schedule includes recommendations in effect as of January 1, 2015. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at [http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.](http://www.cdc.gov/vaccines/hcp/acip-recs/index.html) Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online ([http://www.vaers.hhs.gov)](http://www.vaers.hhs.gov/) or by telephone (800-822-7967). Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (<http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm)> or by telephone (800-CDC-INFO [800-232-4636]).

This schedule is approved by the Advisory Committee on Immunization Practices (http//[www.cdc.gov/vaccines/acip),](http://www.cdc.gov/vaccines/acip)) the American Academy of Pediatrics ([http://www.aap.org),](http://www.aap.org/) the American Academy of Family Physicians ([http://www.aafp.org),](http://www.aafp.org/) and the American College of Obstetricians and Gynecologists ([http://www.acog.org).](http://www.acog.org/)

**NOTE: The above recommendations must be read along with the footnotes of this schedule.**

## Footnotes — Recommended immunization schedule for persons aged 0 through 18 years—United States, 2015

For further guidance on the use of the vaccines mentioned below, see: [http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.](http://www.cdc.gov/vaccines/hcp/acip-recs/index.html) For vaccine recommendations for persons 19 years of age and older, see the Adult Immunization Schedule.

**Additional information**

* For contraindications and precautions to use of a vaccine and for additional information regarding that vaccine, vaccination providers should consult the relevant ACIP statement available online at [http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.](http://www.cdc.gov/vaccines/hcp/acip-recs/index.html)
* For purposes of calculating intervals between doses, 4 weeks = 28 days. Intervals of 4 months or greater are determined by calendar months.
* Vaccine doses administered 4 days or less before the minimum interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum interval or minimum age should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see *MMWR, General Recommendations on Immunization and Reports* / Vol. 60 / No. 2; Table 1. *Recommended and minimum ages and intervals between vaccine doses* available online at [http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.](http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf)
* Information on travel vaccine requirements and recommendations is available at [http://wwwnc.cdc.gov/travel/destinations/list.](http://wwwnc.cdc.gov/travel/destinations/list)
* For vaccination of persons with primary and secondary immunodeficiencies, see Table 13, *“Vaccination of persons with primary and secondary immunodeficiencies,”* in *General Recommendations on Immunization* (ACIP), available at [http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.;](http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.%3B) and American Academy of Pediatrics. “Immunization in Special Clinical Circumstances,” in Pickering LK, Baker CJ, Kimberlin DW, Long SS eds. *Red Book: 2012 report of the Committee on Infectious Diseases. 29th ed.* Elk Grove Village, IL: American Academy of Pediatrics.

1. **Hepatitis B (HepB) vaccine. (Minimum age: birth)**

**Routine vaccination:**

**At birth:**

* + Administer monovalent HepB vaccine to all newborns before hospital discharge.
  + For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer HepB vaccine and

0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of the HepB series at age 9 through 18 months (preferably at the next well-child visit).

* + If mother’s HBsAg status is unknown, within 12 hours of birth administer HepB vaccine regardless of birth weight. For infants weighing less than 2,000 grams, administer HBIG in addition to HepB vaccine within 12 hours of birth. Determine mother’s HBsAg status as soon as possible and, if mother is HBsAg-positive, also administer HBIG for infants weighing 2,000 grams or more as soon as possible, but no later than age 7 days.

**Doses following the birth dose:**

* + The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
  + Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months starting as soon as feasible. See Figure 2.
  + Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks), administer the third dose at least 8 weeks after the second dose AND at least 16 weeks after the **first** dose. The final (third or fourth) dose in the HepB vaccine series should be administered **no earlier than age 24 weeks**.
  + Administration of a total of 4 doses of HepB vaccine is permitted when a combination vaccine containing HepB is administered after the birth dose.

**Catch-up vaccination:**

* + Unvaccinated persons should complete a 3-dose series.
  + A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
  + For other catch-up guidance, see Figure 172-3.

1. **Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV1 [Rotarix] and RV5 [RotaTeq])**

**Routine vaccination:**

Administer a series of RV vaccine to all infants as follows:

1. If Rotarix is used, administer a 2-dose series at 2 and 4 months of age.
2. If RotaTeq is used, administer a 3-dose series at ages 2, 4, and 6 months.
3. If any dose in the series was RotaTeq or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

**Catch-up vaccination:**

* The maximum age for the first dose in the series is 14 weeks, 6 days; vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
* The maximum age for the final dose in the series is 8 months, 0 days.
* For other catch-up guidance, see Figure 172-3.

1. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: 6 weeks. Exception: DTaP-IPV [Kinrix]: 4 years)**

**Routine vaccination:**

* + Administer a 5-dose series of DTaP vaccine at ages 2, 4, 6, 15 through 18 months, and 4 through 6 years. The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose. However, the fourth dose of DTaP need not be repeated if it was administered at least 4 months after the third dose of DTaP.

**Figure 172-2** Recommended immunization schedule for persons aged 0 through 18 yr—United States, 2015. *(From Centers for Disease Control and Prevention. Available at:* [*http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html)*](http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html))

##### Continued

**1252 Part XVII** ◆ Infectious Diseases

1. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine (cont’d)**

**Catch-up vaccination:**

* + The fifth dose of DTaP vaccine is not necessary if the fourth dose was administered at age 4 years or older.
  + For other catch-up guidance, see Figure 172-3.

1. **Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine. (Minimum age: 10 years for both Boostrix and Adacel)**

**Routine vaccination:**

* + Administer 1 dose of Tdap vaccine to all adolescents aged 11 through 12 years.
  + Tdap may be administered regardless of the interval since the last tetanus and diphtheria toxoid- containing vaccine.
  + Administer 1 dose of Tdap vaccine to pregnant adolescents during each pregnancy (preferred during 27 through 36 weeks’ gestation) regardless of time since prior Td or Tdap vaccination.

**Catch-up vaccination:**

* + Persons aged 7 years and older who are not fully immunized with DTaP vaccine should receive Tdap vaccine as 1 dose (preferably the first) in the catch-up series; if additional doses are needed, use Td vaccine. For children 7 through 10 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap vaccine dose at age 11 through 12 years should NOT be administered. Td should be administered instead 10 years after the Tdap dose.
  + Persons aged 11 through 18 years who have not received Tdap vaccine should receive a dose followed by tetanus and diphtheria toxoid (Td) booster doses every 10 years thereafter.
  + Inadvertent doses of DTaP vaccine:
    - If administered inadvertently to a child aged 7 through 10 years may count as part of the catch-up series. This dose may count as the adolescent Tdap dose, or the child can later receive a Tdap booster dose at age 11 through 12 years.
    - If administered inadvertently to an adolescent aged 11 through 18 years, the dose should be counted as the adolescent Tdap booster.
  + For other catch-up guidance, see Figure 172-3.

1. ***Haemophilus influenzae* type b (Hib) conjugate vaccine. (Minimum age: 6 weeks for PRP-T [ACTHIB, DTaP-IPV/Hib (Pentacel) and Hib-MenCY (MenHibrix)], PRP-OMP [PedvaxHIB or COMVAX], 12 months for PRP-T [Hiberix])**

**Routine vaccination:**

* + Administer a 2- or 3-dose Hib vaccine primary series and a booster dose (dose 3 or 4 depending on vaccine used in primary series) at age 12 through 15 months to complete a full Hib vaccine series.
  + The primary series with ActHIB, MenHibrix, or Pentacel consists of 3 doses and should be administered at 2, 4, and 6 months of age. The primary series with PedvaxHib or COMVAX consists of 2 doses and should be administered at 2 and 4 months of age; a dose at age 6 months is not indicated.
  + One booster dose (dose 3 or 4 depending on vaccine used in primary series) of any Hib vaccine should be administered at age 12 through 15 months. An exception is Hiberix vaccine. Hiberix should only be used for the booster (final) dose in children aged 12 months through 4 years who have received at least 1 prior dose of Hib-containing vaccine.
  + For recommendations on the use of MenHibrix in patients at increased risk for meningococcal disease, please refer to the meningococcal vaccine footnotes and also to *MMWR* February 28, 2014 / 63(RR01);1- 13, available at [http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.](http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf)

**Catch-up vaccination:**

* + If dose 1 was administered at ages 12 through 14 months, administer a second (final) dose at least 8 weeks after dose 1, regardless of Hib vaccine used in the primary series.
  + If both doses were PRP-OMP (PedvaxHIB or COMVAX), and were administered before the first birthday, the third (and final) dose should be administered at age 12 through 59 months and at least 8 weeks after the second dose.
  + If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a third (and final) dose at age 12 through 15 months or 8 weeks after second dose, whichever is later.
  + If first dose is administered before the first birthday and second dose administered at younger than 15 months, a third (and final) dose should be given 8 weeks later.
  + For unvaccinated children aged 15 months or older, administer only 1 dose.
  + For other catch-up guidance, see Figure 172-3. For catch-up guidance related to MenHibrix, please see the meningococcal vaccine footnotes and also *MMWR* February 28, 2014 / 63(RR01);1-13, available at [http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.](http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf)

**Vaccination of persons with high-risk conditions:**

* + Children aged 12 through 59 months who are at increased risk for Hib disease, including chemotherapy recipients and those with anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV ) infection, immunoglobulin deficiency, or early component complement deficiency, who have received either no doses or only 1 dose of Hib vaccine before 12 months of age, should receive 2 additional doses of Hib vaccine 8 weeks apart; children who received 2 or more doses of Hib vaccine before 12 months of age should receive 1 additional dose.
  + For patients younger than 5 years of age undergoing chemotherapy or radiation treatment who received a Hib vaccine dose(s) within 14 days of starting therapy or during therapy, repeat the dose(s) at least 3 months following therapy completion.
  + Recipients of hematopoietic stem cell transplant (HSCT) should be revaccinated with a 3-dose regimen of Hib vaccine starting 6 to 12 months after successful transplant, regardless of vaccination history; doses should be administered at least 4 weeks apart.
  + A single dose of any Hib-containing vaccine should be administered to unimmunized\* children and adolescents 15 months of age and older undergoing an elective splenectomy; if possible, vaccine should be administered at least 14 days before procedure.
  + Hib vaccine is not routinely recommended for patients 5 years or older. However, 1 dose of Hib vaccine should be administered to unimmunized\* persons aged 5 years or older who have anatomic or functional asplenia (including sickle cell disease) and unvaccinated persons 5 through 18 years of age with human immunodeficiency virus (HIV) infection.

*\* Patients who have not received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months of age are considered unimmunized.*

1. **Pneumococcal vaccines. (Minimum age: 6 weeks for PCV13, 2 years for PPSV23)**

**Routine vaccination with PCV13:**

* + Administer a 4-dose series of PCV13 vaccine at ages 2, 4, and 6 months and at age 12 through 15 months.
  + For children aged 14 through 59 months who have received an age-appropriate series of 7-valent PCV (PCV7), administer a single supplemental dose of 13-valent PCV (PCV13).

**Catch-up vaccination with PCV13:**

* + Administer 1 dose of PCV13 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
  + For other catch-up guidance, see Figure 172-3.

**Vaccination of persons with high-risk conditions with PCV13 and PPSV23:**

* + All recommended PCV13 doses should be administered prior to PPSV23 vaccination if possible.
  + For children 2 through 5 years of age with any of the following conditions: chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin’s disease; solid organ transplantation; or congenital immunodeficiency:

1. Administer 1 dose of PCV13 if any incomplete schedule of 3 doses of PCV (PCV7 and/or PCV13) were received previously.
2. Administer 2 doses of PCV13 at least 8 weeks apart if unvaccinated or any incomplete schedule of fewer than 3 doses of PCV (PCV7 and/or PCV13) were received previously.
3. Administer 1 supplemental dose of PCV13 if 4 doses of PCV7 or other age-appropriate complete PCV7 series was received previously.
4. The minimum interval between doses of PCV (PCV7 or PCV13) is 8 weeks.
5. For children with no history of PPSV23 vaccination, administer PPSV23 at least 8 weeks after the most recent dose of PCV13.
   * For children aged 6 through 18 years who have cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms,

leukemias, lymphomas, and Hodgkin’s disease; generalized malignancy; solid organ transplantation; or multiple myeloma:

1. If neither PCV13 nor PPSV23 has been received previously, administer 1 dose of PCV13 now and 1 dose of PPSV23 at least 8 weeks later.
2. If PCV13 has been received previously but PPSV23 has not, administer 1 dose of PPSV23 at least 8 weeks after the most recent dose of PCV13.
3. If PPSV23 has been received but PCV13 has not, administer 1 dose of PCV13 at least 8 weeks after the most recent dose of PPSV23.
   * For children aged 6 through 18 years with chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), diabetes mellitus, alcoholism, or chronic liver disease, who have not received PPSV23, administer 1 dose of PPSV23. If PCV13 has been received previously, then PPSV23 should be administered at least 8 weeks after any prior PCV13 dose.
   * A single revaccination with PPSV23 should be administered 5 years after the first dose to children with sickle cell disease or other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated

with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin’s disease; generalized malignancy; solid organ transplantation; or multiple myeloma.

1. **Inactivated poliovirus vaccine (IPV). (Minimum age: 6 weeks)**

**Routine vaccination:**

* + Administer a 4-dose series of IPV at ages 2, 4, 6 through 18 months, and 4 through 6 years. The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.

**Catch-up vaccination:**

* + In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk of imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).
  + If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years and at least 6 months after the previous dose.
  + A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.
  + If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child’s current age. IPV is not routinely recommended for U.S. residents aged 18 years or older.
  + For other catch-up guidance, see Figure 172-3.

1. **Influenza vaccines. (Minimum age: 6 months for inactivated influenza vaccine [IIV], 2 years for live, attenuated influenza vaccine [LAIV])**

**Routine vaccination:**

* + Administer influenza vaccine annually to all children beginning at age 6 months. For most healthy, nonpregnant persons aged 2 through 49 years, either LAIV or IIV may be used. However, LAIV should NOT be administered to some persons, including 1) persons who have experienced severe allergic reactions to LAIV, any of its components, or to a previous dose of any other influenza vaccine; 2) children 2 through 17 years receiving aspirin or aspirin-containing products; 3) persons who are allergic to eggs; 4) pregnant women; 5) immunosuppressed persons; 6) children 2 through 4 years of age with asthma or who had wheezing in the past 12 months; or 7) persons who have taken influenza antiviral medications in the previous 48 hours. For all other contraindications and precautions to use of LAIV, see *MMWR* August 15, 2014 / 63(32);691-697 [40 pages] available at

[http://www.cdc.gov/mmwr/pdf/wk/mm6332.pdf.](http://www.cdc.gov/mmwr/pdf/wk/mm6332.pdf)

### Figure 172-2, cont’d

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1. **Influenza vaccines (cont’d)**

**For children aged 6 months through 8 years:**

* + For the 2014-15 season, administer 2 doses (separated by at least 4 weeks) to children who are receiving influenza vaccine for the first time. Some children in this age group who have been vaccinated previously will also need 2 doses. For additional guidance, follow dosing guidelines in the 2014-15 ACIP influenza vaccine recommendations, *MMWR* August 15, 2014 / 63(32);691-697 [40 pages] available at [http://www.](http://www/) cdc.gov/mmwr/pdf/wk/mm6332.pdf.
  + For the 2015–16 season, follow dosing guidelines in the 2015 ACIP influenza vaccine recommendations.

**For persons aged 9 years and older:**

* + Administer 1 dose.

1. **Measles, mumps, and rubella (MMR) vaccine. (Minimum age: 12 months for routine vaccination)**

**Routine vaccination:**

* + Administer a 2-dose series of MMR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
  + Administer 1 dose of MMR vaccine to infants aged 6 through 11 months before departure from the United States for international travel. These children should be revaccinated with 2 doses of MMR vaccine, the first at age 12 through 15 months (12 months if the child remains in an area where disease risk is high), and the second dose at least 4 weeks later.
  + Administer 2 doses of MMR vaccine to children aged 12 months and older before departure from the United States for international travel. The first dose should be administered on or after age 12 months and the second dose at least 4 weeks later.

**Catch-up vaccination:**

* + Ensure that all school-aged children and adolescents have had 2 doses of MMR vaccine; the minimum interval between the 2 doses is 4 weeks.

1. **Varicella (VAR) vaccine. (Minimum age: 12 months)**

**Routine vaccination:**

* + Administer a 2-dose series of VAR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

**Catch-up vaccination:**

* + Ensure that all persons aged 7 through 18 years without evidence of immunity (see *MMWR* 2007 / 56 [No. RR-4], available at <http://www.cdc.gov/mmwr/pdf/rr/rr5604.pdf> ) have 2 doses of varicella vaccine. For children aged 7 through 12 years, the recommended minimum interval between doses is 3 months (if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid); for persons aged 13 years and older, the minimum interval between doses is 4 weeks.

1. **Hepatitis A (HepA) vaccine. (Minimum age: 12 months)**

**Routine vaccination:**

* + Initiate the 2-dose HepA vaccine series at 12 through 23 months; separate the 2 doses by 6 to 18 months.
  + Children who have received 1 dose of HepA vaccine before age 24 months should receive a second dose 6 to 18 months after the first dose.
  + For any person aged 2 years and older who has not already received the HepA vaccine series, 2 doses of HepA vaccine separated by 6 to 18 months may be administered if immunity against hepatitis A virus infection is desired.

**Catch-up vaccination:**

* + The minimum interval between the two doses is 6 months.

**Special populations:**

* + Administer 2 doses of HepA vaccine at least 6 months apart to previously unvaccinated persons who live in areas where vaccination programs target older children, or who are at increased risk for infection. This includes persons traveling to or working in countries that have high or intermediate endemicity of infection; men having sex with men; users of injection and non-injection illicit drugs; persons who work with HAV-infected primates or with HAV in a research laboratory; persons with clotting-factor disorders; persons with chronic liver disease; and persons who anticipate close personal contact (e.g., household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity. The first dose should be administered as soon as the adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.

1. **Human papillomavirus (HPV) vaccines. (Minimum age: 9 years for HPV2 [Cervarix] and HPV4 [Gardasil])**

**Routine vaccination:**

* + Administer a 3-dose series of HPV vaccine on a schedule of 0, 1-2, and 6 months to all adolescents aged 11 through 12 years. Either HPV4 or HPV2 may be used for females, and only HPV4 may be used for males.
  + The vaccine series may be started at age 9 years.
  + Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks); administer the third dose 24 weeks after the first dose and 16 weeks after the second dose (minimum interval of 12 weeks).

**Catch-up vaccination:**

* + Administer the vaccine series to females (either HPV2 or HPV4) and males (HPV4) at age 13 through 18 years if not previously vaccinated.
  + Use recommended routine dosing intervals (see Routine vaccination above) for vaccine series catch-up.

1. **Meningococcal conjugate vaccines. (Minimum age: 6 weeks for Hib-MenCY [MenHibrix], 9 months for MenACWY-D [Menactra], 2 months for MenACWY-CRM [Menveo])**

**Routine vaccination:**

* + Administer a single dose of Menactra or Menveo vaccine at age 11 through 12 years, with a booster dose at age 16 years.
  + Adolescents aged 11 through 18 years with human immunodeficiency virus (HIV ) infection should receive a 2-dose primary series of Menactra or Menveo with at least 8 weeks between doses.
  + For children aged 2 months through 18 years with high-risk conditions, see below.

**Catch-up vaccination:**

* + Administer Menactra or Menveo vaccine at age 13 through 18 years if not previously vaccinated.
  + If the first dose is administered at age 13 through 15 years, a booster dose should be administered at age 16 through 18 years with a minimum interval of at least 8 weeks between doses.
  + If the first dose is administered at age 16 years or older, a booster dose is not needed.
  + For other catch-up guidance, see Figure 172-3.

**Vaccination of persons with high-risk conditions and other persons at increased risk of disease:**

* + Children with anatomic or functional asplenia (including sickle cell disease):
    1. Menveo
       - *Children who initiate vaccination at 8 weeks through 6 months:* Administer doses at 2, 4, 6, and 12 months of age.
       - *Unvaccinated children 7 through 23 months:* Administer 2 doses, with the second dose at least 12 weeks after the first dose AND after the first birthday.
       - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart.
    2. MenHibrix
       - *Children 6 weeks through 18 months:* Administer doses at 2, 4, 6, and 12 through 15 months of age.
       - If the first dose of MenHibrix is given at or after 12 months of age, a total of 2 doses should be given at least 8 weeks apart to ensure protection against serogroups C and Y meningococcal disease.
    3. Menactra
       - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart. If Menactra is administered to a child with asplenia (including sickle cell disease), do not administer Menactra until 2 years of age and at least 4 weeks after the completion of all PCV13 doses.
  + Children with persistent complement component deficiency:
    1. Menveo
       - *Children who initiate vaccination at 8 weeks through 6 months:* Administer doses at 2, 4, 6, and 12 months of age.
       - *Unvaccinated children 7 through 23 months:* Administer 2 doses, with the second dose at least 12 weeks after the first dose AND after the first birthday.
       - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart.
    2. MenHibrix
       - *Children 6 weeks through 18 months:* Administer doses at 2, 4, 6, and 12 through 15 months of age.
       - If the first dose of MenHibrix is given at or after 12 months of age, a total of 2 doses should be given at least 8 weeks apart to ensure protection against serogroups C and Y meningococcal disease.
    3. Menactra
       - *Children 9 through 23 months:* Administer 2 primary doses at least 12 weeks apart.
       - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart.
  + For children who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, including countries in the African meningitis belt or the Hajj, administer an age-appropriate formulation and series of Menactra or Menveo for protection against serogroups A and W meningococcal disease. Prior receipt of MenHibrix is not sufficient for children traveling to the meningitis belt or the Hajj because it does not contain serogroups A or W.
  + For children at risk during a community outbreak attributable to a vaccine serogroup, administer or complete an age- and formulation-appropriate series of MenHibrix, Menactra, or Menveo.
  + For booster doses among persons with high-risk conditions, refer to *MMWR* 2013 / 62(RR02);1-22, available at [http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm.](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm)

For other catch-up recommendations for these persons, and complete information on use of meningococcal vaccines, including guidance related to vaccination of persons at increased risk of infection, see MMWR March 22, 2013 / 62(RR02);1-22, available at [http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf.](http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf)

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### Figure 172-2, cont’d

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**FIGURE 172-3. Catch-up immunization schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind —United States, 2015.**

The figure below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child’s age. Always use this table in conjunction with Figure 1 and the footnotes that follow.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Children age 4 months through 6 years** | | | | | |
| Vaccine | Minimum Age for Dose 1 | Minimum Interval Between Doses | | | |
| Dose 1 to Dose 2 | Dose 2 to Dose 3 | Dose 3 to Dose 4 | Dose 4 to Dose 5 |
| Hepatitis B*1* | Birth | 4 weeks | 8 weeks  *and* at least 16 weeks after first dose. Minimum age for the final dose is 24 weeks. |  |  |
| Rotavirus*2* | 6 weeks | 4 weeks | 4 weeks*2* |  |  |
| Diphtheria, tetanus, and acel- lular pertussis*3* | 6 weeks | 4 weeks | 4 weeks | 6 months | 6 months*3* |
| *Haemophilus influenzae*  type b*5* | 6 weeks | 4 weeks  if first dose was administered before the 1st birthday.  8 weeks (as final dose)  if first dose was administered at age 12 through 14 months.  No further doses needed if first dose was administered at age 15 months or older. | 4 weeks*5*  if current age is younger than 12 months **and** first dose was administered at younger than age 7 months, **and** at least 1 previous dose was PRP-T (ActHib, Pentacel) or unknown.  8 weeks  *and* age 12 through 59 months (as final dose)*5*   * if current age is younger than 12 months   **and** first dose was administered at age 7 through 11 months;  OR   * if current age is 12 through 59 months   **and** first dose was administered before the 1st birthday, **and** second dose administered at younger than 15 months;  OR   * if both doses were PRP-OMP (PedvaxHIB; Comvax)   **and** were administered before the 1st birthday.  No further doses needed  if previous dose was administered at age 15 months or older. | 8 weeks (as final dose)  This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday. |  |
| Pneumococcal*6* | 6 weeks | 4 weeks  if first dose administered before the 1st birthday.  8 weeks (as final dose for healthy children)  if first dose was administered at the 1st birthday or after.  No further doses needed  for healthy children if first dose administered at age 24 months or older. | 4 weeks  if current age is younger than 12 months and previous dose given at <7months old.  8 weeks (as final dose for healthy children)  if previous dose given between 7-11 months (wait until at least 12 months old); OR  if current age is 12 months or older and at least 1 dose was given before age 12 months.  No further doses needed for healthy children if previous dose administered at age 24 months or older. | 8 weeks (as final dose)  This dose only necessary for children aged 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age. |  |
| Inactivated poliovirus*7* | 6 weeks | 4 weeks*7* | 4 weeks*7* | 6 months*7* (minimum age 4 years for final dose). |  |
| Meningococcal*13* | 6 weeks | 8 weeks*13* | See footnote 13 | See footnote 13 |  |
| Measles, mumps, rubella*9* | 12 months | 4 weeks |  |  |  |
| Varicella*10* | 12 months | 3 months |  |  |  |
| Hepatitis A*11* | 12 months | 6 months |  |  |  |
| **Children and adolescents age 7 through 18 years** | | | | | |
| Tetanus, diphtheria; tetanus, diphtheria, and acellular pertussis*4* | 7 years*4* | 4 weeks | 4 weeks  if first dose of DTaP/DT was administered before the 1st birthday.  6 months (as final dose)  if first dose of DTaP/DT was administered at or after the 1st birthday. | 6 months if first dose of DTaP/DT was administered before the 1st birthday. |  |
| Human papillomavirus*12* | 9 years | Routine dosing intervals are recommended.*12* | | | |
| Hepatitis A*11* | Not applicable (N/A) | 6 months |  |  |  |
| Hepatitis B*1* | N/A | 4 weeks | 8 weeks **and** at least 16 weeks after first dose. |  |  |
| Inactivated poliovirus*7* | N/A | 4 weeks | 4 weeks*7* | 6 months*7* |  |
| Meningococcal*13* | N/A | 8 weeks*13* |  |  |  |
| Measles, mumps, rubella*9* | N/A | 4 weeks |  |  |  |
| Varicella*10* | N/A | 3 months if younger than age 13 years.  4 weeks if age 13 years or older. |  |  |  |

#### NOTE: The above recommendations must be read along with the footnotes of this schedule in Fig. 172-2.

**Figure 172-3** Catch-up immunization schedule for persons aged 4 mo through 18 yr who start late or who are more than 1 mo old–United States, 2015. *(From Centers for Disease Control and Prevention. Available at:* [*http://www.cdc.gov/vaccines/schedules/downloads/child/catchup-schedule-*](http://www.cdc.gov/vaccines/schedules/downloads/child/catchup-schedule-) *pr.pdf)*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table 172-6** Combination Vaccines Licensed and Available in the United States | | | | |
| **VACCINE PRODUCT (MANUFACTURER)**\* | **TRADE NAME (YEAR LICENSED)** | **COMPONENTS** | **Recommended Ages** | |
| **PRIMARY SERIES** | **BOOSTER DOSE** |
| Hib-HepB†‡ (Merck & Co, Inc.) | Comvax (1996) | PRP-OMP + HepB vaccine | 2, 4 mo of age | 12 through 15 mo of age |
| MenCY/Hib (GlaxoSmithKline) | MenHibRix (2013) | MenCY + PRP-T | 2, 4, 6 mo of age | 12 through 15 mo of age |
| DTaP-IPV/Hib (Sanofi Pasteur) | Pentacel (2008) | DTaP-IPV + PRP-T | 2, 4, 6 mo of age | 15 through 18 mo of age |
| DTaP-HepB-IPV  (GlaxoSmithKline) | Pediarix (2002) | DTaP + HepB + IPV | 2, 4, 6 mo of age |  |
| DTaP-IPV (GlaxoSmithKline) | Kinrix (2008) | DTaP + IPV |  | 4 through 6 yr of age:   * booster for 5th dose of DTaP * booster for 4th dose of IPV |
| HepA-HepB (GlaxoSmithKline) | Twinrix (2001) | HepA + HepB | >18 yr of age; 0, 1, and  6 mo schedule |  |
| MMRV (Merck & Co, Inc.) | ProQuad (2005) | MMR + varicella | 12 through 15 mo of age | 4 through 6 yr of age |

\*Dash (-) indicates that products are supplied in their final form by the manufacturer and do not require mixing or reconstitution by user; slash (/) indicates that products are mixed or reconstituted by user.

†If a PRP-OMP vaccine is not administered as both doses in the primary series or if there is uncertainty about which products were administered previously, a 3rd dose of Hib conjugate vaccine is needed to complete the primary series.

‡Preferred for American Indian/Alaska Native children.

DTap, diphtheria and tetanus toxoids and acellular pertussis vaccine; HepA, hepatitis A vaccine; HepB, hepatitis B vaccine; IPV/Hib, trivalent inactivated polio vaccine and *Haemophilus influenzae* type b vaccine; MMRV, measles-mumps-rubella and varicella vaccine.

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| --- | --- | --- | --- | --- |
| **Table 172-8** | Recommended Immunizations for Travelers to Developing Countries\* | | | |
| **IMMUNIZATIONS** | | **BRIEF,**  **<2 WK** | **Length of Travel**  **INTERMEDIATE, LONG-TERM**  **2 WK-3 MO RESIDENTIAL, >3 MO** | |
| Review and complete age-appropriate childhood and adolescent schedule (see text for details) | | + | + | + |
| * DTaP, poliovirus, pneumococcal, and *Haemophilus influenzae* type b vaccines may be given at 4-wk intervals if necessary to complete the recommended schedule before departure * Measles: 2 additional doses given if <12 mo of age at 1st dose * Rotavirus * Varicella * HPV * Hepatitis B† * Tdap * MCV4 | | | | |
| Yellow fever‡ | | + | + | + |
| Hepatitis A§ | | + | + | + |
| Typhoid fever | | ± | + | + |
| Meningococcal disease¶ | | ± | ± | ± |
| Rabies\*\* | | ± | + | + |
| Japanese encephalitis†† | | ± | ± | + |

\*See disease-specific chapters in the Red Book for details. For further sources of information, see text.

†If there is insufficient time to complete 6 mo primary series, accelerated series can be given.

‡For regions with endemic infection, see Health Information for International Travel ([http://www.cdc.gov/travel).](http://www.cdc.gov/travel))

§Indicated for travelers to areas with intermediate or high endemic rates of hepatitis A virus infection. Indicated for travelers who will consume food and liquids in areas of poor sanitation.

¶Recommended for regions of Africa with endemic infection and during local epidemics, and required for travel to Saudi Arabia for the Hajj.

\*\*Indicated for people with high risk for animal exposure (especially to dogs) and for travelers to countries with endemic infection.

††For regions with endemic infection (see Health Information for International Travel). For high-risk activities in areas experiencing outbreaks, vaccine is recommended, even for brief travel.

+, Recommended; ±, consider; DTaP, diphtheria and tetanus toxoids and acellular pertussis.

*Modified Pickering LK, Baker CJ, Kimberlin DW, Long SL, editors:* Red Book 2012: report of the Committee on Infectious Diseases*, Elk Grove Village, IL, 2012,*

|  |  |  |
| --- | --- | --- |
| **Table 172-7** | Vaccines Recommended for Children and Adolescents with Underlying Conditions or at High Risk | |
| **VACCINES** | | **CONDITIONS** |
| PCV13 (and PPSV23 in certain conditions) | | * Immunocompetent children with:   + Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure)   + Chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy)   + Diabetes mellitus   + Cerebrospinal fluid leaks   + Cochlear implant * Anatomic or functional asplenia (including sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia or splenic dysfunction) * Immunocompromising conditions: HIV infection; chronic renal failure and nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease or solid organ transplantation; congenital immunodeficiency |
| MCV4 | | * Anatomic or functional asplenia (including sickle cell disease) * Persistent complement component deficiency * Residents of or travelers to countries in African meningitis belt or pilgrims on the Haj * During outbreaks caused by a vaccine serogroup |
| Hib | | * Anatomic or functional asplenia (including sickle cell disease) * Immunocompromising conditions: HIV disease; immunosuppressive therapy for malignant neoplasms; immunoglobulin deficiency including immunoglobulin G2 subclass deficiency or early complement deficiency; recipients of a hematopoietic stem cell transplant (HSCT) |

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| **Table 172-9** Vaccination of Persons with Primary and | | Secondary Immune Deficiencies | |
| PRIMARY  **CATEGORY** | **SPECIFIC IMMUNODEFICIENCY** | **RISK-SPECIFIC CONTRAINDICATED RECOMMENDED**  **VACCINES**\* **VACCINES**\* | **EFFECTIVENESS AND COMMENTS** |
| B lymphocyte (humoral)  T lymphocyte (cell- mediated and humoral)  Complement Phagocytic function | Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)  Less-severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency)  Complete defects (e.g., SCID, complete DiGeorge syndrome)  Partial defects (e.g., most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)  Persistent complement, properdin, or factor B deficiency  Chronic granulomatous disease, leukocyte adhesion defect, and myeloperoxidase deficiency | OPV† Pneumococcal  Smallpox Consider measles and  LAIV varicella vaccination BCG  Ty21a (live typhoid) YF  OPV† Pneumococcal  BCG YF  Other live vaccines appear to be safe  All live vaccines‡§ Pneumococcal  All live vaccines‡§ Pneumococcal Meningococcal Hib (if not  administered in infancy)  None Pneumococcal Meningococcal  Live bacterial vaccines‡ Pneumococcal¶ | The effectiveness of any vaccine will be uncertain if it depends only on the humoral response (e.g., PPSV, MPSV)  IVIG interferes with the immune response to measles vaccine and possibly varicella vaccine  All vaccines probably effective  Immune response may be attenuated  Vaccines may be ineffective  Effectiveness of any vaccine depends on degree of immune suppression  All routine vaccines probably effective  All inactivated vaccines safe and probably effective  Live viral vaccines probably safe and effective |
| SECONDARY  **SPECIFIC IMMUNODEFICIENCY** | **CONTRAINDICATED VACCINES**\* | **RISK-SPECIFIC RECOMMENDED VACCINES\*** | **EFFECTIVENESS AND COMMENTS** |
| HIV/AIDS  Malignant neoplasm, transplantation, immunosuppressive or radiation therapy  Asplenia  Chronic renal disease | OPV†  Smallpox BCG LAIV  Withhold MMR and varicella in severely immunocompromised persons  Live viral and bacterial, depending on immune status‡§  None LAIV | Pneumococcal  Consider Hib (if not administered in infancy) and meningococcal vaccination  Pneumococcal  Pneumococcal Meningococcal  Hib (if not administered in infancy) Pneumococcal  Hepatitis B\*\* | MMR, varicella, rotavirus, and all inactivated vaccines, including inactivated influenza, may be effective#  Effectiveness of any vaccine depends on degree of immune suppression  All routine vaccines probably effective  All routine vaccines probably effective |

\*Other vaccines that are universally or routinely recommended should be given if not contraindicated.

†OPV is no longer recommended for routine use in the United States.

‡Live bacterial vaccines: BCG and oral Ty21a *Salmonella typhi* vaccine.

§Live viral vaccines: MMR, MMRV, OPV, LAIV, YF, zoster, rotavirus, and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public. Regarding T-lymphocyte immunodeficiency as a contraindication for rotavirus vaccine, data exist only for SCID.

¶Pneumococcal vaccine is not indicated for children with chronic granulomatous disease beyond age-based universal recommendations for PCV. Children with chronic granulomatous disease are not at increased risk for pneumococcal disease.

#HIV-infected children should receive immunoglobulin after exposure to measles and may receive varicella, measles, and YF vaccine if CD4+ lymphocyte count is greater than 15%. (For YF vaccine, CD4+ T-lymphocyte count between 15% and 24% is a precaution.)

\*\*Indicated based on the risk from dialysis-based bloodborne transmission.

BCG, bacille Calmette-Guérin vaccine; Hib, *Haemophilus influenzae* type b vaccine; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; IVIG, intravenous immunoglobulin; LAIV, live-attenuated influenza vaccine; MMR, measles, mumps, rubella vaccine; MPS,Vquadrivalent meningococcal polysaccharide vaccine; OPV, oral poliovirus vaccine (live); PPSV, pneumococcal polysaccharide vaccine; SCID, severe combined immunodeficiency disease; Y,Fyellow fever.

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| **Table 174-1** | Infectious Diseases in the Childcare Setting | |
| **DISEASE** | | **INCREASED INCIDENCE WITH CHILDCARE** |
| RESPIRATORY TRACT INFECTIONS  Otitis media Sinusitis Pharyngitis Pneumonia | | Yes Probably Probably Yes |
| GASTROINTESTINAL TRACT INFECTIONS  Diarrhea (rotavirus, calicivirus, astrovirus, enteric adenovirus, *Giardia lamblia, Cryptosporidium, Shigella, Escherichia coli* O157:H7, and *Clostridium difficile*)  Hepatitis A | | Yes  Yes |
| SKIN DISEASES  Impetigo Scabies Pediculosis Tinea (ringworm) | | Probably Probably Probably Probably |
| INVASIVE BACTERIA INFECTIONS  *Haemophilus influenzae* type b *Neisseria meningitidis Streptococcus pneumoniae* | | No\* Probably Yes |
| ASEPTIC MENINGITIS  Enteroviruses | | Probably |
| HERPESVIRUS INFECTIONS  Cytomegalovirus Varicella-zoster virus Herpes simplex virus | | Yes Yes  Probably |
| BLOOD-BORNE INFECTIONS  Hepatitis B HIV  Hepatitis C | | Few case reports No cases reported No cases reported |
| VACCINE-PREVENTABLE DISEASES  Measles, mumps, rubella, diphtheria, pertussis, tetanus  Polio  *H. influenzae* type b Varicella  Rotavirus | | Not established  No No\* Yes Yes |

\*Not in the postvaccine era; yes in the prevaccine era

|  |  |
| --- | --- |
| **Table 172-10** | Standards for Child and Adolescent Immunization Practices |
| AVAILABILITY OF VACCINES  Vaccination services are readily available.  Vaccinations are coordinated with other healthcare services and provided in a medical home when possible.  Barriers to vaccination are identified and minimized. Patient costs are minimized. | |
| ASSESSMENT OF VACCINATION STATUS  Healthcare professionals review the vaccination and health status of patients at every encounter to determine which vaccines are indicated.  Healthcare professionals assess for and follow only medically accepted contraindications. | |
| EFFECTIVE COMMUNICATION ABOUT VACCINE BENEFITS AND RISKS  Parents or guardians and patients are educated about the benefits and risks of vaccination in a culturally appropriate manner and in easy-to-understand language. | |
| PROPER STORAGE AND ADMINISTRATION OF VACCINES AND DOCUMENTATION OF VACCINATIONS  Healthcare professionals follow appropriate procedures for vaccine storage and handling.  Up-to-date, written vaccination protocols are accessible at all locations where vaccines are administered.  Persons who administer vaccines and staff who manage or support vaccine administration are knowledgeable and receive ongoing education.  Healthcare professionals simultaneously administer as many indicated vaccine doses as possible.  Vaccination records for patients are accurate, complete, and easily accessible.  Healthcare professionals report adverse events following vaccination promptly and accurately to the Vaccine Adverse Event Reporting System (VAERS) and are aware of a separate program, the National Vaccine Injury Compensation Program (VICP).  All personnel who have contact with patients are appropriately vaccinated. | |
| IMPLEMENTATION OF STRATEGIES TO IMPROVE VACCINATION COVERAGE  Systems are used to remind parents or guardians, patients, and healthcare professionals when vaccinations are due and to recall those who are overdue.  Office- or clinic-based patient record reviews and vaccination coverage assessments are performed annually.  Healthcare professionals practice community-based approaches. | |

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| **Table 173-3** | Common Surgical Procedures for Which Perioperative Prophylactic Antibiotics Are Recommended | | | |
| **SURGICAL PROCEDURE** | | **LIKELY PATHOGENS** | **RECOMMENDED DRUGS** | **NON–β-LACTAM ALTERNATIVE** |
| CLEAN WOUNDS  Cardiac surgery (e.g., open heart surgery)  Vascular surgery Neurosurgery  Orthopedic surgery (e.g., joint replacement) | | Skin flora, enteric Gram-negative bacilli | Cefazolin or cefuroxime | Clindamycin or vancomycin |
| CLEAN CONTAMINATED WOUNDS  Head and neck surgery involving Skin flora, oral anaerobes, oral the oral cavity or pharynx streptococci  Gastrointestinal and genitourinary Enteric Gram-negative bacilli, surgery anaerobes, Gram-positive cocci | | | Cefazolin + metronidazole, ampicillin- sulbactam  Cefazolin + metronidazole, cefotetan or piperacillin-tazobactam  If colon is involved, consider bacterial reduction with PO neomycin and erythromycin | Clindamycin Clindamycin |
| CONTAMINATED WOUNDS  Traumatic wounds (e.g., compound fracture) | | Skin flora | Cefazolin | Clindamycin, vancomycin |
| DIRTY WOUNDS  Appendectomy, penetrating abdominal wounds, colorectal surgery | | Enteric Gram-negative bacilli, anaerobes, Gram-positive cocci | Cefazolin + metronidazole, cefoxitin, cefotetan or ampicillin-sulbactam | Clindamycin + aminoglycoside |

**Chapter 174** ◆ Childcare and Communicable Diseases **1267**

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| **Table 174-2** | Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare—cont’d | | |
| **CONDITION** | | **MANAGEMENT OF CASE** | **MANAGEMENT OF CONTACTS** |
| Measles | | Exclusion until 4 days after beginning of rash and when the child is able to participate | Immunize exposed children without evidence of immunity within 72 hr of exposure  Children who do not receive vaccine within 72 hr or who remain unimmunized after exposure should be excluded until at least 2 wk after onset of rash in the last case of measles |
| Mumps | | Exclusion until 5 days after onset of parotid gland swelling | In outbreak setting, people without documentation of immunity should be immunized or excluded  Immediate readmission may occur following immunization Unimmunized people should be excluded for ≥26 days  following onset of parotitis in last case |
| *Pediculosis capitis* (head lice) | | Treatment at end of program day and readmission on completion of 1st treatment | Household and close contacts should be examined and treated if infested  No exclusion is necessary |
| Pertussis | | Exclusion until 5 days of appropriate antimicrobial therapy course have been completed | Immunization and chemoprophylaxis should be administered as recommended for household contacts  Symptomatic children and staff should be excluded until completion of 5 days of antimicrobial therapy course  Untreated adults should be excluded until 21 days after onset of cough |
| Rubella | | Exclusion until 6 days after onset of rash for postnatal infection | Pregnant contacts should be evaluated |
| *Salmonella* serotype Typhi infection | | Exclusion until diarrhea resolves  3 Negative stool culture results required before readmission | Stool cultures should be performed for attendees and staff; infected people should be excluded on the basis of age |
| Non–serotype Typhi  *Salmonella* infection | | Exclusion until diarrhea resolves. Negative stool culture results not required for non– serotype Typhi *Salmonella* species | Symptomatic contacts should be excluded until symptoms resolve  Stool cultures are not required for asymptomatic contacts Antimicrobial therapy is not recommended for asymptomatic  infection or uncomplicated diarrhea or for contacts |
| Scabies | | Exclusion until after treatment given | Close contacts with prolonged skin-to-skin contact should have prophylactic therapy  Bedding and clothing in contact with skin of infected people should be laundered |
| Shiga toxin–producing  *Escherichia coli*, including  *E. coli* O157:H7, or *Shigella*  infection | | Exclusion until diarrhea resolves and results of 2 stool cultures are negative for these organisms, depending on state regulations | Meticulous hand hygiene; stool cultures should be performed for contacts  Center(s) with cases should be closed to new admissions during  *E. coli* O157:H7 outbreak |
| *Staphylococcus aureus* skin infections | | Exclusion only if skin lesions are draining and cannot be covered with a watertight dressing | Meticulous hand hygiene  Cultures of contacts are not recommended |
| Streptococcal pharyngitis | | Exclusion until 24 hr after treatment has been initiated and the child is able to participate in activities | Symptomatic contacts of documented cases of group A streptococcal infection should be tested and treated if test results are positive |
| Tuberculosis | | For active disease, exclusion until determined to be noninfectious by physician or health department authority  May return to activities after therapy is instituted, symptoms have diminished, and adherence to therapy is documented  No exclusion for latent tuberculosis infection | Local health department personnel should be informed for contact investigation |
| Varicella | | Exclusion until all lesions have dried and crusted, usually 6 days after onset of rash in immunocompetent people; may be longer in immunocompromised people | Varicella vaccine should be administered by 3-5 days after exposure, and varicella-zoster Ig should be administered up to 96 hr after exposure when indicated |

HAV, hepatitis A virus; Ig, immunoglobulin.

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| **Table 174-2** | Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare | |
| **CONDITION** | **MANAGEMENT OF CASE** | **MANAGEMENT OF CONTACTS** |
| HAV infection | Serologic testing to confirm HAV infection in suspected cases  Exclusion until 1 wk after onset of jaundice | If ≥1 case is confirmed in child or staff attendees or ≥2 cases in households of staff or attendees, HAV vaccine or Ig should be administered within 14 days of exposure to unimmunized staff and attendees  In centers without diapered children, HAV vaccine or Ig should be given to unimmunized classroom contacts of index case  Asymptomatic Ig recipients may return after receipt of Ig |
| Impetigo | Exclusion until 24 hr after treatment has been initiated  Lesions on exposed skin covered with watertight dressing | No intervention needed unless additional lesions develop |

**Chapter 175** ◆ Health Advice for Children Traveling Internationally **1271**

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| **Table 174-3** | General Recommendations for Exclusion of Children in Out-of-Home Childcare | |
| **SYMPTOM(S)** | | **MANAGEMENT** |
| Illness preventing participation in activities, as determined by childcare staff | | Exclusion until illness resolves and able to participate in activities |
| Illness that requires care greater than staff can provide without compromising health and safety of others | | Exclusion or placement in care environment where appropriate care can be provided without compromising care of others |
| Severe illness suggested by fever with behavior changes, lethargy, irritability, persistent crying, difficulty breathing, progressive rash | | Medical evaluation and exclusion until symptoms have resolved |
| Rash with fever or behavioral change | | Medical evaluation and exclusion until illness is determined not to be communicable |
| Persistent abdominal pain (≥2 hr) or intermittent abdominal pain associated with fever, dehydration, or other systemic signs and symptoms | | Medical evaluation and exclusion until symptoms have resolved |
| Vomiting ≥2 times in preceding 24 hr | | Exclusion until symptoms have resolved, unless vomiting is determined to be caused by a noncommunicable condition and child is able to remain hydrated and participate in activities |
| Diarrhea or stools containing blood or mucus | | Medical evaluation and exclusion until symptoms have resolved |
| Oral lesions | | Exclusion until child or staff member is considered to be noninfectious (lesions crusted and dry) |

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| **Table 175-1** | Travel Vaccinations for Children | | | |
| **VACCINE** | | **PRIMARY SERIES** | **AGE AT VACCINATION** | **BOOSTER/COMMENTS** |
| HEPATITIS A  Havrix, Vaqta Immunoglobulin (Ig) | | 0.5 mL IM × 2 doses ≥6 mo apart  Travel <2 mo: 0.02 mL/kg IM once Travel >2 mo: 0.06 mL/kg IM once | >1 yr Birth | No booster; see text about off-label administration (age 6-11 mo)  See text about restrictions with live virus vaccinations (i.e., MMR) following Ig administration |
| INFLUENZA  Inactivated  Live-attenuated | | 6-35 mo: 0.25 mL IM, 1 or 2 doses  3-8 yr: 0.5 mL IM, 1 or 2 doses  >9 yr: 0.5 mL IM once  0.25 mL in each nostril, 1 or 2 doses | >6 mo  >2 yr | New vaccine yearly  In children 6 mo-9 yr, 2 doses should be given ≥1 mo apart if no prior vaccination  New vaccine yearly |
| JAPANESE B ENCEPHALITIS  Ixiaro (inactivated) | | 2 mo-2 yr: 0.25 mL IM on days 0 and 28  >3 yr: 0.5 mL IM on days 0 and 28 | 2 mo to <3 yr  >3 yr | Booster 1-2 yr after primary series Booster 1-2 yr after primary series |
| MEASLES  MMR | | Recommended schedule: 12-15 mo and 4-6 yr  If >12 mo and traveling internationally, 2nd MMR dose can be administered 4 wk later | >6-11 mo: 1 dose recommended if traveling to measles- endemic area | See text. MMR at 6-11 mo does not count toward primary series; MMR should be administered simultaneously with other recommended/required live-virus travel vaccines (yellow fever) |
| MENINGOCOCCAL DISEASE  Conjugate A/C/Y/W-135  Polysaccharide A/C/Y/W-135 | | 0.5 mL IM  9-23 mo: 2 doses, 3 mo apart  0.5 mL IM once  0.5 mL SC once | 9-23 mo  >2–6 yr  >7 yr  >2 yr | Booster 3 yr after primary series  Booster after 3 yr (age 2-6 yr) Booster after 5 yr (age >7 yr)  Children with functional/anatomic asplenia receive 2 dose primary series, 2 mo apart; conjugate vaccine recommended over polysaccharide A/C/Y/W-135  <4 yr of age: every 2 yr  >4 yr of age: every 3-5 yr |
| RABIES | | Preexposure: 1.0 mL IM × 3 doses, days 0, 7, and 21 or 28 days | Any age | See text for follow-up vaccination if bitten |
| TYPHOID  Intramuscular Vi Oral Ty21 | | 0.5 mL IM once  4 doses: 1 capsule PO every other day | ≥2 yr  ≥6 yr | Every 2-3 yr  Every 5 yr; see text for administration |
| YELLOW FEVER | | 0.5 mL SC once | >9 mo | Every 10 yr (see text) |

A/C/Y/W-135, serogroup A, C, Y, and W135 meningococcal vaccine.

Thorough history: onset, other symptoms, exposures (daycare, school, family, pets, playmates), travel, medications, other underlying disorders, immunizations

Physical examination: complete, with focus on localizing symptoms Laboratory studies on a case-by-case basis:

* Rapid antigen testing
* Nasopharyngeal: respiratory viruses by polymerase chain reaction
* Throat: group A *Streptococcus*
* Stool: rotavirus
* Blood: complete blood count, blood culture, C-reactive protein, sedimentation rate, procalcitonin
* Urine: urinalysis, culture
* Stool: Hemoccult, culture
* Cerebrospinal fluid: cell count, glucose, protein, Gram stain, culture
* Chest radiograph or other imaging studies on a case-by-case basis

Evaluation of Acute Fever

**Table 176-2**

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| **Table 177-1** | Febrile Patients at Increased Risk for Serious Bacterial and Viral Infections |
| **RISK GROUP DIAGNOSTIC CONSIDERATIONS** | |
| IMMUNOCOMPETENT PATIENTS  Neonates (<28 days) Sepsis and meningitis caused by group B  *Streptococcus*, *Escherichia coli, Listeria monocytogenes;* neonatal herpes simplex virus infection, enteroviruses, parechovirus  Infants 1-3 mo Serious bacterial disease in 5-15%,  including bacteremia in 5%; urinary tract infection most common serious bacterial infection; *E. coli* most common pathogen; enterovirus, parechovirus, influenza  Infants and children Occult bacteremia in <0.5% of children 3-36 mo immunized with both *Haemophilus*  *influenzae* type b and pneumococcal conjugate vaccines; urinary tract infections  Hyperpyrexia (>40°C Meningitis, bacteremia, pneumonia, [104°F]) heatstroke, hemorrhagic shock-  encephalopathy syndrome  Fever with petechiae Bacteremia and meningitis caused by  *Neisseria meningitidis, H. influenzae* type b, and *Streptococcus pneumoniae*  Rickettsial disease Viral exanthem | |
| IMMUNOCOMPROMISED PATIENTS  Sickle cell disease Sepsis, pneumonia, and meningitis caused  by *S. pneumoniae*, osteomyelitis caused by *Salmonella* and *Staphylococcus aureus*  Asplenia Bacteremia and meningitis caused by  *N. meningitidis, H. influenzae* type b,  *S. pneumoniae*, and *Capnocytophaga* sp.  Complement or Sepsis caused by *N. meningitidis*  properdin deficiency  Agammaglobulinemia Bacteremia, sinopulmonary infections AIDS *S. pneumoniae, H. influenzae* type b, and  *Salmonella* infections  Congenital heart Infective endocarditis; brain abscess with disease right-to-left shunting  Central venous line *S. aureus*, coagulase-negative  staphylococci, *Candida*  Malignancy Bacteremia with gram-negative enteric bacteria, *S. aureus*, and coagulase- negative staphylococci; fungemia with *Candida* and *Aspergillus* | |

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| **Table 176-1** | Fevers Prone to Relapse |
| INFECTIOUS CAUSES  Relapsing fever *(Borrelia recurrentis)*  Trench fever *(Bartonella quintana)* Q fever *(Coxiella burnetii)* Typhoid fever *(Salmonella typhi)* Syphilis *(Treponema pallidum)* Tuberculosis  Histoplasmosis Coccidioidomycosis Blastomycosis  Melioidosis *(Pseudomonas pseudomallei)* Lymphocytic choriomeningitis (LCM) infection Dengue fever  Yellow fever  Chronic meningococcemia Colorado tick fever Leptospirosis  Brucellosis  Oroya fever *(Bartonella bacilliformis)*  Acute rheumatic fever  Rat bite fever *(Spirillum minus)*  Visceral leishmaniasis  Lyme disease *(Borrelia burgdorferi)*  Malaria Babesiosis  Noninfluenza respiratory viral infection Epstein-Barr virus infection | |
| NONINFECTIOUS CAUSES  Behçet disease Crohn disease  Weber-Christian disease (panniculitis) Leukoclastic angiitis syndromes Sweet syndrome  Systemic lupus erythematosus and other autoimmune disorders | |
| PERIODIC FEVER SYNDROMES (see Chapter 163)  Familial Mediterranean fever Cyclic neutropenia  Periodic fever, aphthous stomatitis, pharyngitis, adenopathy (PFAPA)  Hyperimmunoglobulin D syndrome  Hibernian fever (tumor necrosis factor superfamily immunoglobulin A–associated syndrome [TRAPS])  Muckle-Wells syndrome Others | |

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**Chapter 177** ◆ Fever Without a Focus **1283**

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| **Table 177-3** | Management of Fever Without Localizing Signs | |
| **GROUP** | | **MANAGEMENT** |
| Any toxic-appearing child 0-36 mo Hospitalize, broad cultures plus other tests,\* parenteral antibiotics and temperature ≥38°C (100.4°F) | | |
| Child <1 mo and temperature  ≥38°C (100.4°F) | | Hospitalize, broad cultures plus other tests,\* parenteral antibiotics |
| Child 1-3 mo and temperature  ≥38°C (100.4°F) | | Two-step process   1. Determine risk based on history, physical examination, and laboratory studies. Low risk:    * Uncomplicated medical history    * Normal physical examination    * Normal laboratory studies    * Urine: negative leukocyte esterase, nitrite and <10 WBC/HPF    * Peripheral blood: 5,000-15,000 WBC/mm3; <1,500 bands or band: total neutrophil ratio <0.2    * Stool studies if diarrhea (no RBC and <5 WBC/HPF)    * CSF cell count (<8 WBC/μL) and negative Gram stain    * Chest radiograph without infiltrate 2. If child fulfills all low-risk criteria, administer no antibiotics, ensure follow-up in 24 hr and access to emergency care if child deteriorates. Daily follow-up should occur until blood, urine, and CSF cultures are final. If any cultures are positive, child returns for further evaluation and treatment. If child does not fulfill all low-risk criteria, hospitalize and administer parenteral antibiotics until all cultures are final and definitive diagnosis determined and treated |
| Child 3-36 mo and temperature 38-39°C (100.4-102.2°F) | | Reassurance that diagnosis is likely self-limiting viral infection, but advise return with persistence of fever, temperatures >39°C (102.2°F), and new signs and symptoms |
| Child 3-36 mo and temperature  >39°C (102.2°F) | | Two-step process:   1. Determine immunization status 2. If received conjugate pneumococcal and *Haemophilus influenzae* type b vaccines, obtain urine studies (urine WBC, leukocyte esterase, nitrite, and culture) for all girls, all boys <6 mo old, all uncircumcised boys <2 yr, all children with recurrent urinary tract infections   If did not receive conjugate pneumococcal and *H. influenzae* type b vaccines, manage according to the 1993 Guidelines (see Baraff et al. *Ann Emerg Med* 22:1198-1210, 1993.) |

\*Other tests may include chest radiograph, stool studies, herpes simplex polymerase chain reaction. CSF, cerebrospinal fluid; HPF, high-powered field; RBC, red blood cell; WBC, white blood cell.

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| **Table 177-4** | Summary of Definitions and Major Features of the 4 Subtypes of Fever of Unknown Origin | | | | |
| **FEATURE** | | **CLASSIC FUO** | **HEALTHCARE- ASSOCIATED FUO** | **IMMUNE-DEFICIENT FUO** | **HIV-RELATED FUO** |
| Definition | | >38°C (100.4°F), >3 wk, >2 visits or 1 wk in hospital | ≥38°C (100.4°F),  >1 wk, not present or incubating on admission | ≥38°C (100.4°F), >1 wk,  negative cultures after 48 hr | ≥38°C (100.4°F), >3 wk for  outpatients, >1 wk for inpatients, HIV infection confirmed |
| Patient location | | Community, clinic, or hospital | Acute care hospital | Hospital or clinic | Community, clinic, or hospital |
| Leading causes | | Cancer, infections, inflammatory conditions, undiagnosed, habitual hyperthermia | Healthcare- associated infections, postoperative complications, drug fever | Majority caused by infections, but cause documented in only 40-60% | HIV (primary infection), typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis, immune reconstitution inflammatory syndrome (IRIS) |
| History emphasis | | Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder | Operations and procedures, devices, anatomic considerations, drug treatment | Stage of chemotherapy, drugs administered, underlying immunosuppressive disorder | Drugs, exposures, risk factors, travel, contacts, stage of HIV infection |
| Examination emphasis | | Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower-limb deep veins | Wounds, drains, devices, sinuses, urine | Skin folds, IV sites, lungs, perianal area | Mouth, sinuses, skin, lymph nodes, eyes, lungs, perianal area |
| Investigation emphasis | | Imaging, biopsies, sedimentation rate, skin tests | Imaging, bacterial cultures | CXR, bacterial cultures | Blood and lymphocyte count; serologic tests; CXR; stool examination; biopsies of lung, bone marrow, and liver for cultures and cytologic tests; brain imaging |
| Management | | Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments | Depends on situation | Antimicrobial treatment protocols | Antiviral and antimicrobial protocols, vaccines, revision of treatment regimens, good nutrition |
| Time course of disease | | Months | Weeks | Days | Weeks to months |
| Tempo of investigation | | Weeks | Days | Hours | Days to weeks |

CMV, cytomegalovirus; CXR, chest radiograph; FUO, fever of unknown origin.

*Adapted from Mandell GL, Bennett, JE, Dolin R, editors:* Mandell, Douglas, and Bennett’s principles and practice of infectious diseases*, ed 7, Philadelphia, 2010, Churchill Livingstone/Elsevier, p. 780, Table 51-1.*

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| **Table 177-5** Diagnostic Considerations of Fever of Unknown Origin in Children | |
| ABSCESSES  Abdominal Brain Dental Hepatic Pelvic Perinephric Rectal Subphrenic Psoas | RHEUMATOLOGIC DISEASES  Behçet disease  Juvenile dermatomyositis Juvenile idiopathic arthritis Rheumatic fever  Systemic lupus erythematosus |
| HYPERSENSITIVITY DISEASES  Drug fever  Hypersensitivity pneumonitis Serum sickness  Weber-Christian disease |
| BACTERIAL DISEASES  Actinomycosis  *Bartonella henselae* (cat-scratch disease) Brucellosis  *Campylobacter*  *Francisella tularensis* (tularemia) *Listeria monocytogenes* (listeriosis) Meningococcemia (chronic) *Mycoplasma pneumoniae*  Rat bite fever (*Streptobacillus moniliformis;* streptobacillary form of rat bite fever)  *Salmonella* Tuberculosis Whipple disease Yersiniosis |
| NEOPLASMS  Atrial myxoma Cholesterol granuloma Hodgkin disease  Inflammatory pseudotumor Leukemia  Lymphoma Pheochromocytoma Neuroblastoma Wilms tumor |
| GRANULOMATOUS DISEASES  Crohn disease Granulomatous hepatitis Sarcoidosis  Angiitis |
| LOCALIZED INFECTIONS  Cholangitis  Infective endocarditis Mastoiditis Osteomyelitis Pneumonia Pyelonephritis Sinusitis |
| FAMILIAL AND HEREDITARY DISEASES  Anhidrotic ectodermal dysplasia Autonomic neuropathies  Fabry disease  Familial dysautonomia Familial Hibernian fever  Familial Mediterranean fever and the many other autoinflammatory diseases (see Chapter 163)  Hypertriglyceridemia Ichthyosis  Sickle cell crisis  Spinal cord/brain injury |
| SPIROCHETES  *Borrelia burgdorferi* (Lyme disease) Relapsing fever *(Borrelia recurrentis)* Leptospirosis  Rat bite fever (*Spirillum minus;* spirillary form of rat bite fever) Syphilis |
| FUNGAL DISEASES  Blastomycosis (extrapulmonary) Coccidioidomycosis (disseminated) Histoplasmosis (disseminated) *Chlamydia*  Lymphogranuloma venereum Psittacosis | MISCELLANEOUS  Addison disease Castleman disease Chronic active hepatitis Cyclic neutropenia  Diabetes insipidus (nonnephrogenic and nephrogenic) Factitious fever  Hemophagocytic syndromes Hypothalamic-central fever Infantile cortical hyperostosis Inflammatory bowel disease Kawasaki disease  Kikuchi-Fujimoto disease Metal fume fever Pancreatitis  Periodic fever syndromes Poisoning  Pulmonary embolism Thrombophlebitis Thyrotoxicosis, thyroiditis |
| RICKETTSIA  *Ehrlichia canis*  Q fever  Rocky Mountain spotted fever Tick-borne typhus |
| VIRUSES  Cytomegalovirus Hepatitis viruses HIV  Epstein-Barr virus |
| PARASITIC DISEASES  Amebiasis Babesiosis Giardiasis Malaria Toxoplasmosis Trichinosis Trypanosomiasis  Visceral larva migrans *(Toxocara)* |

**Chapter 177** ◆ Fever Without a Focus **1285**

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| **Table 177-6** | Examples of Subtle Physical Findings Having Special Significance in Patients with Fever of Unknown Origin | | |
| **BODY SITE** | | **PHYSICAL FINDING** | **DIAGNOSIS** |
| Head | | Sinus tenderness | Sinusitis |
| Temporal artery | | Nodules, reduced pulsations | Temporal arteritis |
| Oropharynx | | Ulceration  Tender tooth | Disseminated histoplasmosis, SLE, IBD, Behcet syndrome, periodic fever syndromes  Periapical abscess |
| Fundi or conjunctivae | | Choroid tubercle Petechiae, Roth spot | Disseminated granulomatosis\* Endocarditis |
| Thyroid | | Enlargement, tenderness | Thyroiditis |
| Heart | | Murmur | Infective or marantic endocarditis |
| Abdomen | | Enlarged iliac crest lymph nodes, splenomegaly | Lymphoma, endocarditis, disseminated granulomatosis\* |
| Rectum | | Perirectal fluctuance, tenderness Prostatic tenderness, fluctuance | Abscess Abscess |
| Genitalia | | Testicular nodule Epididymal nodule | Periarteritis nodosa, cancer Disseminated granulomatosis |
| Lower extremities | | Deep venous tenderness | Thrombosis or thrombophlebitis |
| Skin and nails | | Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing | Vasculitis, endocarditis |

\*Includes tuberculosis, histoplasmosis, coccidioidomycosis, sarcoidosis, granulomatosis with polyangiitis, and syphilis.

*From Mandell GL, Bennett, JE, Dolin R, editors:* Mandell, Douglas, and Bennett’s principles and practice of infectious diseases*, ed 7, Philadelphia, 2010, Churchill Livingstone/Elsevier, p. 785, Table 51-8.*

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| **Table 177-2** | Low-Risk Criteria in a Child 1-3 Months Old with Fever |
| BOSTON CRITERIA  Infants are at low risk if they appear well, have a normal physical examination, and have a caretaker reachable by telephone and if laboratory tests are as follows:   * CBC: <20,000 WBC/μL * Urine: negative leukocyte esterase * CSF: leukocyte count less than 10 × 106/L | |
| PHILADELPHIA PROTOCOL  Infants are at low risk if they appear well and have a normal physical examination and if laboratory tests are as follows:   * CBC: <15,000 WBC/μL; band: total neutrophil ratio <0.2 * Urine: <10 WBC/HPF; no bacteria on Gram stain * CSF: <8 WBC/μL; no bacteria on Gram stain * Chest radiograph: no infiltrate * Stool: no RBC; few to no WBC | |
| PITTSBURGH GUIDELINES  Infants are at low risk if they appear well and have a normal physical examination and if laboratory tests are as follows:   * CBC: 5,000-15,000 WBC/μL; peripheral absolute band count   <1,500/μL   * Urine (enhanced urinalysis): 9 WBC/μL and no bacteria on Gram stain * CSF: 5 WBC/μL and negative Gram stain; if bloody tap, then WBC:RBC ≤1 : 500 * Chest radiograph: no infiltrate * Stool: 5 WBC/HPF with diarrhea | |
| ROCHESTER CRITERIA  Infants are at low risk if they appear well and have a normal physical examination and if laboratory findings are as follows:   * CBC: 5,000-15,000 WBC/μL; absolute band count ≤1,500/μL * Urine: <10 WBC/HPF at 40× * Stool: <5 WBC/HPF if diarrhea | |

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| **Table 178-3** | Possible Causes of Fever in Neutropenic Patients Not Responding to Broad- Spectrum Antibiotics | |
| **CAUSES** | | **APPROXIMATE FREQUENCY IN HIGH-RISK PATIENTS (%)** |
| Fungal infections susceptible to empirical therapy | | 40 |
| Fungal infections resistant to empirical antifungal therapy | | 5 |
| Bacterial infections (with cryptic foci, biofilms, and resistant organisms) | | 10 |
| *Toxoplasma gondii*, mycobacteria, or fastidious pathogens *(Legionella, Mycoplasma, Chlamydophila pneumoniae, Bartonella)* | | 5 |
| Viral infections (herpesviruses, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, varicella-zoster virus, herpes simplex virus, parainfluenza virus, respiratory syncytial virus, influenzaviruses) | | 5 |
| Graft-versus-host disease after hematopoietic stem cell transplantation | | 10 |
| Undefined (e.g., drug fever, toxic effects of chemotherapy, antitumor responses, undefined pathogens) | | 25 |

CBC, complete blood count; CSF, cerebrospinal fluid; HPF, high-powered field; RBC, red blood cell; WBC, white blood cell.

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| **Table 178-2** | Most Common Causes of Infections in Immunocompromised Children |
| BACTERIA, AEROBIC\*  *Acinetobacter Bacillus*  *Burkholderia cepacia Citrobacter Corynebacterium Enterobacter* spp.  *Enterococcus faecalis Enterococcus faecium Escherichia coli Klebsiella* spp.  *Listeria monocytogenes Mycobacterium* spp.  *Neisseria meningitidis Nocardia*  *Pseudomonas aeruginosa Staphylococcus aureus Staphylococcus,* coagulase-negative *Streptococcus pneumoniae Streptococcus,* viridans group | |
| BACTERIA, ANAEROBIC\*  *Bacillus Clostridium Fusobacterium Peptococcus*  *Peptostreptococcus Propionibacterium Veillonella* | |
| FUNGI\*  *Aspergillus Candida albicans* Other *Candida* spp.  *Cryptococcus neoformans Fusarium* spp.  *Pneumocystis jiroveci*  Zygomycoses *(Mucor, Rhizopus, Rhizomucor)* | |
| VIRUSES\*  Adenoviruses Cytomegalovirus Epstein-Barr virus Herpes simplex virus Human herpesvirus 6 Polyomavirus (BK)  Respiratory and enteric community-acquired viruses Varicella-zoster virus | |
| PROTOZOA\*  *Cryptosporidium parvum Giardia lamblia Toxoplasma gondii* | |

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| **Table 178-1** | Major Causes of Increased Risk for Infection in Immunocompromised Hosts |
| PRIMARY IMMUNODEFICIENCIES  Antibody deficiency (B-cell defects; see Chapter 124)   * X-linked agammaglobulinemia * Common variable immunodeficiency * Selective immunoglobulin IgA deficiency * IgG subclass deficiencies * Hyper-IgM syndrome * Transient hypogammaglobulinemia of infancy Cell-mediated deficiency (T-cell defects) * Thymic dysplasia (DiGeorge syndrome) * Defective T-cell receptor * Defective cytokine production * T-cell activation defects * CD8 lymphocytopenia * Chronic mucocutaneous candidiasis   Combined B- and T-cell defects (see Chapter 126)   * Severe combined immunodeficiency * Combined immunodeficiency * Omenn syndrome * Thrombocytopenia and eczema (Wiskott-Aldrich syndrome) * Ataxia-telangiectasia * Hyper-IgE syndrome   Phagocyte defects (see Chapter 130)   * Leukocyte adhesion deficiency * Chédiak-Higashi syndrome * Myeloperoxidase deficiency * Chronic granulomatous disease Leukopenia (see Chapter 131) * Congenital neutropenia (Kostmann syndrome) * Shwachman-Diamond syndrome   Disorders of the complement system (see Chapter 133) | |
| SECONDARY IMMUNODEFICIENCIES  HIV (see Chapter 276)  Malignancies (and cancer chemotherapy)  Transplantation (see Chapters 135, 339, 368, 443, 444, and 536)   * Bone marrow and hematopoietic stem cell * Solid organ Burns   Sickle cell disease  Cystic fibrosis (see Chapter 403) Diabetes mellitus Immunosuppressive drugs  Asplenia including heterotaxy syndrome Implanted foreign body  Malnutrition | |

\*Listed alphabetically.

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| **Table 178-4** | Host Defense Defects and Common Pathogens by Time After Bone Marrow Transplantation/Hematopoietic Stem Cell Transplantation | | | |
| **TIME PERIOD** | | **HOST DEFENSE DEFECTS** | **CAUSES** | **COMMON PATHOGENS** |
| Pretransplant | | Neutropenia  Abnormal anatomic barriers | Underlying disease Prior chemotherapy | Aerobic Gram-negative bacilli |
| Preengraftment | | Neutropenia  Abnormal anatomic barriers | Chemotherapy Radiation Indwelling catheters | Aerobic Gram-positive cocci Aerobic Gram-negative bacilli *Candida*  *Aspergillus*  Herpes simplex virus (in previously infected patients)  Community-acquired viral pathogens |
| Postengraftment | | Abnormal cell-mediated immunity Abnormal anatomic barriers | Chemotherapy Immunosuppressive medications Radiation  Indwelling catheters Unrelated cord blood donor | Gram-positive cocci  Aerobic Gram-negative bacilli Cytomegalovirus Adenoviruses  Community-acquired viral pathogens  *Pneumocystis jiroveci* |
| Late posttransplant | | Delayed recovery of immune function (cell-mediated, humoral, and abnormal anatomic barriers) | Time required to develop  donor-related immune function Graft-versus-host disease | Varicella-zoster virus  *Streptococcus pneumoniae* |

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| **Table 178-6** | Timing of Infectious Complications Following Solid-Organ Transplantation |
| EARLY PERIOD (0-30 DAYS)  *Bacterial Infections*  Gram-negative enteric bacilli   * Small bowel, liver, neonatal heart   *Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes*   * Cystic fibrosis lung Gram-positive organisms * All transplant types   *Fungal Infections* All transplant types *Viral Infections*  Herpes simplex virus   * All transplant types Nosocomial respiratory viruses * All transplant types | |
| MIDDLE PERIOD (1-6 MO)  *Viral Infections*  Cytomegalovirus   * All transplant types * Seronegative recipient of seropositive donor Epstein-Barr virus * All transplant types (small bowel highest risk group) * Seronegative recipient Varicella-zoster virus * All transplant types * Opportunistic infections   *Pneumocystis jiroveci*   * All transplant types   *Toxoplasma gondii*   * Seronegative recipient of cardiac transplant from a seropositive donor   *Bacterial Infections*  *Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes*   * Cystic fibrosis lung   Gram-negative enteric bacilli   * Small bowel | |
| LATE PERIOD (**>**6 MO)  *Viral Infections*  Epstein-Barr virus   * All transplant types, but less risk than middle period Varicella-zoster virus * All transplant types   Community-acquired viral infections   * All transplant types   *Bacterial Infections*  *Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes*   * Cystic fibrosis lung * Lung transplants with chronic rejection Gram-negative bacillary bacteremia * Small bowel *Fungal Infections Aspergillus* * Lung transplants with chronic rejection | |

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| **Table 178-5** | Risk Factors for Infections Following Solid-Organ Transplantation in Children |
| PRETRANSPLANTATION FACTORS  Age of patient  Underlying disease, malnutrition Specific organ transplanted  Previous exposures to infectious agents Previous immunizations  Presence of infection in the donor | |
| INTRAOPERATIVE FACTORS  Duration of transplant surgery Exposure to blood products Technical problems  Organisms transmitted with donor organ | |
| POSTTRANSPLANTATION FACTORS  Immunosuppression  Induction immunosuppression Maintenance immunosuppression Augmented treatment for rejection Indwelling catheters  Nosocomial exposures Community exposures | |

**Chapter 180** ◆ Principles of Antibacterial Therapy **1301**

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| **Table 180-3** Antibacterial | Medications (Antibiotics)\* | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **INDICATIONS (MECHANISM OF ACTION) AND DOSING** | **COMMENTS** |
| Amikacin sulfate  Amikin  Injection: 50 mg/mL, 250 mg/ mL | Aminoglycoside antibiotic active against Gram-negative bacilli, especially *Escherichia coli, Klebsiella, Proteus, Enterobacter, Serratia,* and *Pseudomonas*  Neonates: Postnatal age ≤7 days: weight 1,200-2,000 g:  7.5 mg/kg q 12-18 hr IV or IM; weight >2,000 g: 10 mg/ kg q 12 hr IV or IM; postnatal age >7 days: weight 1,200-2,000 g IV or IM: 7.5 mg/kg q 8-12 hr IV or IM; weight >2,000 g: 10 mg/kg q 8 hr IV or IM  Children: 15-25 mg/kg/24 hr divided q 8-12 hr IV or IM Adults: 15 mg/kg/24 hr divided q 8-12 hr IV or IM | *Cautions:* Anaerobes, *Streptococcus* (including *S. pneumoniae*) are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min  *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs  *Target serum concentrations:* Peak 25-40 mg/L; trough <10 mg/L |
| Amoxicillin  Amoxil, Polymox Capsule: 250, 500 mg  Tablet: chewable: 125, 250 mg Suspension: 125 mg/5 mL,  250 mg/5 mL  Drops: 50 mg/mL | Penicillinase-susceptible **β**-lactam: Gram-positive pathogens except *Staphylococcus; Salmonella, Shigella, Neisseria, E. coli*, and *Proteus mirabilis*  Children: 20-50 mg/kg/24 hr divided q 8-12 hr PO. Higher dose of 80-90 mg/kg 24 hr PO for otitis media  Adults: 250-500 mg q 8-12 hr PO  Uncomplicated gonorrhea: 3 g with 1 g probenecid PO | *Cautions:* Rash, diarrhea, abdominal cramping. Drug eliminated renally  *Drug interaction:* Probenecid |
| Amoxicillin-clavulanate  Augmentin  Tablet: 250, 500, 875 mg  Tablet, chewable: 125, 200,  250, 400 mg  Suspension: 125 mg/5 mL, 200 mg/5 mL, 250 mg/5 mL,  400 mg/5 mL | **β**-Lactam (amoxicillin) combined with **β**-lactamase inhibitor (clavulanate) enhances amoxicillin activity against penicillinase-producing bacteria. *S. aureus* (not methicillin-resistant organism), *Streptococcus, Haemophilus influenzae, Moraxella catarrhalis, E. coli, Klebsiella, Bacteroides fragilis*  Neonates: 30 mg/kg/24 hr divided q 12 hr PO  Children: 20-45 mg/kg 24 hr divided q 8-12 hr PO. Higher dose 80-90 mg/kg/24 hr PO for otitis media | *Cautions:* Drug dosed on amoxicillin component. May cause diarrhea, rash. Drug eliminated renally  *Drug interaction:* Probenecid  *Comment:* Higher dose may be active against penicillin-tolerant/resistant  *S. pneumoniae* |
| Ampicillin  Polycillin, Omnipen Capsule: 250, 500 mg Suspension: 125 mg/5 mL,  250 mg/5 mL, 500 mg/5 mL Injection | **β**-Lactam with same spectrum of antibacterial activity as amoxicillin  Neonates: Postnatal age ≤7 days weight ≤2,000 g: 50 mg/ kg/24 hr IV or IM q 12 hr (meningitis: 100 mg/kg/24 hr divided q 12 hr IV or IM); weight >2,000 g: 75 mg/ kg/24 hr divided q 8 hr IV or IM (meningitis: 150 mg/ kg/24 hr divided q 8 hr IV or IM). Postnatal age >7 days weight <1,200 g: 50 mg/kg/24 hr IV or IM q 12 hr (meningitis: 100 mg/kg/24 hr divided q 12 hr IV or IM); weight 1,200-2,000 g: 75 mg/kg/24 hr divided q 8 hr IV or IM (meningitis: 150 mg/kg/24 hr divided q 8 hr IV or IM); weight >2,000 g: 100 mg/kg/24 hr divided q 6 hr IV or IM (meningitis: 200 mg/kg/24 hr divided q 6 hr IV or IM)  Children: 100-200 mg/kg/24 hr divided q 6 hr IV or IM (meningitis: 200-400 mg/kg/24 hr divided q 4-6 hr IV or IM)  Adults: 250-500 mg q 4-8 hr IV or IM | *Cautions:* Less bioavailable than amoxicillin, causing greater diarrhea  *Drug interaction:* Probenecid |
| Ampicillin-sulbactam  Unasyn Injection | **β**-Lactam (ampicillin) and **β**-lactamase inhibitor (sulbactam) enhances ampicillin activity against penicillinase-producing bacteria: *S. aureus, H. influenzae, M. catarrhalis, E. coli, Klebsiella, B. fragilis*  Children: 100-200 mg/kg/24 hr divided q 4-8 hr IV or IM Adults: 1-2 g q 6-8 hr IV or IM (max daily dose: 8 g) | *Cautions:* Drug dosed on ampicillin component. May cause diarrhea, rash. Drug eliminated renally  *Note:* Higher dose may be active against penicillin-tolerant/resistant *S. pneumoniae*  *Drug interaction:* Probenecid |

\*In the Drug column, the generic drug name is in bold. In the Indications column, bold indicates major organisms targeted and mechanisms of action.

##### Continued

**1302 Part XVII** ◆ Infectious Diseases

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| **Table 180-3** Antibacterial | Medications (Antibiotics)—cont’d | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **INDICATIONS (MECHANISM OF ACTION) AND DOSING** | **COMMENTS** |
| Azithromycin Zithromax Tablet: 250 mg  Suspension: 100 mg/5 mL, 200 mg/5 mL | Azalide antibiotic with activity against *S. aureus, Streptococcus, H. influenzae, Mycoplasma, Legionella, Chlamydia trachomatis*  Children: 10 mg/kg PO on day 1 (max dose: 500 mg) followed by 5 mg/kg PO q 24 hr for 4 days  Group A streptococcus pharyngitis: 12 mg/kg/24 hr PO (max dose: 500 mg) for 5 days.  Adults: 500 mg PO day 1 followed by 250 mg for 4 days Uncomplicated *C. trachomatis* infection: single 1 g dose  PO | *Note:* Very long half-life permitting  once-daily dosing. No metabolic-based drug interactions (unlike erythromycin and clarithromycin), limited gastrointestinal distress. Shorter-course regimens (e.g.,  1-3 days) under investigation. 3 day, therapy (10 mg/kg/24 hr × 3 days) and single-dose therapy (30 mg/kg): use with increasing frequency (not for streptococcus pharyngitis) |
| Aztreonam Azactam Injection | **β**-Lactam (monobactam) antibiotic with activity against Gram-negative aerobic bacteria, *Enterobacteriaceae*, and *Pseudomonas aeruginosa*  Neonates: Postnatal age ≤7 days weight ≤2,000 g: 60 mg/ kg/24 hr divided q 12 hr IV or IM; weight >2,000 g:  90 mg/kg/24 hr divided q 8 hr IV or IM; postnatal age  >7 days weight <1,200 g: 60 mg/kg/24 hr divided q 12 hr IV or IM; weight 1,200-2,000 g: 90 mg/kg/24 hr divided q 8 hr IV or IM; weight >2,000 g: 120 mg/ kg/24 hr divided q 6-8 hr IV or IM  Children: 90-120 mg/kg/24 hr divided q 6-8 hr IV or IM. For cystic fibrosis up to 200 mg/kg/24 hr IV  Adults: 1-2 g IV or IM q 8-12 hr (max dose: 8 g/24 hr) | *Cautions:* Rash, thrombophlebitis, eosinophilia. Renally eliminated  *Drug interaction:* Probenecid |
| Carbenicillin Geopen Injection Geocillin oral tablet | Extended-spectrum penicillin (remains susceptible to penicillinase destruction) active against *Enterobacter*, indole-positive *Proteus*, and *Pseudomonas*  Neonates: Postnatal age ≤7 days weight ≤2,000 g: 225 mg/kg/24 hr divided q 8 hr IV or IM; weight  >2,000 g: 300 mg/kg/24 hr divided q 6 hr IV or IM; >7 days: 300-400 mg/kg/24 hr divided q 6 hr IV or IM  Children: 400-600 mg/kg/24 hr divided q 4-6 hr IV or IM | *Cautions:* Painful given intramuscularly; rash; each gram contains 5.3 mEq sodium. Interferes with platelet aggregation at high doses, increases in liver transaminase levels. Renally eliminated. Oral tablet for treatment of urinary tract infection only  *Drug interaction:* Probenecid |
| Cefaclor  Ceclor  Capsule: 250, 500 mg Suspension: 125 mg/5 mL,  187 mg/5 mL, 250 mg/5 mL,  375 mg/5 mL | Second-generation cephalosporin active against  *S. aureus, Streptococcus* including *S. pneumoniae,*  *H. influenzae, E. coli, Klebsiella,* and *Proteus*  Children: 20-40 mg/kg/24 hr divided q 8-12 hr PO (max dose: 2 g)  Adults: 250-500 mg q 6-8 hr PO | *Cautions:* β-Lactam safety profile (rash, eosinophilia) with high incidence of serum sickness reaction. Renally eliminated  *Drug interaction:* Probenecid |
| Cefadroxil Duricef, Ultracef Capsule: 500 mg  Tablet: 1,000 mg Suspension: 125 mg/5 mL,  250 mg/5 mL, 500 mg/5 mL | First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus*  Children: 30 mg/kg/24 hr divided q 12 hr PO (max dose: 2 g)  Adults: 250-500 mg q 8-12 hr PO | *Cautions:* β-lactam safety profile (rash, eosinophilia). Renally eliminated. Long half-life permits q 12-24 hr dosing  *Drug interaction:* Probenecid |
| Cefazolin Ancef, Kefzol Injection | First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus*  Neonates: Postnatal age ≤7 days 40 mg/kg/24 hr divided q 12 hr IV or IM; >7 days 40-60 mg/kg/24 hr divided q 8 hr IV or IM  Children: 50-100 mg/kg/24 hr divided q 8 hr IV or IM Adults: 0.5-2g q 8 hr IV or IM (max dose: 12 g/24 hr) | *Caution:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS  *Drug interaction:* Probenecid |
| Cefdinir Omnicef Capsule: 300 mg  Oral suspension: 125 mg/5 mL | Extended-spectrum, semisynthetic cephalosporin  Children 6 mo-12 yr: 14 mg/kg/24 hr in 1 or 2 doses PO (max dose: 600 mg/24 hr)  Adults: 600 mg q 24 hr PO | *Cautions:* Reduce dosage in renal insufficiency (creatinine clearance <60 mL/ min). Avoid taking concurrently with  iron-containing products and antacids because absorption is markedly decreased; take at least 2 hr apart  *Drug interaction:* Probenecid |
| Cefepime Maxipime Injection | Expanded-spectrum, fourth-generation cephalosporin active against many Gram-positive and Gram-negative pathogens, including *P. aeruginosa* many multidrug- resistant pathogens  Children: 100-150 mg/kg/24 hr q 8-12 hr IV or IM Adults: 2-4 g/24 hr q 12 hr IV or IM | *Adverse events:* Diarrhea, nausea, vaginal candidiasis  Cautions: β-lactam safety profile (rash, eosinophilia). Renally eliminated  *Drug interaction:* Probenecid |

\*In the Drug column, the generic drug name is in bold. In the Indications column, bold indicates major organisms targeted and mechanisms of action.

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| **Table 180-3** Antibacterial | Medications (Antibiotics)—cont’d | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **INDICATIONS (MECHANISM OF ACTION) AND DOSING** | **COMMENTS** |
| Cefixime  Suprax  Tablet: 200, 400 mg Suspension: 100 mg/5 mL | Third-generation cephalosporin active against streptococci*, H. influenzae, M. catarrhalis, Neisseria gonorrhoeae, Serratia marcescens*, and *Proteus vulgaris*. No antistaphylococcal or antipseudomonal activity  Children: 8 mg/kg/24 hr divided q 12-24 hr PO Adults: 400 mg/24 hr divided q 12-24 hr PO | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS  *Drug interaction:* Probenecid |
| Cefoperazone sodium  Cefobid Injection | Third-generation cephalosporin active against many Gram-positive and Gram-negative pathogens  Neonates: 100 mg/kg/24 hr divided q 12 hr IV or IM Children: 100-150 mg/kg/24 hr divided q 8-12 hr IV or IM Adults: 2-4 g/24 hr divided q 8-12 hr IV or IM (max dose:  12 g/24 hr) | *Cautions:* Highly protein-bound cephalosporin with limited potency reflected by weak antipseudomonal activity. Variable Gram-positive activity. Primarily hepatically eliminated in bile  *Drug interaction:* Disulfiram-like reaction with alcohol |
| Cefotaxime sodium  Claforan Injection | Third-generation cephalosporin active against Gram- positive and Gram-negative pathogens. No antipseudomonal activity  Neonates: ≤7 days: 100 mg/kg/24 hr divided q 12 hr IV or IM; >7 days: weight <1,200 g 100 mg/kg/24 hr divided q 12 hr IV or IM; weight >1,200 g: 150 mg/kg/24 hr divided q 8 hr IV or IM  Children: 150 mg/kg/24 hr divided q 6-8 hr IV or IM (meningitis: 200 mg/kg/24 hr divided q 6-8 hr IV)  Adults: 1-2 g q 8-12 hr IV or IM (max dose: 12 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Each gram of drug contains 2.2 mEq sodium. Active metabolite  *Drug interaction:* Probenecid |
| Cefotetan disodium  Cefotan Injection | Second-generation cephalosporin active against  *S. aureus, Streptococcus, H. influenzae, E. coli, Klebsiella, Proteus*, and *Bacteroides*. Inactive against *Enterobacter*  Children: 40-80 mg/kg/24 hr divided IV or IM q 12 hr Adults: 2-4 g/24 hr divided q 12 hr IV or IM (max dose:  6 g/24 hr) | *Cautions:* Highly protein-bound cephalosporin, poor CNS penetration;  β-lactam safety profile (rash, eosinophilia), disulfiram-like reaction with alcohol.  Renally eliminated (~20% in bile) |
| Cefoxitin sodium  Mefoxin Injection | Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, Klebsiella, Proteus*, and *Bacteroides*. Inactive against *Enterobacter*  Neonates: 70-100 mg/kg/24 hr divided q 8-12 hr IV or IM Children: 80-160 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 1-2 g q 6-8 hr IV or IM (max dose: 12 g/24 hr) | *Cautions:* Poor CNS penetration; β-lactam safety profile (rash, eosinophilia). Renally eliminated. Painful given intramuscularly  *Drug interaction:* Probenecid |
| Cefpodoxime proxetil  Vantin  Tablet: 100 mg, 200 mg Suspension: 50 mg/5 mL,  100 mg/5 mL | Third-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, M. catarrhalis,*  *N. gonorrhoeae, E. coli, Klebsiella*, and *Proteus*. No antipseudomonal activity  Children: 10 mg/kg/24 hr divided q 12 hr PO  Adults: 200-800 mg/24 hr divided q 12 hr PO (max dose: 800 mg/24 hr)  Uncomplicated gonorrhea: 200 mg PO as single-dose therapy | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS. Increased bioavailability when taken with food  *Drug interaction:* Probenecid; antacids and H-2 receptor antagonists may decrease absorption |
| Ceftaroline fosamil  Teflaro Injection | Fifth-generation cephalosporin active against *S. aureus* (including MRSA when used for skin and soft-tissue infection), *Streptococcus pyogenes, Streptococcus agalactiae, Escherichia coli, Klebsiella pneumoniae,*  *H. influenzae,* and *Klebsiella oxytoca*  \*Children: 24 mg/kg/24 hr divided q 8 hr IV (<6 mo of age); 36 mg/kg/24 hr divided q 8 hr IV (weight ≤33 kg); 400 mg q 8 hr IV (weight >33 kg)  Adults: 600 mg q 12 hr IV  \*Suggested dose; safety and effectiveness in pediatric patients have not yet been established | *Caution:* β-Lactam safety profile (rash, eosinophilia)  *Drug interaction:* Probenecid |
| Cefprozil  Cefzil  Tablet: 250, 500 mg Suspension: 125 mg/5 mL,  250 mg/5 mL | Second-generation cephalosporin active against  *S. aureus, Streptococcus, H. influenzae, E. coli,*  *M. catarrhalis, Klebsiella*, and *Proteus* Children: 30 mg/kg/24 hr divided q 8-12 hr PO Adults: 500-1,000 mg/24 hr divided q 12 hr PO  (max dose: 1.5 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Good bioavailability; food does not affect bioavailability  *Drug interaction:* Probenecid |

\*In the Drug column, the generic drug name is in bold. In the Indications column, bold indicates major organisms targeted and mechanisms of action.

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**1304 Part XVII** ◆ Infectious Diseases

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| **Table 180-3** Antibacterial | Medications (Antibiotics)—cont’d | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **INDICATIONS (MECHANISM OF ACTION) AND DOSING** | **COMMENTS** |
| Ceftazidime  Fortaz, Ceptaz, Tazicef, Tazidime  Injection | Third-generation cephalosporin active against Gram- positive and Gram-negative pathogens, including  *P. aeruginosa*  Neonates: Postnatal age ≤7 days: 100 mg/kg/24 hr divided q 12 hr IV or IM; >7 days weight ≤1,200 g: 100 mg/kg/24 hr divided q 12 hr IV or IM; weight  >1,200 g: 150 mg/kg/24 hr divided q 8 hr IV or IM Children: 150 mg/kg/24 hr divided q 8 hr IV or IM  (meningitis: 150 mg/kg/24 hr IV divided q 8 hr)  Adults: 1-2 g q 8-12 hr IV or IM (max dose: 8-12 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated.  Increasing pathogen resistance developing with long-term, widespread use  *Drug interaction:* Probenecid |
| Ceftizoxime Cefizox Injection | Third-generation cephalosporin active against Gram- positive and Gram-negative pathogens. No antipseudomonal activity  Children: 150 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 1-2 g q 6-8 hr IV or IM (max dose: 12 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated  *Drug interaction:* Probenecid |
| Ceftriaxone sodium  Rocephin Injection | Third-generation cephalosporin active against Gram- positive and Gram-negative pathogens. No antipseudomonal activity  Neonates: 50-75 mg/kg q 24 hr IV or IM  Children: 50-75 mg/kg q 24 hr IV or IM (meningitis: 75 mg/kg dose 1 then 80-100 mg/kg/24 hr divided q 12-24 hr IV or IM)  Adults: 1-2 g q 24 hr IV or IM (max dose: 4 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Eliminated via kidney (33-65%) and bile; can cause sludging.  Long half-life and dose-dependent protein binding favors q 24 hr rather than q 12 hr dosing. Can add 1% lidocaine for IM injection  *Drug interaction:* Probenecid. In neonates, coadministration with calcium-containing products can result in severe precipitation and attendant embolic complications |
| Cefuroxime (cefuroxime axetil for oral administration)  Ceftin, Kefurox, Zinacef Injection  Suspension: 125 mg/5 mL Tablet: 125, 250, 500 mg | Second-generation cephalosporin active against  *S. aureus, Streptococcus, H. influenzae, E. coli,*  *M. catarrhalis, Klebsiella*, and *Proteus*  Neonates: 40-100 mg/kg/24 hr divided q 12 hr IV or IM Children: 200-240 mg/kg/24 hr divided q 8 hr IV or IM; PO administration: 20-30 mg/kg/24 hr divided q 8 hr  PO  Adults: 750-1,500 mg q 8 hr IV or IM (max dose: 6 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Food increases PO bioavailability  *Drug interaction:* Probenecid |
| Cephalexin  Keflex, Keftab Capsule: 250, 500 mg  Tablet: 500 mg, 1 g Suspension: 125 mg/5 mL,  250 mg/5 mL, 100 mg/mL drops | First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus*  Children: 25-100 mg/kg/24 hr divided q 6-8 hr PO Adults: 250-500 mg q 6 hr PO (max dose: 4 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated  *Drug interaction:* Probenecid |
| Cephradine  Velosef  Capsule: 250, 500 mg Suspension: 125 mg/5 mL,  250 mg/5 mL | First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus*  Children: 50-100 mg/kg/24 hr divided q 6-12 hr PO Adults: 250-500 mg q 6-12 hr PO (max dose: 4 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated  *Drug interaction:* Probenecid |
| Chloramphenicol Chloromycetin Injection Capsule: 250 mg  Ophthalmic, otic solutions Ointment | Broad-spectrum protein synthesis inhibitor active against many Gram-positive and Gram-negative bacteria, *Salmonella*, vancomycin-resistant *Enterococcus faecium, Bacteroides*, other anaerobes, *Mycoplasma, Chlamydia*, and *Rickettsia*; usually inactive against *Pseudomonas*  Neonates: Initial loading dose 20 mg/kg followed 12 hr later by: postnatal age ≤7 days: 25 mg/kg/24 hr q 24 hr IV; >7 days: weight ≤2,000 g: 25 mg/kg/24 hr q 24 hr IV; weight >2,000 g: 50 mg/kg/24 hr divided q 12 hr IV  Children: 50-75 mg/kg/24 hr divided q 6-8 hr IV or PO (meningitis: 75-100 mg/kg/24 hr IV divided q 6 hr)  Adults: 50 mg/kg/24 hr divided q 6 hr IV or PO (max dose: 4 g/24 hr) | *Cautions:* Gray-baby syndrome (from  too-high dose in neonate), bone marrow suppression aplastic anemia (monitor hematocrit, free serum iron)  *Drug interactions:* Phenytoin, phenobarbital, rifampin may decrease levels  *Target serum concentrations:* Peak 20-30 mg/L; trough 5-10 mg/L |

\*In the Drug column, the generic drug name is in bold. In the Indications column, bold indicates major organisms targeted and mechanisms of action.

**Chapter 180** ◆ Principles of Antibacterial Therapy **1305**

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| **Table 180-3** Antibacterial | Medications (Antibiotics)—cont’d | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **INDICATIONS (MECHANISM OF ACTION) AND DOSING** | **COMMENTS** |
| Ciprofloxacin  Cipro  Tablet: 100, 250, 500, 750 mg  Injection  Ophthalmic solution and ointment  Otic suspension  Oral suspension: 250 and 500 mg/5 mL | Quinolone antibiotic active against *P. aeruginosa, Serratia, Enterobacter, Shigella, Salmonella, Campylobacter, N. gonorrhoeae, H. influenzae,*  *M. catarrhalis,* some *S. aureus*, and some  *Streptococcus*  Neonates: 10 mg/kg q 12 hr PO or IV  Children: 15-30 mg/kg/24 hr divided q 12 hr PO or IV; cystic fibrosis: 20-40 mg/kg/24 hr divided q 8-12 hr PO or IV  Adults: 250-750 mg q 12 hr; 200-400 mg IV q 12 hr PO (max dose: 1.5 g/24 hr) | *Cautions:* Concerns of joint destruction in juvenile animals not seen in humans; tendonitis, superinfection, dizziness, confusion, crystalluria, some photosensitivity  *Drug interactions:* Theophylline; magnesium-, aluminum-, or calcium- containing antacids; sucralfate; probenecid; warfarin; cyclosporine |
| Clarithromycin  Biaxin  Tablet: 250, 500 mg Suspension: 125 mg/5 mL,  250 mg/5 mL | Macrolide antibiotic with activity against *S. aureus, Streptococcus, H. influenzae, Legionella, Mycoplasma,* and *C. trachomatis*  Children: 15 mg/kg/24 hr divided q 12 hr PO  Adults: 250-500 mg q 12 hr PO (max dose: 1 g/24 hr) | *Cautions:* Adverse events less than erythromycin; gastrointestinal upset, dyspepsia, nausea, cramping  *Drug interactions:* Same as erythromycin: astemizole carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus |
| Clindamycin  Cleocin  Capsule: 75, 150, 300 mg Suspension: 75 mg/5 mL Injection  Topical solution, lotion, and gel  Vaginal cream | Protein synthesis inhibitor active against most Gram- positive aerobic and anaerobic cocci except *Enterococcus*  Neonates: Postnatal age ≤7 days weight <2,000 g; 10 mg/ kg/24 hr divided q 12 hr IV or IM; weight >2,000 g:  15 mg/kg/24 hr divided q 8 hr IV or IM; >7 days weight  <1,200 g: 10 mg/kg/24 hr IV or IM divided q 12 hr; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 8 hr IV or IM; weight >2,000 g: 20 mg/kg/24 hr divided q 8 hr IV or IM  Children: 10-40 mg/kg/24 hr divided q 6-8 hr IV, IM, or PO  Adults: 150-600 mg q 6-8 hr IV, IM, or PO (max dose: 5 g/24 hr IV or IM or 2 g/24 hr PO) | *Cautions:* Diarrhea, nausea, *Clostridium difficile*–associated colitis, rash Administer slow IV over 30-60 min Topically active as an acne treatment |
| Cloxacillin sodium  Tegopen  Capsule: 250, 500 mg Suspension: 125 mg/5 mL | Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci  Children: 50-100 mg/kg/24 hr divided q 6 hr PO Adults: 250-500 mg q 6 hr PO (max dose: 4 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Primarily hepatically eliminated; requires dose reduction in renal disease. Food decreases bioavailability  *Drug interaction:* Probenecid |
| Colistin (Colistimethate sodium; polymyxin E)  Injection Inhalation | Treatment of multidrug resistant Gram-negative organisms (*Enterobacteriaceae* including extended- spectrum betalactamase and carbapenemase- producing strains)  Children: 2.5-5 mg/kg/day divided in 2-4 divided doses IV  Adults: 300 mg/day in 2-4 divided doses IV | *Cautions:* Nephrotoxicity (~3% in young children; higher rates in adolescents and adults); adjust dose for renal insufficiency; neurotoxicity (headaches, paresthesia, ataxia)  *Drug interactions:* Should not be administered concomitantly with polymyxins or aminoglycosides |
| Co-trimoxazole (trimethoprim- sulfamethoxazole; TMP-SMZ)  Bactrim, Cotrim, Septra, Sulfatrim  Tablet: SMZ 400 mg and TMP 80 mg  Tablet DS: SMZ 800 mg and TMP 160 mg  Suspension: SMZ 200 mg and TMP 40 mg/5 mL  Injection | Antibiotic combination with sequential antagonism of bacterial folate synthesis with broad antibacterial activity: *Shigella, Legionella, Nocardia, Chlamydia, Pneumocystis jiroveci.* Dosage based on TMP component  Children: 6-20 mg TMP/kg/24 hr or IV divided q 12 hr PO  *Pneumocystis carinii* pneumonia: 15-20 mg TMP/kg/24 hr divided q 12 hr PO or IV  *P. carinii* prophylaxis: 5 mg TMP/kg/24 hr or 3 times/wk PO  Adults: 160 mg TMP q 12 hr PO | *Cautions:* Drug dosed on TMP (trimethoprim) component. Sulfonamide skin reactions: rash, erythema multiforme, Stevens-Johnson syndrome, nausea, leukopenia. Renal and hepatic elimination; reduce dose in renal failure  *Drug interactions:* Protein displacement with warfarin, possibly phenytoin, cyclosporine |

\*In the Drug column, the generic drug name is in bold. In the Indications column, bold indicates major organisms targeted and mechanisms of action.

##### Continued

**1306 Part XVII** ◆ Infectious Diseases

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| **Table 180-3** Antibacterial | Medications (Antibiotics)—cont’d | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **INDICATIONS (MECHANISM OF ACTION) AND DOSING** | **COMMENTS** |
| Daptomycin  Cubicin | Disrupts bacterial cell membrane function, causing depolarization leading to inhibition of protein, DNA and RNA synthesis, which results in bacterial cell death. Active against enterococci (including glycopeptide-resistant strains), staphylococci (including MRSA), streptococci, and corynebacteria. Approved for skin and soft-tissue infections. Acceptable for bacteremia and right-sided endocarditis with susceptible strains  Adults: In skin and soft-tissue infections, 4 mg/kg daptomycin is given intravenously once daily. For  *S. aureus* bacteremia or right-sided endocarditis, the approved dose is 6 mg/kg given intravenously once daily  Children: Unknown. Doses of 5-9 mg/kg/day in once- daily dosing have been reported in pediatric clinical trials | *Cautions:* Should not be used for pneumonia as drug inactivated by surfactants. Associated with rash, renal failure, anemia, headache. Is reported to cause myopathy, rhabdomyolysis, and eosinophilic pneumonia  *Drug interactions:* Should not be administered with statins |
| Demeclocycline  Declomycin  Tablet: 150, 300 mg  Capsule: 150 mg | Tetracycline active against most Gram-positive cocci except *Enterococcus*, many Gram-negative bacilli, anaerobes, *Borrelia burgdorferi* (Lyme disease), *Mycoplasma,* and *Chlamydia*  Children: 8-12 mg/kg/24 hr divided q 6-12 hr PO Adults: 150 mg PO q 6-8 hr  Syndrome of inappropriate antidiuretic hormone secretion: 900-1,200 mg/24 hr or 13-15 mg/kg/24 hr divided q 6-8 hr PO with dose reduction based on response to 600-900 mg/24 hr | *Cautions:* Teeth staining, possibly permanent (if administered <8 yr of age) with prolonged use; photosensitivity, diabetes insipidus, nausea, vomiting, diarrhea, superinfections  *Drug interactions:* Aluminum-, calcium-, magnesium-, zinc- and iron-containing food, milk, dairy products may decrease absorption |
| Dicloxacillin  Dynapen, Pathocil Capsule: 125, 250, 500 mg Suspension: 62.5 mg/5 mL | Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci  Children: 12.5-100 mg/kg/24 hr divided q 6 hr PO Adults: 125-500 mg q 6 hr PO | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Primarily renally (65%) and bile (30%) elimination. Food may decrease bioavailability  *Drug interaction:* Probenecid |
| Doripenem Doribax Injection | Carbapenem antibiotic with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including *P. aeruginosa* and anaerobes  Children: dose unknown. Adults: 500 mg q 8 hr IV | *Cautions:* β-Lactam safety profile; does not undergo hepatic metabolism. Renal elimination (70-75%); dose adjustment for renal failure  *Drug interactions:* Valproic acid, probenecid |
| Doxycycline Vibramycin, Doxy Injection  Capsule: 50, 100 mg  Tablet: 50, 100 mg Suspension: 25 mg/5 mL Syrup: 50 mg/5 mL | Tetracycline antibiotic active against most Gram-positive cocci except *Enterococcus*, many Gram-negative bacilli, anaerobes, *B. burgdorferi* (Lyme disease), *Mycoplasma*, and *Chlamydia*  Children: 2-5 mg/kg/24 hr divided q 12-24 hr PO or IV (max dose: 200 mg/24 hr)  Adults: 100-200 mg/24 hr divided q 12-24 hr PO or IV | *Cautions:* Teeth staining, possibly permanent (<8 yr of age) with prolonged use; photosensitivity, nausea, vomiting, diarrhea, superinfections  *Drug interactions:* Aluminum-, calcium-, magnesium-, zinc-, iron-, kaolin-, and pectin-containing products, food, milk, dairy products may decrease absorption. Carbamazepine, rifampin, barbiturates may decrease half-life |
| Erythromycin  E-Mycin, Ery-Tab, Eryc, Ilosone  Estolate 125, 500 mg Tablet EES: 200 mg  Tablet base: 250, 333, 500 mg Suspension: estolate  125 mg/5 mL, 250 mg/5 mL, EES 200 mg/5 mL,  400 mg/5 mL  Estolate drops: 100 mg/mL. EES drops: 100 mg/2.5 mL. Available in combination with sulfisoxazole (Pediazole), dosed on erythromycin content | Bacteriostatic macrolide antibiotic most active against Gram-positive organisms, *Corynebacterium diphtheriae*, and *Mycoplasma pneumoniae*  Neonates: Postnatal age ≤7 days: 20 mg/kg/24 hr divided q 12 hr PO; >7 days weight <1,200 g: 20 mg/kg/24 hr divided q 12 hr PO; weight >1,200 g: 30 mg/kg/24 hr divided q 8 hr PO (give as 5 mg/kg/dose q 6 hr to improve feeding intolerance)  Children: Usual max dose 2 g/24 hr  Base: 30-50 mg/kg/24 hr divided q 6-8 hr PO Estolate: 30-50 mg/kg/24 hr divided q 8-12 hr PO Stearate: 20-40 mg/kg/24 hr divided q 6 hr PO Lactobionate: 20-40 mg/kg/24 hr divided q 6-8 hr IV  Gluceptate: 20-50 mg/kg/24 hr divided q 6 hr IV; usual max dose 4 g/24 hr IV  Adults: Base: 333 mg PO q 8 hr; estolate/stearate/base: 250-500 mg q 6 hr PO | *Cautions:* Motilin agonist leading to marked abdominal cramping, nausea, vomiting, diarrhea. Associated with hypertrophic pyloric stenosis in young infants. Many different salts with questionable tempering of gastrointestinal adverse events. Rare cardiac toxicity with IV use. Dose of salts differ. Topical formulation for treatment of acne  *Drug interactions:* Antagonizes hepatic CYP 3A4 activity: astemizole, carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus, carbamazepine |

\*In the Drug column, the generic drug name is in bold. In the Indications column, bold indicates major organisms targeted and mechanisms of action.

**Chapter 180** ◆ Principles of Antibacterial Therapy **1307**

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| **Table 180-3** Antibacterial | Medications (Antibiotics)—cont’d | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **INDICATIONS (MECHANISM OF ACTION) AND DOSING** | **COMMENTS** |
| Gentamicin Garamycin Injection  Ophthalmic solution, ointment, topical cream | Aminoglycoside antibiotic active against Gram-negative bacilli, especially *E. coli, Klebsiella, Proteus, Enterobacter, Serratia,* and *Pseudomonas*  Neonates: Postnatal age ≤7 days weight 1,200-2,000 g:  2.5 mg/kg q 12-18 hr IV or IM; weight <2,000 g: 2.5 mg/ kg q 12 hr IV or IM; postnatal age >7 days weight 1,200- 2,000 g: 2.5 mg/kg q 8-12 hr IV or IM; weight >2,000 g:  2.5 mg/kg q 8 hr IV or IM  Children: 2.5 mg/kg/24 hr divided q 8-12 hr IV or IM. Alternatively may administer 5-7.5 mg/kg/24 hr IV once daily  Intrathecal: Preservative-free preparation for intraventricular or intrathecal use: neonate: 1 mg/24 hr; children: 1-2 mg/24 hr intrathecal; adults: 4-8 mg/24 hr  Adults: 3-6 mg/kg/24 hr divided q 8 hr IV or IM | Cautions: Anaerobes, *S. pneumoniae,* and other *Streptococcus* are resistant. May cause ototoxicity and nephrotoxicity.  Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min  *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs  *Target serum concentrations:* Peak 6-12 mg/L; trough >2 mg/L with  intermittent daily dose regimens only |
| Imipenem-cilastatin  Primaxin Injection | Carbapenem antibiotic with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including *P. aeruginosa* and anaerobes. No activity against *Stenotrophomonas maltophilia*  Neonates: Postnatal age ≤7 days weight <1,200 g: 20 mg/ kg q 18-24 hr IV or IM; weight >1,200 g: 40 mg/kg divided q 12 hr IV or IM; postnatal age >7 days weight 1,200-2,000 g: 40 mg/kg q 12 hr IV or IM; weight  >2,000 g: 60 mg/kg q 8 hr IV or IM  Children: 60-100 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 2-4 g/24 hr divided q 6-8 hr IV or IM (max dose:  4 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia), nausea, seizures. Cilastatin possesses no antibacterial activity; reduces renal imipenem metabolism.  Primarily renally eliminated  *Drug interaction:* Possibly ganciclovir |
| Linezolid  Zyvox  Tablet: 400, 600 mg  Oral suspension: 100 mg/5 mL Injection: 100 mg/5 mL | Oxazolidinone antibiotic active against Gram-positive cocci (especially drug-resistant organisms), including *Staphylococcus, Streptococcus, E. faecium,* and *Enterococcus faecalis*. Interferes with protein synthesis by binding to 50S ribosome subunit  Children: 10 mg/kg q 12 hr IV or PO  Adults: Pneumonia: 600 mg q 12 hr IV or PO; skin infections: 400 mg q 12 hr IV or PO | *Adverse events:* Myelosuppression, pseudomembranous colitis, nausea, diarrhea, headache  *Drug interaction:* Probenecid |
| Loracarbef Lorabid Capsule: 200 mg  Suspension: 100 mg/5 mL, 200 mg/5 mL | Carbacephem very closely related to cefaclor (second- generation cephalosporin) active against *S. aureus, Streptococcus, H. influenzae, M. catarrhalis, E. coli, Klebsiella*, and *Proteus*  Children: 30 mg/kg/24 hr divided q 12 hr PO (max dose: 2 g)  Adults: 200-400 mg q 12 hr PO (max dose: 800 mg/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated  *Drug interaction:* Probenecid |
| Meropenem Merrem Injection | Carbapenem antibiotic with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including *P. aeruginosa* and anaerobes. No activity against *S. maltophilia*  Children: 60 mg/kg/24 hr divided q 8 hr IV meningitis: 120 mg/kg/24 hr (max dose: 6 g/24 hr) q 8 hr IV  Adults: 1.5-3 g q 8 hr IV | *Cautions:* β-Lactam safety profile; appears to possess less CNS excitation than imipenem. 80% renal elimination  *Drug interaction:* Probenecid |
| Metronidazole  Flagyl, Metro I.V., Topical gel, vaginal gel Injection  Tablet: 250, 500 mg | Highly effective in the treatment of infections caused by anaerobes. Oral therapy of *C. difficile* colitis  Neonates: weight <1,200 g: 7.5 mg/kg 48 hr PO or IV; postnatal age ≤7 days weight 1,200-2,000 g: 7.5 mg/ kg/24 hr q 24 hr PO or IV; weight 2,000 g: 15 mg/ kg/24 hr divided q 12 hr PO or IV; postnatal age <7 days weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 12 hr PO or IV; weight >2,000 g: 30 mg/kg/24 hr divided q 12 hr PO or IV  Children: 30 mg/kg/24 hr divided q 6-8 hr PO or IV Adults: 30 mg/kg/24 hr divided q 6 hr PO or IV (max  dose: 4 g/24 hr) | *Cautions:* Dizziness, seizures, metallic taste, nausea, disulfiram-like reaction with alcohol. Administer IV slow over  30-60 min. Adjust dose with hepatic impairment  *Drug interactions:* Carbamazepine, rifampin, phenobarbital may enhance metabolism; may increase levels of warfarin, phenytoin, lithium |

\*In the Drug column, the generic drug name is in bold. In the Indications column, bold indicates major organisms targeted and mechanisms of action.

##### Continued

**1308 Part XVII** ◆ Infectious Diseases

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| **Table 180-3** Antibacterial | Medications (Antibiotics)—cont’d | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **INDICATIONS (MECHANISM OF ACTION) AND DOSING** | **COMMENTS** |
| Mezlocillin sodium  Mezlin Infection | Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia*, and *Bacteroides;* limited antipseudomonal activity  Neonates: Postnatal age ≤7 days: 150 mg/kg/24 hr divided q 12 hr IV; >7 days: 225 mg/kg divided q 8 hr IV  Children: 200-300 mg/kg/24 hr divided q 4-6 hr IV; cystic fibrosis 300-450 mg/kg/24 hr IV  Adults: 2-4 g/dose q 4-6 hr IV (max dose: 12 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains  1.8 mEq sodium. Interferes with platelet aggregation with high doses; increases noted in liver function test results. Renally eliminated. Inactivated by β-lactamase enzyme  *Drug interaction:* Probenecid |
| Mupirocin Bactroban Ointment | Topical antibiotic active against *Staphylococcus* and  *Streptococcus*  Topical application: Nasal (eliminate nasal carriage) and to the skin 2-4 times per day | *Caution:* Minimal systemic absorption as drug metabolized within the skin. |
| Nafcillin sodium Nafcil, Unipen Injection Capsule: 250 mg  Tablet: 500 mg | Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci, except *Enterococcus* and coagulase-negative staphylococci  Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q 12 hr IV or IM; weight  >2,000 g: 75 mg/kg/24 hr divided q 8 hr IV or IM; postnatal age >7 days weight 1,200-2,000 g: 75 mg/  kg/q 8 hr; weight >2,000 g: 100 mg/kg divided q 6-8 hr IV (meningitis: 200 mg/kg/24 hr divided q 6 hr IV)  Children: 100-200 mg/kg/24 hr divided q 4-6 hr IV Adults: 4-12 g/24 hr divided q 4-6 hr IV (max dose:  12 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia), phlebitis; painful given intramuscularly; oral absorption highly variable and erratic (not recommended)  *Adverse effect:* Neutropenia |
| Nalidixic acid  NegGram  Tablet: 250, 500, 1,000 mg Suspension: 250 mg/5 mL | First-generation quinolone effective for short-term treatment of lower urinary tract infections caused by  *E. coli, Enterobacter, Klebsiella*, and *Proteus*  Children: 50-55 mg/kg/24 hr divided q 6 hr PO; suppressive therapy 25-33 mg/kg/24 hr divided q 6-8 hr PO  Adults: 1 g q 6 hr PO; suppressive therapy: 500 mg q 6 hr PO | *Cautions:* Vertigo, dizziness, rash. Not for use in systemic infections  *Drug interactions:* Liquid antacids |
| Neomycin sulfate  Mycifradin Tablet: 500 mg  Topical cream, ointment Solution: 125 mg/5 mL | Aminoglycoside antibiotic used for topical application or orally before surgery to decrease gastrointestinal flora (nonabsorbable) and hyperammonemia  Infants: 50 mg/kg/24 hr divided q 6 hr PO Children: 50-100 mg/kg/24 hr divided q 6-8 hr PO Adults: 500-2,000 mg/dose q 6-8 hr PO | *Cautions:* In patients with renal dysfunction because small amount absorbed may accumulate  *Adverse events:* Primarily related to topical application, abdominal cramps, diarrhea, rash  Aminoglycoside ototoxicity and nephrotoxicity if absorbed |
| Nitrofurantoin  Furadantin, Furan, Macrodantin  Capsule: 50, 100 mg Extended-release capsule:  100 mg  Macrocrystal: 50, 100 mg Suspension: 25 mg/5 mL | Effective in the treatment of lower urinary tract infections caused by Gram-positive and Gram-negative pathogens  Children: 5-7 mg/kg/24 hr divided q 6 hr PO (max dose: 400 mg/24 hr); suppressive therapy 1-2.5 mg/kg/24 hr divided q 12-24 hr PO (max dose: 100 mg/24 hr)  Adults: 50-100 mg/24 hr divided q 6 hr PO | *Cautions:* Vertigo, dizziness, rash, jaundice, interstitial pneumonitis. Do not use with moderate to severe renal dysfunction  *Drug interactions:* Liquid antacids |
| Ofloxacin  Ocuflox 0.3% ophthalmic  solution: 1, 5, 10 mL  Floxin 0.3% otic solution: 5,  10 mL | Quinolone antibiotic for treatment of conjunctivitis or corneal ulcers (ophthalmic solution) and otitis externa or chronic suppurative otitis media (otic solution) caused by susceptible Gram-positive, Gram-negative, anaerobic bacteria, or *C. trachomatis*  *Child >1-12 yr:*  Conjunctivitis: 1-2 drops in affected eye(s) q 2-4 hr for 2 days, then 1-2 drops qid for 5 days  Corneal ulcers: 1-2 drops q 30 min while awake and at  4 hr intervals at night for 2 days, then 1-2 drops hourly for 5 days while awake, then 1-2 drops q 6 hr for 2 days Otitis externa (otic solution): 5 drops into affected ear bid  for 10 days  Chronic suppurative otitis media: treat for 14 days  *Child >12 yr and adults:* Ophthalmic solution doses same as for younger children. Otitis externa (otic solution): Use 10 drops bid for 10 or 14 days as for younger children | *Adverse events:* Burning, stinging, eye redness (ophthalmic solution), dizziness with otic solution if not warmed |

\*In the Drug column, the generic drug name is in bold. In the Indications column, bold indicates major organisms targeted and mechanisms of action.

**Chapter 180** ◆ Principles of Antibacterial Therapy **1309**

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| **Table 180-3** Antibacterial | Medications (Antibiotics)—cont’d | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **INDICATIONS (MECHANISM OF ACTION) AND DOSING** | **COMMENTS** |
| Oxacillin sodium Prostaphlin Injection  Capsule: 250, 500 mg Suspension: 250 mg/5 mL | Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci, except *Enterococcus* and coagulase-negative staphylococci  Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q 12 hr IV; weight >2,000 g: 75 mg/kg/24 hr IV divided q 8 hr IV; postnatal age >7 days weight <1,200 g: 50 mg/kg/24 hr IV divided q  12 hr IV; weight 1,200-2,000 g: 75 mg/kg/24 hr divided q 8 hr IV; weight >2,000 g: 100 mg/kg/24 hr IV divided q 6 hr IV  Infants: 100-200 mg/kg/24 hr divided q 4-6 hr IV Children: PO 50-100 mg/kg/24 hr divided q 4-6 hr IV Adults: 2-12 g/24 hr divided q 4-6 hr IV (max dose:  12 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia)  Moderate oral bioavailability (35-65%) Primarily renally eliminated  *Drug interaction:* Probenecid  *Adverse effect:* Neutropenia |
| Penicillin G Injection Tablets | Penicillin active against most Gram-positive cocci;  *S. pneumoniae* (resistance is increasing), group A *Streptococcus,* and some Gram-negative bacteria (e.g., *N. gonorrhoeae, N. meningitidis*)  Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50,000 units/kg/24 hr divided q 12 hr IV or IM (meningitis: 100,000 units/kg/24 hr divided q 12 hr IV or IM); weight >2,000 g: 75,000 units/kg/24 hr divided q  8 hr IV or IM (meningitis: 150,000 units/kg/24 hr divided q 8 hr IV or IM); postnatal age >7 days weight ≤1,200 g: 50,000 units/kg/24 hr divided q 12 hr IV (meningitis: 100,000 units/kg/24 hr divided q 12 hr IV); weight  1,200-2,000 g: 75,000 units/kg/24 hr q 8 hr IV (meningitis: 225,000 units/kg/24 hr divided q 8 hr IV); weight >2,000 g: 100,000 units/kg/24 hr divided q 6 hr IV (meningitis: 200,000 units/kg/24 hr divided q 6 hr IV)  Children: 100,000-250,000 units/kg/24 hr divided q 4-6 hr IV or IM (max dose: 400,000 units/kg/24 hr)  Adults: 2-24 million units/24 hr divided q 4-6 hr IV or IM | *Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with marked renal disease. Substantial pathogen resistance. Primarily renally eliminated  *Drug interaction:* Probenecid |
| Penicillin G, benzathine  Bicillin Injection | Long-acting repository form of penicillin effective in the treatment of infections responsive to persistent, low penicillin concentrations (1-4 wk), e.g., group A *Streptococcus* pharyngitis, rheumatic fever prophylaxis  Neonates weight >1,200 g: 50,000 units/kg IM once Children: 300,000-1.2 million units/kg q 3-4 wk IM (max  dose: 1.2-2.4 million units/dose) Adults: 1.2 million units IM q 3-4 wk | *Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy. Administer by IM injection only. Substantial pathogen resistance. Primarily renally eliminated  *Drug interaction:* Probenecid |
| Penicillin G, procaine  Crysticillin Injection | Repository form of penicillin providing low penicillin concentrations for 12 hr  Neonates weight >1,200 g: 50,000 units/kg/24 hr IM Children: 25,000-50,000 units/kg/24 hr IM for 10 days  (max dose: 4.8 million units/dose)  Gonorrhea: 100,000 units/kg (max dose: 4.8 million units/24 hr) IM once with probenecid 25 mg/kg (max dose: 1 g)  Adults: 0.6-4.8 million units q 12-24 hr IM | *Cautions:* β-Lactam safety profile (rash, eosinophilia) allergy. Administer by IM injection only. Substantial pathogen resistance. Primarily renally eliminated  *Drug interaction:* Probenecid |
| Penicillin V  Pen VK, V-Cillin K Tablet: 125, 250, 500 mg  Suspension: 125 mg/5 mL, 250 mg/5 mL | Preferred oral dosing form of penicillin, active against most Gram-positive cocci; *S. pneumoniae* (resistance is increasing), other streptococci, and some  Gram-negative bacteria (e.g., N*. gonorrhoeae, N. meningitidis*)  Children: 25-50 mg/kg/24 hr divided q 4-8 hr PO Adults: 125-500 mg q 6-8 hr PO (max dose: 3 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with renal disease. Substantial pathogen resistance. Primarily renally eliminated. Inactivated by penicillinase  *Drug interaction:* Probenecid |
| Piperacillin Pipracil Injection | Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia, P. aeruginosa,* and *Bacteroides*  Neonates: Postnatal age ≤7 days 150 mg/kg/24 hr divided q 8-12 hr IV; >7 days; 200 mg/kg divided q 6-8 hr IV  Children: 200-300 mg/kg/24 hr divided q 4-6 hr IV; cystic fibrosis: 350-500 mg/kg/24 hr IV  Adults: 2-4 g/dose q 4-6 hr (max dose: 24 g/24 hr) IV | *Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains  1.9 mEq sodium. Interferes with platelet aggregation/serum sickness-like reaction with high doses; increases in liver function tests. Renally eliminated. Inactivated by penicillinase  *Drug interaction:* Probenecid |

\*In the Drug column, the generic drug name is in bold. In the Indications column, bold indicates major organisms targeted and mechanisms of action.

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**1310 Part XVII** ◆ Infectious Diseases

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| **Table 180-3** Antibacterial | Medications (Antibiotics)—cont’d | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **INDICATIONS (MECHANISM OF ACTION) AND DOSING** | **COMMENTS** |
| Piperacillin-tazobactam  Zosyn Injection | Extended-spectrum penicillin (piperacillin) combined with a **β**-lactamase inhibitor (tazobactam) active against *S. aureus, H. influenzae, E. coli, Enterobacter, Serratia, Acinetobacter, P. aeruginosa,* and *Bacteroides*  Children: 300-400 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 3.375 g q 6-8 hr IV or IM | *Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains  1.9 mEq sodium  Interferes with platelet aggregation, serum sickness–like reaction with high doses, increases in liver function test results.  Renally eliminated  *Drug interaction:* Probenecid |
| Quinupristin/dalfopristin  Synercid  IV injection: powder for reconstitution, 10 mL  contains 150 mg  quinupristin, 350 mg dalfopristin | Streptogramin antibiotic (quinupristin) active against vancomycin-resistant *E. faecium* (VRE) and methicillin- resistant *S. aureus* (MRSA). Not active against  *E. faecalis*  Children and adults: VRE: 7.5 mg/kg q 8 hr IV for VRE; skin infections: 7.5 mg/kg q 12 hr IV | *Adverse events:* Pain, edema, or phlebitis at injection site, nausea, diarrhea  *Drug interactions*: Synercid is a potent inhibitor of CYP 3A4 |
| Sulfadiazine  Tablet: 500 mg | Sulfonamide antibiotic primarily indicated for the treatment of lower urinary tract infections caused by  *E. coli, P. mirabilis,* and *Klebsiella*  Toxoplasmosis:  Neonates: 100 mg/kg/24 hr divided q 12 hr PO with pyrimethamine 1 mg/kg/24 hr PO (with folinic acid)  Children: 120-200 mg/kg/24 hr divided q 6 hr PO with pyrimethamine 2 mg/kg/24 hr divided q 12 hr PO ≥3 days then 1 mg/kg/24 hr (max dose: 25 mg/24 hr) with folinic acid  Rheumatic fever prophylaxis: weight ≤30 kg:  500 mg/24 hr q 24 hr PO; weight >30 kg: 1 g/24 hr q 24 hr PO | *Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life ~10 hr  *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate |
| Sulfamethoxazole  Gantanol Tablet: 500 mg  Suspension: 500 mg/5 mL | Sulfonamide antibiotic used for the treatment of otitis media, chronic bronchitis, and lower urinary tract infections due to susceptible bacteria  Children: 50-60 mg/kg/24 hr divided q 12 hr PO Adults: 1 g/dose q 12 hr PO (max dose: 3 g/24 hr) | *Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life 12 hr. Initial dose often a loading dose (doubled)  *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate |
| Sulfisoxazole Gantrisin Tablet: 500 mg  Suspension: 500 mg/5 mL Ophthalmic solution, ointment | Sulfonamide antibiotic used for the treatment of otitis media, chronic bronchitis, and lower urinary tract infections caused by susceptible bacteria  Children: 120-150 mg/kg/24 hr divided q 4-6 hr PO (max dose: 6 g/24 hr)  Adults: 4-8 g/24 hr divided q 4-6 hr PO | *Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life ~7-12 hr. Initial dose often a loading dose (doubled)  *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate |
| Ticarcillin Ticar Injection | Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia, P. aeruginosa,* and *Bacteroides*  Neonates: Postnatal age ≤7 days weight <2,000 g:  150 mg/kg/24 hr divided q 8-12 hr IV; >7 days weight  <2,000 g: 225 mg/kg/24 hr divided q 8 hr IV; >7 days weight <1,200 g: 150 mg/kg/24 hr divided q 12 hr IV; weight 1,200-2,000 g: 225 mg/kg/24 hr divided q 8 hr IV; weight >2,000 g: 300 mg/kg/24 hr divided q 6-8 hr IV  Children: 200-400 mg/kg/24 hr divided q 4-6 hr IV; cystic fibrosis: 400-600 mg/kg/24 hr IV  Adults: 2-4 g/dose q 4-6 hr IV (max dose: 24 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains  5-6 mEq sodium. Interferes with platelet aggregation; increases in liver function tests. Renally eliminated. Inactivated by penicillinase  *Drug interaction:* Probenecid |
| Ticarcillin-clavulanate  Timentin Injection | Extended-spectrum penicillin (ticarcillin) combined with a **β**-lactamase inhibitor (clavulanate) active against  *S. aureus, H. influenzae, Enterobacter, E. coli, Serratia,*  *P. aeruginosa, Acinetobacter,* and *Bacteroides*  Children: 280-400 mg/kg/24 hr q 4-8 hr IV or IM  Adults: 3.1 g q 4-8 hr IV or IM (max dose: 18-24 g/24 hr) | *Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains  5-6 mEq sodium. Interferes with platelet aggregation; increases in liver function tests. Renally eliminated  *Drug interaction:* Probenecid |

\*In the Drug column, the generic drug name is in bold. In the Indications column, bold indicates major organisms targeted and mechanisms of action.

**Chapter 180** ◆ Principles of Antibacterial Therapy **1311**

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| **Table 180-3** Antibacterial | Medications (Antibiotics)—cont’d | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **INDICATIONS (MECHANISM OF ACTION) AND DOSING** | **COMMENTS** |
| Tigecycline Tygacil Injection | Tetracycline-class antibiotic (glycylcycline) active against Enterobacteriaceae, including extended spectrum  **β**-lactamase producers; streptococci (including VRE); staphylococci (including MRSA); and anaerobes  Children: unknown  Adults: 100 mg loading dose followed by 50 mg q 12 hr IV | *Cautions:* Pregnancy; children <8 yr of age; photosensitivity; hypersensitivity to tetracyclines; hepatic impairment (~60% hepatic clearance)  *Drug interaction:* Warfarin; mycophenolate mofetil |
| Tobramycin Nebcin, Tobrex Injection  Ophthalmic solution, ointment | Aminoglycoside antibiotic active against Gram-negative bacilli, especially *E. coli, Klebsiella, Enterobacter, Serratia, Proteus,* and *Pseudomonas*  Neonates: Postnatal age ≤7 days, weight 1,200-2,000 g:  2.5 mg/kg q 12-18 hr IV or IM; weight >2,000 g: 2.5 mg/ kg q 12 hr IV or IM; postnatal age >7 days, weight 1,200-2,000 g: 2.5 mg/kg q 8-12 hr IV or IM; weight  >2,000 g: 2.5 mg/kg q 8 hr IV or IM  Children: 2.5 mg/kg/24 hr divided q 8-12 hr IV or IM. Alternatively may administer 5-7.5 mg/kg/24 hr IV. Preservative-free preparation for intraventricular or intrathecal use: neonate: 1 mg/24 hr; children:  1-2 mg/24 hr; adults: 4-8 mg/24 hr  Adults: 3-6 mg/kg/24 hr divided q 8 hr IV or IM | *Cautions: S. pneumoniae*, other *Streptococcus,* and anaerobes are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min  *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs  *Target serum concentrations:* Peak 6-12 mg/L; trough <2 mg/L |
| Trimethoprim Proloprim, Trimpex Tablet: 100, 200 mg | Folic acid antagonist effective in the prophylaxis and treatment of *E. coli, Klebsiella, P. mirabilis,* and *Enterobacter* urinary tract infections; *P. carinii* pneumonia  Children: For urinary tract infection: 4-6 mg/kg/24 hr divided q 12 hr PO  Children >12 yr and adults: 100-200 mg q 12 hr PO.  *P. carinii* pneumonia (with dapsone): 15-20 mg/kg/24 hr divided q 6 hr for 21 days PO | *Cautions:* Megaloblastic anemia, bone marrow suppression, nausea, epigastric distress, rash  *Drug interactions:* Possible interactions with phenytoin, cyclosporine, rifampin, warfarin |
| Vancomycin Vancocin, Lyphocin Injection  Capsule: 125 mg, 250 mg Suspension | Glycopeptide antibiotic active against most Gram- positive pathogens including staphylococci (including MRSA and coagulase-negative staphylococci), *S. pneumoniae* including penicillin-resistant strains, *Enterococcus* (resistance is increasing), and *C. difficile*– associated colitis  Neonates: Postnatal age ≤7 days, weight <1,200 g: 15 mg/kg/24 hr divided q 24 hr IV; weight 1,200-  2,000 g: 15 mg/kg/24 hr divided q 12-18 hr IV; weight  >2,000 g: 30 mg/kg/24 hr divided q 12 hr IV; postnatal age >7 days, weight <1,200 g: 15 mg/kg/24 hr divided q 24 hr IV; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 8-12 hr IV; weight >2,000 g: 45 mg/kg/24 hr divided q 8 hr IV  Children: 45-60 mg/kg/24 hr divided q 8-12 hr IV; *C. difficile*–associated colitis; 40-50 mg/kg/24 hr divided q 6-8 hr PO.40-50 mg/kg/24 hr divided q 6-8 hr PO | *Cautions:* Ototoxicity and nephrotoxicity particularly when co-administered with other ototoxic and nephrotoxic drugs  Infuse IV over 45-60 min. Flushing (red man syndrome) associated with rapid IV infusions, fever, chills, phlebitis (central line is preferred). Renally eliminated  *Target serum concentrations:* Peak (1 hr after 1 hr infusion) 30-40 mg/L; trough 5-10 mg/L |

\*In the Drug column, the generic drug name is in bold. In the Indications column, bold indicates major organisms targeted and mechanisms of action.

**1312 Part XVII** ◆ Infectious Diseases

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| **Table 180-6** | Potential Adverse Effects of Cephalosporins | |
| **TYPE** | **SPECIFIC** | **FREQUENCY** |
| Hypersensitivity | Rash Urticaria  Serum sickness Anaphylaxis | 1-3%  <1%  <1%  0.01% |
| Gastrointestinal | Diarrhea  Nausea, vomiting Transient transaminase  elevation Biliary sludge | 1-19%  1-6%  1-7%  20-46%\* |
| Hematologic | Eosinophilia Neutropenia Thrombocytopenia Hypoprothrombinemia Impaired platelet  aggregation Hemolytic anemia | 1-10%  <1%  <1-3%  <1%  <1%  <1% |
| Renal | Interstitial nephritis | <1% |
| Central nervous system | Seizures Encephalopathy | <1%  <1% |
| False-positive laboratory | Coombs positive Glucosuria Serum creatinine | 3%  Rare Rare |
| Other | Drug fever  Disulfiram-like reaction\* Superinfection  Phlebitis  Calcium-antibiotic precipitation (ceftriaxone) | Rare Rare Rare Rare  Unknown; is associated with embolic events |

\*Cephalosporins with thiomethyl tetrazole ring (MTT) side chain.

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| **Table 180-4** | Adverse | Reactions to Penicillins\* | |
| **TYPE OF REACTION** | | **FREQUENCY (%)** | **OCCURS MOST FREQUENTLY WITH**\* |
| ALLERGIC | |  |  |
| Immunoglobulin E | | 0.004-0.4 | Penicillin G |
| antibody | |  |  |
| * Anaphylaxis | |  |  |
| * Early urticaria (<72 hr) | |  |  |
| Cytotoxic antibody | | Rare | Penicillin G |
| * Hemolytic anemia | |  |  |
| Antigen–antibody | | Rare | Penicillin G |
| complex disease | |  |  |
| * Serum sickness | |  |  |
| Delayed hypersensitivity   * Contact dermatitis | | 4-8 | Ampicillin |
| IDIOPATHIC  Skin rash Fever  Late-onset urticaria | | 4-8 | Ampicillin |
| GASTROINTESTINAL | | 2-5 |  |
| Diarrhea | | 2-5 | Ampicillin |
| Enterocolitis | | <1 | Ampicillin |
| HEMATOLOGIC | |  | Penicillin G  Penicillin G, nafcillin, oxacillin, piperacillin  Ticarcillin |
| Hemolytic anemia | | Rare |
| Neutropenia | | 1-4 |
| Platelet dysfunction | | 3 |
| HEPATIC  Elevated serum aspartate transaminase level | | 1-4 | Flucloxacillin, nafcillin, oxacillin |
| ELECTROLYTE DISTURBANCE | | |  |
| Sodium overload Variable | | | Ticarcillin |
| Hypokalemia Variable | | | Ticarcillin |
| Hyperkalemia—acute Rare | | | Penicillin G |
| NEUROLOGIC  Seizures  Bizarre sensations | | Rare | Penicillin G Procaine penicillin |
| RENAL  Interstitial nephritis | | <1% | Any penicillin |

\*All the reactions can occur with any of the penicillins.

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| **Table 180-5** | Classification of Parenteral and Oral Cephalosporins | | | | | | |
| **CEPHALOSPORINS** | | **FIRST GENERATION** | **SECOND GENERATION** | **CEPHAMYCINS** | **THIRD GENERATION** | **FOURTH GENERATION** | **FIFTH GENERATION** |
| Parenteral | | Cefazolin (Ancef, Kefzol)  Cephalothin (Keflin, Seffin)  Cephapirin (Cefadyl) Cephradine (Velosef) | Cefamandole (Mandol)  Cefonicid (Monocid)  Cefuroxime (Kefurox, Zinacef) | Cefmetazole (Zefazone)  Cefotetan (Cefotan)  Cefoxitin (Mefoxin) | Cefoperazone (Cefobid)  Cefotaxime (Claforan)  Ceftazidime (Fortaz) Ceftizoxime (Cefizox)  Ceftriaxone (Rocephin) | Cefepime (Maxipime)  Cefpirome (Cefrom)  Ceftolozane (combined with tazobactam; CXA-101) | Ceftaroline (Teflaro)  Ceftobiprole (Zeftera) |
| Oral | | Cefadroxil (Duricef, Ultracef)  Cephalexin (Keflex, Biocef, Keftab)  Cephradine  (Velosef) | Cefaclor (Ceclor)  Cefprozil (Cefzil) Cefuroxime-  axetil (Ceftin)  Loracarbef (Lorabid) |  | Cefdinir (Omnicef)  Cefditoren (Spectracef)  Cefixime (Suprax)  Cefpodoxime (Vantin) |  |  |
|  | |  |  |  | Ceftibuten (Cedax) |  |  |

*Adapted from Mandell GL, Bennett JE, Dolin R, editors:* Principles and practice of infectious diseases*, ed 7. Philadelphia, 2010, Elsevier, Table 22-1.*

**Chapter 181** ◆ *Staphylococcus* **1319**

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| **Table 181-1** Parenteral Antimicrobial Agent(s) for Treatment of Bacteremia and Other Serious *Staphylococcus aureus*  Infections | |
| **SUSCEPTIBILITY ANTIMICROBIAL AGENTS** | **COMMENTS** |
| I. INITIAL EMPIRIC THERAPY (ORGANISM OF UNKNOWN SUSCEPTIBILITY)  Drugs of choice: Vancomycin (15 mg/kg Q6-H + nafcillin or oxacillin)  Vancomycin (15 mg/kg Q8H)  Clindamycin | For life-threatening infections (i.e., septicemia, endocarditis, CNS infection); linezolid could be substituted if the patient has received several recent courses of vancomycin  For non–life-threatening infection without signs of severe sepsis (e.g., skin infection, cellulitis, osteomyelitis, pyarthrosis) when rates of MRSA colonization and infection in the community are substantial  For non–life-threatening infection without signs of severe sepsis when rates of MRSA colonization and infection in the community are substantial and prevalence of clindamycin resistance is low |
| II. METHICILLIN-SUSCEPTIBLE, PENICILLIN-RESISTANT *S. AUREUS*  Drugs of choice: Nafcillin or oxacillin† Alternatives (depending on Cefazolin  susceptibility results): Clindamycin Vancomycin  Ampicillin + sulbactam | Only for patients with a serious penicillin allergy and clindamycin-susceptible strain  Only for penicillin- and cephalosporin-allergic patients |
| III. MRSA (OXACILLIN MIC, 4 **µ**G/ML OR GREATER)  *A. Healthcare-Associated (Multidrug-Resistant)*  Drugs of choice: Vancomycin + gentamicin† Alternatives: susceptibility Trimethoprim-sulfamethoxazole  testing results available before Linezolid‡  alternative drugs are used Quinupristin-dalfopristin‡  Fluoroquinolones | Not recommended for people younger than 18 yr of age or as monotherapy |
| *B. Community (Not Multidrug-Resistant)*  Drugs of choice: Vancomycin + gentamicin† Clindamycin (if strain susceptible) Trimethoprim-sulfamethoxazole  Alternatives: Vancomycin | For life-threatening infections  For pneumonia, septic arthritis, osteomyelitis, skin or soft tissue infections  For skin or soft tissue infections |
| IV. VANCOMYCIN INTERMEDIATELY SUSCEPTIBLE OR *S. AUREUS*† (MIC, 4 TO 16 **µ**G/ML)‡  Drugs of choice: Optimal therapy is not known Dependent on in vitro susceptibility test results Linezolid‡  Daptomycin§ Quinupristin-dalfopristin‡ Tigecycline‡ | |
| Alternatives: Vancomycin + linezolid ± gentamicin Vancomycin + trimethoprim-sulfamethoxazole† | |

†One of the adjunctive agents, gentamicin or rifampin, should be added to the therapeutic regimen for life-threatening infections such as endocarditis or CNS infection or infections with a vancomycin-intermediate *S. aureus* strain. Consultation with an infectious diseases specialist should be considered to determine which agent to use and duration of use.

‡Linezolid, quinupristin-dalfopristin, and tigecycline are agents with activity in vitro and efficacy in adults with multidrug-resistant, Gram-positive organisms, including *S. aureus*. Because experience with these agents in children is limited, consultation with an infectious diseases specialist should be considered before use.

§Daptomycin is active in vitro against multidrug-resistant, Gram-positive organisms, including *S. aureus*, but has not been evaluated in children. Daptomycin is approved by the US FDA only for the treatment of complicated skin and skin structure infections and for *S. aureus* bloodstream infections. Daptomycin is ineffective for treatment of pneumonia and is not indicated for patients 18 yr of age and older.

CNS, central nervous system; MRSA, methicillin-resistant *S. aureus*; MIC, minimum inhibitory concentration.

*From Pickering LK, editor:* Red book: 2012 report of the Committee on Infectious Diseases*, ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

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| **Table 182-5** | Medical Conditions or Other Indications for Administration of PCV13,\* and Indications for PPSV23† Administration, and Revaccination for Children Age 6–18 Years‡ | | | |
| **RISK GROUP** | | **UNDERLYING MEDICAL CONDITION** | **PCV13 PPSV23 RECOMMENDED RECOMMENDED** | **REVACCINATION 5 YR AFTER 1ST DOSE** |
| Immunocompetent persons | | Chronic heart disease§ Chronic lung disease|| Diabetes mellitus Cerebrospinal fluid leaks Cochlear implants Alcoholism  Chronic liver disease Cigarette smoking | ✓  ✓  ✓  ✓ ✓  ✓ ✓  ✓  ✓  ✓ |  |
| Persons with functional or anatomic asplenia | | Sickle cell disease/other hemoglobinopathies Congenital or acquired asplenia | ✓ ✓  ✓ ✓ | ✓  ✓ |

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| **Table 182-4** | | Recommended Transition Schedule from  7-Valent Pneumococcal Conjugate Vaccine (PCV7) to 13-Valent Vaccine (PCV13) Vaccination Among Infants and Children, According to Number of Previous PCV7 Doses Received—Advisory Committee on Immunization Practices (ACIP), United States, 2010 | | | |
| **INFANT SERIES** | | |  | **BOOSTER DOSE** | **SUPPLEMENTAL PCV13 DOSE** |
| 2 mo | 4 mo | | 6 mo | ≥12 mo\* | 14-59 mo† |
| PCV7 | PCV13 | | PCV13 | PCV13 | — |
| PCV7 | PCV7 | | PCV13 | PCV13 | — |
| PCV7 | PCV7 | | PCV7 | PCV13 | — |
| PCV7 | PCV7 | | PCV7 | PCV7 | PCV13 |

\*Minimum interval between doses is 8 wk except for children vaccinated at age

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| **Table 182-3** | Recommended Routine Vaccination Schedule for 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Among Infants and Children Who Have Not Received Previous Doses of 7-Valent Vaccine (PCV7) or PCV13, by Age at First Dose—Advisory Committee on Immunization Practices (ACIP), United States, 2010 | | |
| **AGE AT 1ST DOSE (MO)** | | **PRIMARY PCV13 SERIES\*** | **PCV13 BOOSTER DOSE†** |
| 2-6 | | 3 doses | 1 dose at age 12-15 mo |
| 7-11 | | 2 doses | 1 dose at age 12-15 mo |
| 12-23 | | 2 doses | — |
| 24-59 (healthy children) | | 1 dose | — |
| 24-71 (children with certain chronic diseases or immunocompromising conditions) | | 2 doses | — |

<12 mo for whom minimum interval between doses is 4 wk. Minimum age for administration of 1st dose is 6 wk.

†Given at least 8 wk after the previous dose.

*From Centers for Disease Control and Prevention (CDC): Licensure of a*

*13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children—Advisory Committee on Immunization Practices (ACIP), 2010,* MMWR Morb Mortal Wkly Rep *59:258–261, 2010, Table 2.*

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| **Table 183-1** | Definition of Streptococcal Toxic Shock Syndrome |
| CLINICAL CRITERIA  Hypotension plus 2 or more of the following: Renal impairment  Coagulopathy Hepatic involvement  Adult respiratory distress syndrome Generalized erythematous macular rash Soft-tissue necrosis | |
| DEFINITE CASE  Clinical criteria plus group A streptococcus from a normally sterile site | |
| PROBABLE CASE  Clinical criteria plus group A streptococcus from a nonsterile site | |

\*No additional PCV13 doses are indicated for children age 12-23 mo who have received 2 or 3 doses of PCV before age 12 mo and at least 1 dose of PCV13 at age ≥12 mo.

†For children with underlying medical conditions (see Table 182-1), a single supplemental PCV13 dose is recommended through age 71 mo.

*From Centers for Disease Control and Prevention (CDC): Licensure of a*

*13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children—Advisory Committee on Immunization Practices (ACIP), 2010,* MMWR Morb Mortal Wkly Rep *59:258–261, 2010, Table 3.*

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| **Table 181-2** | Diagnostic Criteria of Staphylococcal Toxic Shock Syndrome |
| MAJOR CRITERIA (ALL REQUIRED)  Acute fever; temperature >38.8°C (101.8°F)  Hypotension (orthostatic, shock; blood pressure below age- appropriate norms)  Rash (erythroderma with convalescent desquamation) | |
| MINOR CRITERIA (ANY 3 OR MORE)  Mucous membrane inflammation (vaginal, oropharyngeal or conjunctival hyperemia, strawberry tongue)  Vomiting, diarrhea  Liver abnormalities (bilirubin or transaminase greater than twice upper limit of normal)  Renal abnormalities (urea nitrogen or creatinine greater than twice upper limit of normal, or greater than 5 white blood cells per high-power field)  Muscle abnormalities (myalgia or creatinine phosphokinase greater than twice upper limit of normal)  Central nervous system abnormalities (alteration in consciousness without focal neurologic signs)  Thrombocytopenia (100,000/mm3 or less) | |
| EXCLUSIONARY CRITERIA  Absence of another explanation  Negative blood cultures (except occasionally for *Staphylococcus aureus*) | |

*Data from Pickering LK, editor:* Red book: 2012 report of the Committee on Infectious Diseases*, ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

**Chapter 183** ◆ Group A Streptococcus **1333**

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| **Table 183-2** | Guidelines for the Diagnosis of Initial or Recurrent Attack of Rheumatic Fever (Jones Criteria, Updated 2015)1-5 | | |
| **MAJOR MANIFESTATIONS** | | **MINOR MANIFESTATIONS** | **SUPPORTING EVIDENCE OF ANTECEDENT GROUP A STREPTOCOCCAL INFECTION** |
| Carditis Polyarthritis  Erythema marginatum Subcutaneous nodules Chorea | | Clinical features:  Arthralgia Fever  Laboratory features:  Elevated acute phase reactants: Erythrocyte sedimentation rate C-reactive protein | Positive throat culture or rapid streptococcal antigen test  Elevated or increasing streptococcal antibody titer |
| Prolonged P-R interval | | | |

*From Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 2015 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association (in press).*

1. *Initial attack:* 2 major manifestations, or 1 major and 2 minor manifestations, plus evidence of recent GAS infection. *Recurrent attack:* 2 major, or 1 major and 2 minor, or 3 minor manifestations (the latter only in the Moderate/High-Risk population), plus evidence of recent GAS infection (see text).
2. Low-Risk population is defined as ARF incidence <2 per 100,000 school-age children per year, or all-age RHD prevalence of <1 per 1000 population. Moderate/ High-Risk population is defined as ARF incidence >2 per 100,000 school-age children per year, or all-age RHD prevalence of >1 per 1000 population.
3. Carditis is now defined as clinical and/or subclinical (echocardiographic valvulitis). See Table 183-3.
4. Arthritis (major) refers only to polyarthritis in Low-Risk populations, but also to monoarthritis or polyarthralgia in Moderate/High-Risk populations.
5. Minor criteria for Moderate/High-Risk populations only include monoarthralgia (polyarthralgia for Low-Risk populations), fever of >38° C (>38.5° C in Low-Risk populations), ESR >30 mm/hr (>60 mm/hr in Low-Risk populations).

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| **Table 183-4** | Differential Diagnosis of Acute Rheumatic Fever | | |
| **ARTHRITIS** | | **CARDITIS** | **CHOREA** |
| Juvenile idiopathic arthritis | | Viral myocarditis | Huntington chorea |
| Reactive arthritis (e.g., *Shigella, Salmonella, Yersinia*) | | Viral pericarditis | Wilson disease |
| Serum sickness | | Infective endocarditis | Systemic lupus erythematosus |
| Sickle cell disease | | Kawasaki disease | Cerebral palsy |
| Malignancy | | Congenital heart disease | Tic disorder |
| Systemic lupus erythematosus | | Mitral valve prolapse | Hyperactivity |
| Lyme disease *(Borrelia burgdorferi)* | | Innocent murmurs |  |
| Pyogenic arthritis | | | |
| Poststreptococcal reactive arthritis | | | |

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| **Table 183-5** | Chemoprophylaxis for Recurrences of Acute Rheumatic Fever (Secondary Prophylaxis) | |
| **DRUG** | **DOSE** | **ROUTE** |
| Penicillin G benzathine | 600,000 IU for children weighing ≤60 lb  1.2 million IU for children weighing >60 lb, every 4 wk\* | Intramuscular |
| *or* Penicillin V *or*  Sulfadiazine or sulfisoxazole | 250 mg, twice a day  0.5 g, once a day for patients weighing ≤60 lb  1.0 g, once a day for patients weighing >60 lb | Oral Oral |
| FOR PEOPLE WHO ARE ALLERGIC TO PENICILLIN AND SULFONAMIDE DRUGS  Macrolide or Variable Oral azalide | | |

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| **Table 183-3** | Echocardiographic Findings in Rheumatic Valvulitis |
| **PATHOLOGIC MITRAL PATHOLOGIC AORTIC REGURGITATION (ALL 4 MET) REGURGITATION (ALL 4 MET)** | |
| 1. Seen in at least 2 views 1. Seen in at least 2 views 2. Jet length ≥2 cm in at least 1 2. Jet length ≥1 cm in at least 1 view view 3. Peak velocity >3 meters/ 3. Peak velocity >3 meters/ second second 4. Pan-systolic jet in at least 1 4. Pan-diastolic jet in at least 1 envelope envelope | |

\*In high-risk situations, administration every 3 wk is recommended.

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| **Table 183-6** | Duration of Prophylaxis for People Who Have Had Acute Rheumatic Fever: Recommendations of the American Heart  Association | |
| **CATEGORY** | | **DURATION** |
| Rheumatic fever without carditis | | 5 yr or until 21 yr of age, whichever is longer |
| Rheumatic fever with carditis but without residual heart disease (no valvular disease\*) | | 10 yr or until 21 yr of age, whichever is longer |
| Rheumatic fever with carditis and residual heart disease (persistent valvular disease\*) | | 10 yr or until 40 yr of age, whichever is longer; sometimes lifelong prophylaxis |

\*Clinical or echocardiographic evidence.

**Chapter 184** ◆ Group B Streptococcus **1339**

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 184-1** | Characteristics of Early- and Late-Onset Group B Streptococcus Disease | | |
|  | | **EARLY-ONSET DISEASE** | **LATE-ONSET DISEASE** |
| Age at onset | | 0-6 days | 7-90 days |
| Increased risk after obstetric complications | | Yes | No |
| Common clinical manifestations | | Sepsis, pneumonia, meningitis | Bacteremia, meningitis, other focal infections |
| Common serotypes | | Ia, Ib, II, III, V | III predominates |
| Case fatality rate | | 4.7% | 2.8% |

*Adapted from Schrag SJ, Zywicki S, Farley MM, et al: Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis,* N Engl J Med *342:15–20, 2000.*

Yes

Full diagnostic evaluation\* Antibiotic therapy†

Signs of neonatal sepsis?

Either <37 weeks or duration of membrane rupture ≥18 hours?

≥37 weeks and duration of membrane rupture

<18 hours?

No

Limited evaluation¶ Antibiotic therapy†

Routine clinical care††

Observation for

≥48 hours††§§

Maternal chorioamnionitis?§

Observation for

≥48 hours††¶¶

Yes

Mother received intravenous

penicillin, ampicillin, or cefazolin for ≥4 hours

before delivery?

GBS prophylaxis indicated

for mother?

Yes

No

No

Yes

No

|  |  |  |
| --- | --- | --- |
| **Table 184-2** | Recommended Duration of Therapy for Manifestations of Group B Streptococcus Disease | |
| **TREATMENT** | | **DURATION** |
| Bacteremia without a focus | | 10 days |
| Meningitis | | 2-3 wk |
| Ventriculitis | | At least 4 wk |
| Septic arthritis or osteomyelitis | | 3-4 wk |

Yes

Listeriosis in pregnancy Neonatal listeriosis:

Early onset Late onset

Foodborne outbreaks/febrile gastroenteritis Listeriosis in normal children and adults (rare)

Focal listeria infections (e.g., meningitis, endocarditis, pneumonia, liver abscess, osteomyelitis, septic arthritis)

Listeriosis in immunocompromised persons: Lymphohematogenous malignancies Collagen vascular diseases

Diabetes mellitus HIV infection Transplantation

Renal failure with peritoneal dialysis Listeriosis in the elderly

Types of *Listeria monocytogenes*

Infections

**Table 188-1**

No

Yes

Limited evaluation¶ Observation for ≥48 hours††

\* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).

|  |  |  |
| --- | --- | --- |
| **Table 188-2** | Characteristic Features of Early- and Late-Onset Neonatal Listeriosis | |
| **EARLY ONSET (<5 DAYS)** | | **LATE ONSET (≥5 DAYS)** |
| Positive result of maternal *Listeria*  culture | | Negative results of maternal  *Listeria* culture |
| Obstetric complications | | Uncomplicated pregnancy |
| Premature delivery | | Term delivery |
| Low birthweight | | Normal birthweight |
| Neonatal sepsis | | Neonatal meningitis |
| Mean age at onset 1.5 days | | Mean age at onset 14.2 days |
| Mortality rate >30% | | Mortality rate <10% Nosocomial outbreaks |

† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns.

§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

¶ Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life).

†† If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.

§§ If ≥37 weeks’ gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily

available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge

criteria are achieved.

¶¶ Some experts recommend a CBC with differential and platelets at age 6–12 hours.

**Figure 184-2** Algorithm for secondary prevention of early- onset group B streptococcal disease among newborns.

**Chapter 188** ◆ *Listeria monocytogenes* **1351**

General recommendations to prevent an infection with *Listeria:*

Prevention of Food-Borne Listeriosis

**Table 188-3**

FDA recommendations for washing and handling food.

* Rinse raw produce, such as fruits and vegetables, thoroughly under running tap water before eating, cutting, or cooking. Even if the produce will be peeled, it should still be washed first.
* Scrub firm produce, such as melons and cucumbers, with a clean produce brush.
* Dry the produce with a clean cloth or paper towel.
* Separate uncooked meats and poultry from vegetables, cooked foods, and ready-to-eat foods. Keep your kitchen and environment cleaner and safer.
* Wash hands, knives, countertops, and cutting boards after handling and preparing uncooked foods.
* Be aware that *Listeria monocytogenes* can grow in foods in the refrigerator. Use an appliance thermometer, such as a refrigerator thermometer, to check the temperature inside your refrigerator. The refrigerator should be 4.5°C (40°F) or lower and the freezer −17.8°C (0°F) or lower.
* Clean up all spills in your refrigerator right away–especially juices from hot dog and lunch meat packages, raw meat, and raw poultry.
* Clean the inside walls and shelves of your refrigerator with hot water and liquid soap, then rinse. Cook meat and poultry thoroughly.
* Thoroughly cook raw food from animal sources, such as beef, pork, or poultry to a safe internal temperature. For a list of recommended temperatures for meat and poultry, visit the safe minimum cooking temperatures chart at [http://www.FoodSafety.gov.](http://www.FoodSafety.gov/)

Store foods safely.

* Use precooked or ready-to-eat food as soon as you can. Do not store the product in the refrigerator beyond the use-by date; follow USDA refrigerator storage time guidelines:
  + Hot dogs–store opened package no longer than 1 wk and unopened package no longer than 2 wk in the refrigerator.
  + Luncheon and deli meat–store factory-sealed, unopened package no longer than 2 wk. Store- opened packages and meat sliced at a local deli no longer than 3-5 days in the refrigerator.
* Divide leftovers into shallow containers to promote rapid, even cooling. Cover with airtight lids or enclose in plastic wrap or aluminum foil. Use leftovers within 3-4 days.

Choose safer foods.

* Do not drink raw (unpasteurized) milk, and do not eat foods that have unpasteurized milk in them.

##### Continued

|  |  |
| --- | --- |
| **Table 188-3** | Prevention of Food-Borne Listeriosis—cont’d |
| Recommendations for persons at Meats  higher risk, such as pregnant • Do not eat hot dogs, luncheon meats, cold cuts, other deli meats (e.g., bologna), or fermented or women, persons with weakened dry sausages unless they are heated to an internal temperature of 73.9°C (165°F) or until steaming immune systems, and older hot just before serving.  adults in addition to the • Avoid getting fluid from hot dog and lunch meat packages on other foods, utensils, and food recommendations listed above, preparation surfaces, and wash hands after handling hot dogs, luncheon meats, and deli include: meats.   * Pay attention to labels. Do not eat refrigerated pâté or meat spreads from a deli or meat counter or from the refrigerated section of a store. Foods that do not need refrigeration, like canned or shelf-stable pâté and meat spreads, are safe to eat. Refrigerate after opening.   Cheeses   * Do not eat soft cheese such as feta, queso blanco, queso fresco, brie, Camembert, blue-veined, or panela (queso panela) unless it is labeled as made with pasteurized milk. Make sure the label says, “MADE WITH PASTEURIZED MILK.”   Seafood   * Do not eat refrigerated smoked seafood, unless it is contained in a cooked dish, such as a casserole, or unless it is a canned or shelf-stable product. * Refrigerated smoked seafood, such as salmon, trout, whitefish, cod, tuna, and mackerel, is most often labeled as “nova-style,” “lox,” “kippered,” “smoked,” or “jerky.”   + These fish are typically found in the refrigerator section or sold at seafood and deli counters of grocery stores and delicatessens. * Canned and shelf stable tuna, salmon, and other fish products are safe to eat. Follow this general FDA advice for melon safety: * Consumers and food preparers should wash their hands with warm water and soap for at least 20 sec before and after handling any whole melon, such as cantaloupe, watermelon, or honeydew. * Scrub the surface of melons, such as cantaloupes, with a clean produce brush under running water and dry them with a clean cloth or paper towel before cutting. Be sure that your scrub brush is sanitized after each use, to avoid transferring bacteria between melons. * Promptly consume cut melon or refrigerate promptly. Keep your cut melon refrigerated at, or less than 4.5°C (40°F) (0-1.1°C [32-34°F] is best), for no more than 7 days. * Discard cut melons left at room temperature for more than 4 hr. | |

*Adapted from the Centers for Disease Control and Prevention:* Listeria *(Listeriosis): prevention. Available at:* [*http://www.cdc.gov/listeria/prevention.html*](http://www.cdc.gov/listeria/prevention.html)

**Chapter 191** ◆ *Neisseria meningitidis* (Meningococcus) **1361**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 191-2** Treatment of *Neisseria meningitidis* Invasive Infections | | | | | |
| **DRUG** | **ROUTE OF ADMINISTRATION** | **DOSE** | **DOSING INTERVAL (hr)** | **MAXIMUM DAILY DOSE** | **NOTES** |
| Penicillin G | IM or IV | 300,000 units/kg/day | 4-6 | 12-24 million units | Does not clear carriage and |
|  | | | |  | “prophylaxis” is required |
|  | | | |  | at the end of treatment |
| Ampicillin | IM or IV | 200-400 mg/kg/day | 6 | 6-12 g | Does not clear carriage and |
|  | | | |  | “prophylaxis” is required |
|  | | | |  | at the end of treatment |
| Cefotaxime | IM or IV | 200-300 mg/kg/day | 6-8 | 8-12 g | Recommended in the |
|  | | | |  | neonate |
| Ceftriaxone | IM or IV | 100 mg/kg/day | 12-24 | 2-4 g | Preferred treatment as only |
|  | | | |  | once or twice daily and |
|  | | | |  | may reduce skin |
|  | | | |  | complications |
| ALTERNATIVE THERAPY IN THE FACE OF LIFE-THREATENING **β**-LACTAM ALLERGY | | | |  |  |
| Chloramphenicol\* | IV | 50-100 mg/kg/day | 6 | 2-4 g |  |
| Ciprofloxacin† | IV | 30-40 mg/kg/day | 12 | 1-1.5 g |  |
| Meropenem‡ | IV | 60-120 mg/kg/day | 8 | 1.5-6 g |  |

\*Monitor blood levels to avoid toxicity.

†Licensed for individuals older than age 18 yr.

‡Rate of crossreactivity in penicillin-allergic adults is 2-3%. IM, intramuscular; IV, intravenous.

#### Management of Petechial Rash

If petechiae are not spreading and the child or young person does not appear ill, consider:

* Other possible diagnoses
* Performing full blood count and coagulation screen

If the child or young person has an unexplained petechial rash, carry out the following investigations:

* Full blood count
* CRP
* Coagulation screen
* Blood culture
* Whole-blood PCR for

*N. meningitidis*

* Blood glucose
* Blood gas

Child or young person has a petechial rash

Manage for bacterial meningitis or meningococcal disease per local/national guidelines

Examine for signs of underlying meningitis or

septicemia (including shock) (use the lists of symptoms and signs in the pre-hospital management pathway)

Yes

Clinical diagnosis of

meningitis or septicemia?

No

Give intravenous ceftriaxone if any of the following

occur at any point during assessment, and go to bacterial meningitis or meningococcal disease pathway:

* Petechiae start to spread
* A rash becomes purpuric
* There are signs of meningitis or septicemia
* The child or young person appears ill

Yes

Does the child or young

person have a fever or history of fever?

No

Meningococcal disease less likely but not ruled out

Doubt remains about the child’s or young person’s condition?

If the child or young person is at low risk of

meningococcal disease and discharged after initial observation, advise parents to return to hospital if the child or young person appears ill

Admit to hospital and

monitor vital signs closely

3 See Medicines and Healthcare products Regulatory Agency (2009) Drug Safety Update Vol. 3 Issue 3.

Assess clinical progress

(vital signs) and carry out observations at least hourly over the next

4–6 hours

No

Yes

Treat with intravenous ceftriaxone

immediately, or with cefotaxime if administering calcium containing infusions3

Yes

No

Is CRP and/or white

blood cell count raised?

Available from [www.mhra.gov.uk](http://www.mhra.gov.uk/)

**Figure 191-3** An approach to management of petechial rash. *(From National Collaborating Center for Women’s and Children’s Health (UK):* Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. NICE clinical guidelines, No. 102*. London, 2010, RCOG Press.)*

**Chapter 191** ◆ *Neisseria meningitidis* (Meningococcus) **1363**

|  |  |
| --- | --- |
| **Table 198-3** | Treatment of *Salmonella* Gastroenteritis |
| **ORGANISM AND DOSE AND DURATION INDICATION OF TREATMENT** | |
| *Salmonella* infections in Cefotaxime 100-200 mg/kg/day every infants <3 mo of age or 6-8 hr for 5-14 days immunocompromised *or*  persons (in addition to Ceftriaxone 75 mg/kg/day once daily appropriate treatment for 7 days  for underlying disorder) *or*  Ampicillin 100 mg/kg/day every 6-8 hr for 7 days  *or*  Cefixime 15 mg/kg/day for 7-10 days | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table 191-3** | Antibiotic Prophylaxis to Prevent *Neisseria meningitidis* Infection\* | | | |
| **DRUG** | | **DOSE** |  | **DURATION** |
| RIFAMPIN† | |  |  |  |
| Infants <1 mo | | 5 mg/kg PO every 12 hr | 2 | days (4 doses) |
| Children ≥1 mo | | 10 mg/kg PO every | 2 | days (4 doses) |
|  | | 12 hr (maximum: |  |  |
|  | | 600 mg) |  |  |
| Adults | | 600 mg PO every 12 hr | 2 | days (4 doses) |
| CEFTRIAXONE  Children <15 yr Children ≥15 yr | | 125 mg IM  250 mg IM | 1  1 | dose dose |
| CIPROFLOXACIN  Children ≥1 mo†‡ | | 20 mg/kg (maximum:  500 mg) PO | 1 | dose |

\*Recommended for household and kissing contacts. In the United States, chemoprophylaxis is recommended for:

* + Household contact, especially children younger than 2 yr of age
  + Childcare or preschool contact at any time during 7 days before onset of illness
  + Direct exposure to index patient’s secretions through kissing, sharing toothbrushes or eating utensils at any time during 7 days before onset of illness
  + Mouth-to-mouth resuscitation, unprotected contact during endotracheal intubation during 7 days before onset of illness
  + Frequently slept in same dwelling as index patient during 7 days before onset of illness
  + Passengers seated directly next to the index case during airline flights lasting more than 8 hr

†Not recommended for pregnant women.

‡Not recommended routinely for people younger than 18 yr of age; use only if fluoroquinolone-resistant strains of *N. meningitidis* have not been identified in the community.

IM, intramuscular; PO, by mouth.

|  |  |  |
| --- | --- | --- |
| **Table 198-5** | Common Clinical Features of Typhoid Fever in Children\* | |
| **FEATURE** | | **RATE (%)** |
| High-grade fever | | 95 |
| Coated tongue | | 76 |
| Anorexia | | 70 |
| Vomiting | | 39 |
| Hepatomegaly | | 37 |
| Diarrhea | | 36 |
| Toxicity | | 29 |
| Abdominal pain | | 21 |
| Pallor | | 20 |
| Splenomegaly | | 17 |
| Constipation | | 7 |
| Headache | | 4 |
| Jaundice | | 2 |
| Obtundation | | 2 |
| Ileus | | 1 |
| Intestinal perforation | | 0.5 |

**1364 Part XVII** ◆ Infectious Diseases

|  |  |  |
| --- | --- | --- |
| **Table 191-4** | Recommendations for Meningococcal Vaccination | |
| GENERAL POPULATION  **<2 YR 2-10 YR 11-21 YR** | | **22-55 YR** |
| Not recommended Not recommended A single dose of MenACWY-D or MenACWY-CRM at age 11-12 yr  or at 13-18 yr if not previously vaccinated. Age 19-21 yr: not routinely recommended but may be given as catch-up for those who have not received a dose after their 16th birthday. A booster dose 5 yr later (see text)\* | | Not recommended |
| SPECIAL POPULATIONS AT INCREASED RISK OF MENINGOCOCCAL DISEASE‡  **RISK FACTOR 2-18 MONTHS 9-23 MONTHS** | | **2-55 YR**† |
| Persistent complement deficiencies, 4 doses of Hib-MenCY-TT at 2, 4, 6, and 2 doses of MenACWY-D functional or anatomic asplenia 12-15 months 12 wk apart§ | | 2 doses of MenACWY 8-12 wk apart |
| At risk during a community outbreak 4 doses of Hib-MenCY-TT at 2, 4, 6, and 2 doses of MenACWY-D with a vaccine serogroup 12-15 months 12 wk apart | | 1 dose of MenACWY |
| Travel to or resident of countries Should receive a quadrivalent 2 doses of MenACWY-D where meningococcal disease is meningococcal vaccination licensed 12 wk apart\*\* hyperendemic or epidemic¶ for children aged ≥9 mo prior to travel | | 1 dose of MenACWY |
| Have HIV, if another indication for — 2 doses of MenACWY-D  vaccination exists 12 wk apart | | 2 doses of MenACWY 8-12 wk apart |
| Other risk factors — — | | 1 dose MenACWY |

\*Otherwise healthy adolescents who received a 1st dose at age 11-12 yr should receive a booster dose of a meningococcal conjugate vaccine at 16 yr of age. For those given a 1st dose at age 13-15 yr, and who have not yet reached their 21st birthday, the booster dose should be given 5 yr after the 1st dose.

†Assuming not previously vaccinated.

‡Persons previously vaccinated at 7 yr of age or older who are at prolonged increased risk should be revaccinated 5 yr after their previous meningococcal vaccine and every 5 yr thereafter. Persons previously vaccinated at ages 2 mo-6 yr who are at prolonged increased risk should be revaccinated 3 yr after their previous meningococcal vaccination and every 5 yr thereafter.

§Because of high risk for invasive pneumococcal disease, children with functional or anatomic asplenia should not be immunized with MenACWY-D before age 2 yr to avoid interference with the immune response to the pneumococcal conjugate vaccine (PCV).

If MenACWY-D is used, it should be administered at least 4 wk after completion of all PCV doses.

¶For example, visitors to the “meningitis belt” of sub-Saharan Africa. Vaccination also is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj.

\*\*If receiving the vaccine prior to travel, 2 doses may be administered as early as 8 wk apart.

*Adapted from American Academy of Pediatrics Committee on Infectious Diseases: Updated recommendations on the use of meningococcal vaccines.* Pediatrics

*134:400–403, 2014.*

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 197-2** | Recommended Antimicrobial Treatment and Postexposure Prophylaxis for Pertussis, By Age Group | | |
| **AGE GROUP** | **Primary Agents**  **AZITHROMYCIN ERYTHROMYCIN** | **Alternate Agent**\* | |
| **CLARITHROMYCIN** | **TMP-SMZ** |
| <1 mo | Recommended agent Not preferred  10 mg/kg/day in a single Erythromycin is substantially dose for 5 days (only associated with infantile limited safety data hypertrophic pyloric stenosis  available) Use if azithromycin is unavailable; 40-50 mg/kg/day in 4 divided doses for 14 days | Not recommended (safety data unavailable) | Contraindicated for infants  <2 mo of age (risk for kernicterus) |
| 1-5 mo | 10 mg/kg/day in a single 40-50 mg/kg/day in 4 divided dose for 5 days doses for 14 days | 15 mg/kg/day in 2 divided doses for 7 days | Contraindicated at age <2 mo For infants age ≥2 mo: TMP  8 mg/kg/day plus SMZ  40 mg/kg/day in 2 divided doses for 14 days |
| Infants age  ≥6 mo and children | 10 mg/kg in a single dose 40-50 mg/kg/day (maximum: on day 1 (maximum: 2 g/day) in 4 divided doses 500 mg), then 5 mg/kg/ for 14 days  day (maximum: 250 mg) on days 2-5 | 15 mg/kg/day in 2 divided doses (maximum: 1 g/day)  for 7 days | TMP 8 mg/kg/day plus SMZ 40 mg/kg/day in 2 divided doses (maximum TMP: 320 mg/day) for 14 days |
| Adults | 500 mg in a single dose on 2 g/day in 4 divided doses for day 1 then 250 mg/day 14 days  on days 2-5 | 1 g/day in 2 divided doses for 7 days | TMP 320 mg/day, SMZ 1,600 mg/day in 2 divided doses for 14 days |

\*Trimethoprim-sulfamethoxazole (TMP-SMZ) can be used as an alternative agent to macrolides in patients age ≥2 mo who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of *Bordetella pertussis*.

*From Centers for Disease Control and Prevention (CDC): Recommended antimicrobial agents for treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines,* MMWR Morb Mortal Wkly Rep *54:1–16, 2005.*

**Chapter 198** ◆ *Salmonella* **1391**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table 198-6** | Extraintestinal Infectious Complications of Typhoid Fever Caused By *Salmonella enterica* Serotype Typhi | | | |
| **ORGAN SYSTEM INVOLVED** | | **PREVALENCE (%)** | **RISK FACTORS** | **COMPLICATIONS** |
| Central nervous system | | 3-35 | Residence in endemic region, malignancy, endocarditis, congenital heart disease, paranasal sinus infections, pulmonary infections, meningitis, trauma, surgery, and osteomyelitis of the skull | Encephalopathy, cerebral edema, subdural empyema, cerebral abscess, meningitis, ventriculitis, transient parkinsonism, motor neuron disorders, ataxia, seizures, Guillain-Barré syndrome, psychosis |
| Cardiovascular system | | 1-5 | Cardiac abnormalities—e.g., existing valvular abnormalities, rheumatic heart disease, or congenital heart defects | Endocarditis, myocarditis, pericarditis, arteritis, congestive heart failure |
| Pulmonary system | | 1-6 | Residence in endemic region, past pulmonary infection, sickle cell anemia, alcohol abuse, diabetes, HIV infection | Pneumonia, empyema, bronchopleural fistula |
| Bone and joint | | <1 | Sickle cell anemia, diabetes, systemic lupus erythematosus, lymphoma, liver disease, previous surgery or trauma, extremes of age, and steroid use | Osteomyelitis, septic arthritis |
| Hepatobiliary system | | 1-26 | Residence in endemic region, pyogenic infections, intravenous drug use, splenic trauma, HIV, hemoglobinopathy | Cholecystitis, hepatitis, hepatic abscesses, splenic abscess, peritonitis, paralytic ileus |
| Genitourinary system | | <1 | Urinary tract, pelvic pathology, and systemic abnormalities | Urinary tract infection, renal abscess, pelvic infections, testicular abscess, prostatitis, epididymitis |
| Soft-tissue infections | | At least 17 cases reported in the English language literature | Diabetes | Psoas abscess, gluteal abscess, cutaneous vasculitis |
| Hematologic | | At least 5 cases reported in the English language literature |  | Hemophagocytosis syndrome |

*From Huang DB, DuPont HL: Problem pathogens: extra-intestinal complications of* Salmonella enterica *serotype Typhi infection,* Lancet Infect Dis *5:341–348, 2005.*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table 198-7** | Treatment of Typhoid Fever in Children | | | | | |
| **SUSCEPTIBILITY** | | **Optimal Therapy**  **DAILY DOSE**  **ANTIBIOTIC (mg/kg/day)** | **DAYS** | **Alternative Effective Drugs**  **DAILY DOSE**  **ANTIBIOTIC (mg/kg/day)** | | **DAYS** |
| UNCOMPLICATED TYPHOID FEVER | | |  | Fluoroquinolone, e.g., ofloxacin or ciprofloxacin  Azithromycin  Cefixime Cefixime | 15  8-10  15-20  20 |  |
| Fully sensitive | | Chloramphenicol 50-75 | 14-21 | 5-7\* |
| Amoxicillin 75-100 | | | 14 |  |
| Multidrug-resistant | | Fluoroquinolone 15 | 5-7 | 7 |
| *or* | | |  |  |
| Cefixime 15-20 | | | 7-14 | 7-14 |
| Quinolone-resistant† | | Azithromycin 8-10 | 7 | 7-14 |
| *or* | | |  |  |
| Ceftriaxone 75 | | | 10-14 |  |
| SEVERE TYPHOID FEVER | | |  |  |  |  |
| Fully sensitive | | Fluoroquinolone, e.g., ofloxacin 15 | 10-14 | Chloramphenicol | 100 | 14-21 |
|  | | |  | Amoxicillin | 100 |  |
| Multidrug-resistant | | Fluoroquinolone 15 | 10-14 | Ceftriaxone | 60 | 10-14 |
|  | | |  | *or* |  |  |
|  | | |  | Cefotaxime | 80 | 10-14 |
| Quinolone-resistant | | Ceftriaxone 60 | 10-14 | Azithromycin | 10-20 | 7 |
| Cefotaxime 80 | | | 10-14 | Fluoroquinolone | 20 | 7-14 |

\*A 3-day course is also effective, particularly for epidemic containment.

†The optimum treatment for quinolone-resistant typhoid fever has not been determined. Azithromycin, third-generation cephalosporins, or high-dose fluoroquinolones for 10-14 days is effective.

*Modified from World Health Organization: Treatment of typhoid fever. In: World Health Organization:* Background document: the diagnosis, prevention and treatment of typhoid fever. Communicable disease surveillance and response: vaccines and biologicals, *Geneva, 2003, World Health Organization, pp. 19–23. Available at:* [*http://whqlibdoc.who.int/hq/2003/WHO\_V&B\_03.07.pdf*](http://whqlibdoc.who.int/hq/2003/WHO_V%26B_03.07.pdf)

**Chapter 200** ◆ *Escherichia coli* **1397**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 200-1** | | Clinical Characteristics, Pathogenesis, and Diagnosis of Diarrheagenic *E. coli* | | | | | | |
| **PATHOGEN** | **POPULATIONS AT RISK** | | **Characteristics of Diarrhea**  **WATERY BLOODY DURATION** | | | **Main Virulence Factors**  **ADHERENCE**  **FACTORS TOXINS** | | **DIAGNOSIS** |
| ETEC | >1 yr old and travelers | | +++ | — | Acute | Colonization factor antigens (CFs or CFAs); ECP | Heat-labile enterotoxin (LT)  Heat-stable enterotoxin (ST) | Detection of enterotoxins (LT and ST) by enzyme  immunoassays or PCR (*lt, st*) |
| EIEC | >1 yr old | | + | ++ | Acute | Invasion plasmid antigen (IpaABCD) | | Detection of invasion plasmid antigen of *Shigella* (*ipaH*) by PCR |
| EPEC | <2 yr old | | + + + | + | Acute, prolonged or persistent | A/E lesion, intimin/Tir, EspABD,  Bfp | EspF, Map, EAST1, SPATEs  (*EspC*) | Detection of intimin gene (*eae*)  ± bundle-forming pili (*bfp*A) by PCR, and absence of *Shiga* toxins; HEp-2 cells adherence assay (LA, LLA) |
| STEC  (EHEC/ VTEC) | 6 mo-10 yr and the elderly | | + | +++ | Acute | A/E lesion, intimin/Tir, EspABD | *Shiga* toxins (Stx1, Stx2, and variants of Stx2) | Detection of *Shiga* toxins by enzyme immunoassays or PCR (*Stx*1, *Stx*2); stool culture on MacConkey-sorbitol media to detect *E. coli* O157. Simultaneous culture for O157 and nonculture assays to detect *Shiga* toxins |
| EAEC | <2 yr old,  HIV-infected patients, and travelers | | +++ | + | Acute, prolonged, or persistent | Aggregative adherence fimbriae (AAF) | SPATEs (Pic, Pet), ShET1, EAST1 | Detection of *AggR*, AA plasmid, and other virulence genes: *aap*, *aa*t*A*, *astA*, *set1A* by PCR; HEp-2 cells adherence assay (AA) |
| DAEC | >1 yr old and travelers | | ++ | — | Acute | Afa/Dr, AIDA-I | SPATEs (Sat) | Detection of Dr adhesins (daaC or daaD) and  Dr-associated genes by PCR; HEp-2 cells adherence assay (DA) |

—, Not present; +, present; ++, common; +++, very common; A/E lesion, attaching and effacing lesion; AA, aggregative adherence; Bfp, bundle-forming pili;

DA, diffuse adherence; DAEC, diffusely adherent *E. coli;* EAEC, enteroaggregative *E. coli;* EAST1, enteroaggregative heat stable toxin; ECP, *E. coli* common pilus; EHEC, enterohemorrhagic *E. coli;* EIEC, enteroinvasive *E. coli;* EPEC, enteropathogenic *E. coli;* EspABD, *E. coli* secreted proteins A, B, and D; ETEC, enterotoxigenic

*E. coli;* LA, localized adherence; LLA, localized-like adherence; PCR, polymerase chain reaction; ShET1, *Shigella* enterotoxin 1; SPATEs, serine protease autotransporter of Enterobacteriaceae; STEC, *Shiga* toxin–producing *E. coli;* Tir, translocated intimin receptor; VTEC, verotoxin-producing *E. coli.*

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| **Table 210-1** | Diagnoses Considered in Subsequently Laboratory-Confirmed Cases of Infant Botulism | |
| **ADMISSION DIAGNOSIS** | | **SUBSEQUENTLY CONSIDERED DIAGNOSES** |
| Suspected sepsis, meningitis | | Guillain-Barré syndrome |
| Pneumonia | | Myasthenia gravis |
| Dehydration | | Disorders of amino acid metabolism  Hypothyroidism |
| Viral syndrome | |
| Hypotonia of unknown etiology | | Drug ingestion Organophosphate poisoning |
| Constipation | | Brainstem encephalitis |
| Failure to thrive | | Heavy metal poisoning (Pb, Mg, As) |
| Spinal muscular atrophy type 1 (Werdnig-Hoffmann disease) | | Poliomyelitis Viral polyneuritis  Hirschsprung disease Metabolic encephalopathy  Medium chain acetyl–coenzyme A dehydrogenase deficiency |

Acute gastroenteritis Myasthenia gravis Guillain-Barré syndrome

Organophosphate poisoning Meningitis

Encephalitis Psychiatric illness

Cerebrovascular accident Poliomyelitis Hypothyroidism

Aminoglycoside-associated paralysis Tick paralysis

Hypocalcemia Hypermagnesemia

Carbon monoxide poisoning Hyperemesis gravidarum Laryngeal trauma

Diabetic complications Inflammatory myopathy Overexertion

Diagnoses Considered in Foodborne and Wound Botulism

**Table 210-2**

**Chapter 205** ◆ *Pseudomonas, Burkholderia,* and *Stenotrophomonas* **1413**

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| **Table 205-1** | *Pseudomonas aeruginosa* Infections | |
| **INFECTION** | | **COMMON CLINICAL CHARACTERISTICS** |
| Endocarditis | | Native right-sided (tricuspid) valve disease with intravenous drug abuse |
| Pneumonia | | Compromised local (lung) or systemic host defense mechanisms; nosocomial (respiratory), bacteremic (malignancy), or abnormal mucociliary clearance (cystic fibrosis) may be pathogenetic; cystic fibrosis is associated with mucoid  *P. aeruginosa* organisms producing capsular slime |
| Central nervous system infection | | Meningitis, brain abscess; contiguous spread (mastoiditis, dermal sinus tracts, sinusitis); bacteremia or direct inoculation (trauma, surgery) |
| External otitis | | Swimmer’s ear; humid warm climates, swimming pool contamination |
| Malignant otitis externa | | Invasive, indolent, febrile toxic, destructive necrotizing lesion in young infants, immunosuppressed neutropenic patients, or diabetic patients; associated with 7th nerve palsy and mastoiditis |
| Chronic mastoiditis | | Ear drainage, swelling, erythema; perforated tympanic membrane |
| Keratitis | | Corneal ulceration; contact lens keratitis |
| Endophthalmitis | | Penetrating trauma, surgery, penetrating corneal ulceration; fulminant progression |
| Osteomyelitis/septic arthritis | | Puncture wounds of foot and osteochondritis; intravenous drug abuse; fibrocartilaginous joints, sternum, vertebrae, pelvis; open fracture osteomyelitis; indolent pyelonephritis and vertebral osteomyelitis |
| Urinary tract infection | | Iatrogenic, nosocomial; recurrent urinary tract infections in children, instrumented patients, and those with obstruction or stones |
| Intestinal tract infection | | Immunocompromised, neutropenia, typhlitis, rectal abscess, ulceration, rarely diarrhea; peritonitis in peritoneal dialysis |
| Ecthyma gangrenosum | | Metastatic dissemination; hemorrhage, necrosis, erythema, eschar, discrete lesions with bacterial invasion of blood vessels; also subcutaneous nodules, cellulitis, pustules, deep abscesses |
| Primary and secondary skin infections | | Local infection; burns, trauma, decubitus ulcers, toe web infection, green nail (paronychia); whirlpool dermatitis; diffuse, pruritic, folliculitis, vesiculopustular or maculopapular, erythematous lesions |

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| **Table 207-1** | Recommended Therapy for the Treatment of Brucellosis | | | | |
| **AGE AND CONDITION** | | **ANTIMICROBIAL AGENT** | **DOSE** | **ROUTE** | **DURATION** |
| ≥8 yr | | Doxycycline  +  Rifampin Alternative: Doxycycline  +  Streptomycin or Gentamicin | 2-4 mg/kg/day; maximum: 200 mg/day  15-20 mg/kg/day; maximum: 600-900 mg/day  2-4 mg/kg/day; maximum: 200 mg/day  15-30 mg/kg/day; maximum: 1 g/day  3-5 mg/kg/day | PO PO PO IM  IM/IV | 6 wk  6 wk  6 wk  2-3 wk  1-2 wk |
| <8 yr | | Trimethoprim-sulfamethoxazole (TMP-SMZ)  +  Rifampin | TMP (10 mg/kg/day; maximum: 480 mg/day) and SMZ (50 mg/kg/day; maximum: 2.4 g/day)  15-20 mg/kg/day | PO  PO | 4-8 wk  6 wk |
| Meningitis, osteomyelitis, endocarditis | | Doxycycline  +  Gentamicin  ±  Rifampin | 2-4 mg/kg/day; maximum: 200 mg/day  3-5 mg/kg/day  15-20 mg/kg/day; maximum: 600-900 mg/day | PO IV  PO | 4-6 mo  1-2 wk  4-6 mo |

\*Such as, but not limited to, wounds contaminated with dirt, feces, and saliva; puncture wounds; avulsions; wounds resulting from missiles, crushing, burns,

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| --- | --- | --- | --- | --- |
| **Table 211-1** | Tetanus Prophylaxis in Routine Wound Management | | | |
|  | | **Clean, Minor Wounds** | **All Other Wounds\*** | |
| **HISTORY OF ABSORBED TETANUS TOXOID** | | **TDAP OR**  **TD**† **TIG**‡ | **TDAP OR**  **TD**† | **TIG**‡ |
| Uncertain or <3 doses | | Yes No | Yes | Yes |
| 3 or more doses | | No§ No | No | No |

and frostbite.

†For children younger than 7 yr of age, DTaP is preferred to tetanus toxoid alone if <3 doses of DTaP have been previously given. If pertussis vaccine is contraindicated, DT is given. For persons 7 yr of age or older, Td (or Tdap for adolescents 11-18 yr of age) is preferred to tetanus toxoid alone. Tdap is preferred to Td for adolescents 11-18 yr of age who have never received Tdap. Td is preferred to tetanus toxoid for adolescents who received Tdap previously or when Tdap is not available.

‡TIG should be administered for tetanus-prone wounds in HIV-infected patients regardless of the history of tetanus immunizations.

§Yes, if 10 yr or longer since the last tetanus toxoid–containing vaccine dose. Yes, if 5 yr or longer since the last tetanus toxoid–containing vaccine dose.

(More frequent boosters are not needed and can accentuate adverse events.)

DT, diphtheria and tetanus toxoid vaccine; DTaP, combined diphtheria toxoid–tetanus toxoid–acellular pertussis vaccine; Td, tetanus toxoid and reduced diphtheria toxoid vaccine; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; TIG, tetanus immune globulin.

**Chapter 213** ◆ Other Anaerobic Infections **1437**

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| **Table 213-1** Infections Associated with | Anaerobic Bacteria | |
| **SITE AND INFECTION** | **MAJOR RISK FACTORS** | **ANAEROBIC BACTERIA**\* |
| CENTRAL NERVOUS SYSTEM  Cerebral abscess | Cyanotic heart disease Cystic fibrosis Penetrating trauma  Direct extension from contiguous sinusitis, otitis media, mastoiditis, or anatomic defect involving the dura | Polymicrobial |
| Epidural and subdural empyemas, meningitis | *Bacteroides fragilis*† *Fusobacterium Peptostreptococcus Veillonella* |
| UPPER RESPIRATORY TRACT  Dental abscess  Ludwig angina (cellulitis of sublingual- submandibular space)  Necrotizing gingivitis (Vincent stomatitis) Chronic otitis-mastoiditis-sinusitis  Peritonsillar abscess Retropharyngeal abscess Lemierre syndrome | Poor periodontal hygiene  Drugs producing gingival hypertrophy  Tympanic perforation Tympanostomy tubes Streptococcal pharyngitis Penetrating injury  Preexisting viral or bacterial pharyngitis | *Peptostreptococcus Fusobacterium*  *Prevotella melaninogenica*  *Fusobacterium* |
| LOWER RESPIRATORY TRACT  Aspiration pneumonia Necrotizing pneumonitis Lung abscess  Septic pulmonary emboli | Periodontal disease Bronchial obstruction  Altered gag or consciousness Aspirated foreign body Sequestered lobe  Vascular anomaly | Polymicrobial  *P. melaninogenica Bacteroides intermedius Fusobacterium*  *Peptostreptococcus, Eubacterium*  *B. fragilis, Veillonella Fusobacterium* |
| INTRAABDOMINAL |  |  |
| Abscess | Appendicitis | Polymicrobial |
| Secondary peritonitis | Penetrating trauma (especially of the colon) | *Bacteroides* spp. |
|  |  | *Clostridium* |
|  |  | *Peptostreptococcus* |
|  |  | *Eubacterium* |
|  |  | *Fusobacterium* |
| FEMALE GENITAL TRACT |  |  |
| Bartholin abscess | Vaginosis | *B. fragilis* |
| Tuboovarian abscess | Intrauterine device | *Bacteroides bivius* |
| Endometritis |  | *Peptostreptococcus* |
| Pelvic thrombophlebitis |  | *Clostridium* |
| Salpingitis |  | *Mobiluncus* |
| Chorioamnionitis |  | *Actinomyces* |
| Septic abortion |  | *Clostridium* |
| SKIN AND SOFT TISSUE  Cellulitis | Decubitus ulcers | Varies with site and contamination with oral or enteric flora  *Clostridium perfringens* (myonecrosis)  *Bacteroides Clostridia Fusobacterium Clostridium tertium Clostridium septicum*  Anaerobic streptococci |
| Perirectal cellulitis Myonecrosis (gas gangrene) | Abdominal wounds Pilonidal sinus |
| Necrotizing fasciitis and synergistic gangrene | Trauma  Human and animal bites Immunosuppressed or neutropenic patients Varicella |
| BLOOD |  |  |
| Bacteremia | Intraabdominal infection, abscesses, myonecrosis, necrotizing fasciitis | *B. fragilis Clostridium* |
|  |  | *Peptostreptococcus* |
|  |  | *Fusobacterium* |

\*Infections may also be from or may involve aerobic bacteria as the sole agent or as part of a mixed infection; brain abscess may contain microaerophilic streptococci; intraabdominal infections may contain Gram-negative enteric organisms and enterococci; and salpingitis may contain *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.

†*Bacteroides fragilis* is usually isolated from infections below the diaphragm except for brain abscesses.

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Acute respiratory distress syndrome Aspiration

*Clostridium difficile* enterocolitis Hypotension

Inappropriate antidiuretic hormone secretion Long bone fractures

Misplaced or plugged endotracheal tube Nosocomial anemia

Otitis media Pneumonia Pneumothorax Recurrent atelectasis

Seizures secondary to hyponatremia Sepsis

Subglottic stenosis Tracheal granuloma Tracheitis Transfusion reaction

Urinary tract infection

Complications of Infant Botulism

**Table 210-3**

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| **Table 214-2** | Isoniazid Drug–Drug Interactions | |
| **DRUG USED WITH ISONIAZID** | | **EFFECTS** |
| Acetaminophen, alcohol, rifampin | | Increased hepatotoxicity of isoniazid or listed drugs |
| Aluminum salts (antacids) | | Decreased absorption of isoniazid |
| Carbamazepine, phenytoin, theophylline, diazepam, warfarin | | Increased level, effect, or toxicity of listed drugs due to decreased metabolism |
| Itraconazole, ketoconazole, oral hypoglycemic agents | | Decreased level or effect of listed drugs due to increased metabolism |
| Cycloserine, ethionamide | | Increased central nervous system adverse effects of cycloserine and ethionamide |
| Prednisolone | | Increased isoniazid metabolism |

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| **Table 214-1** | Recommended Treatment Regimens for Drug-Susceptible Tuberculosis in Infants, Children, and Adolescents | |
| **INFECTION OR DISEASE**  **CATEGORY REGIMEN** | | **REMARKS** |
| LATENT TUBERCULOSIS INFECTION\*  Isoniazid susceptible 9 mo of isoniazid, once a day Isoniazid resistant 6 mo of rifampin, once a day  Isoniazid-rifampin resistant‡ Consult a tuberculosis specialist | | If daily therapy is not possible, DOT twice a week can be used for 9 mo  If daily therapy is not possible, DOT twice a week can be used for 6 mo |
| PULMONARY AND EXTRAPULMONARY INFECTION  Except meningitis 2 mo of isoniazid, rifampin, pyrazinamide, and  ethambutol daily, followed by 4 mo of isoniazid and rifampin† by DOT§ for drug-susceptible *Mycobacterium tuberculosis*  9-12 mo of isoniazid and rifampin for drug- susceptible *Mycobacterium bovis*  Meningitis 2 mo of isoniazid, rifampin, pyrazinamide, and an aminoglycoside or ethambutol or ethionamide, once a day, followed by 7-10 mo of isoniazid and rifampin, once a day or twice a week (9-12 mo total) for drug-susceptible *M. tuberculosis*  ≥12 mo of therapy without pyrazinamide for drug-susceptible *M. bovis* | | If possible drug resistance is a concern (see text), another drug (ethambutol or an aminoglycoside) is added to the initial 3 drug therapy until drug susceptibilities are determined; DOT is highly desirable  If hilar adenopathy only, a 6-mo course of isoniazid and rifampin is sufficient  Drugs can be given 2 or 3×/wk under DOT in the initial phase if nonadherence is likely  A 4th drug, such as an aminoglycoside, is given with initial therapy until drug susceptibility is known  For patients who might have acquired tuberculosis in geographic areas where resistance to streptomycin is common, kanamycin, amikacin, or capreomycin can be used instead of streptomycin |

\*Positive TST or IGRA result, no disease.

†Duration of therapy is longer for human immunodeficiency virus (HIV)-infected people, and additional drugs may be indicated.

‡Medications should be administered daily for the 1st 2 wk to 2 mo of treatment and then can be administered 2-3×/wk by DOT.

§If initial chest radiograph shows cavitary lesions and sputum after 2 mo of therapy remains positive, duration of therapy is extended to 9 mo. DOT, directly observed therapy; IGRA, interferon-γ release assay; TST, tuberculin skin test.

*From American Academy of Pediatrics: Tuberculosis. In Pickering LK, Baker CJ, Kimberlin DW, Long SS, editors:* Red book 2012: report of the Committee on Infectious Diseases*, ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

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| **Table 214-3** | Treatment of Nontuberculous Mycobacteria Infections in Children | | |
| **ORGANISM** | | **DISEASE** | **TREATMENT** |
| SLOWLY GROWING SPECIES  *Mycobacterium avium* complex (MAC); *Mycobacterium haemophilum; Mycobacterium lentiflavum* | | Lymphadenitis Pulmonary infection | Complete excision of lymph nodes; if excision is incomplete or disease recurs, clarithromycin or azithromycin plus ethambutol or rifampin (or rifabutin)  Clarithromycin or azithromycin plus ethambutol with rifampin or rifabutin (pulmonary resection in some patients who fail to respond to drug therapy). For severe disease, an initial course of amikacin or streptomycin often is included. Clinical data in adults support that 3×/wk therapy is as effective as daily therapy, with less toxicity. For patients with advanced disease, drugs should be given daily  See text  Rifampin plus ethambutol with isoniazid  Surgical debridement and prolonged antimicrobial therapy using rifampin plus ethambutol with isoniazid  Trimethoprim-sulfamethoxazole, clarithromycin, or doxycycline for mild disease; ethambutol with clarithromycin or rifampicin for extensive disease; extensive lesions might require surgical debridement.  Daily intramuscular streptomycin and oral rifampin × 8 wk; excision of tissue |
| *Mycobacterium kansasii* | | Disseminated Pulmonary infection Osteomyelitis |
| *Mycobacterium marinum* | | Cutaneous infection |
| *Mycobacterium ulcerans* | | Cutaneous and bone infections |
| RAPIDLY GROWING SPECIES  *Mycobacterium fortuitum* group  *Mycobacterium abscessus*  *Mycobacterium chelonae* | | Cutaneous infection  Catheter infection Otitis media  Pulmonary infection (in cystic fibrosis)  Catheter infection  Disseminated cutaneous infection | Initial therapy for serious disease is amikacin plus cefoxitin or imipenem IV, followed by clarithromycin, doxycycline,\* or trimethoprim-sulfamethoxazole or ciprofloxacin, orally, on the basis of in vitro susceptibility testing; might require surgical excision  Catheter removal and amikacin plus cefoxitin or imipenem, IV; clarithromycin, trimethoprim-sulfamethoxazole, or ciprofloxacin, orally, on the basis of in vitro susceptibility testing  Clarithromycin plus initial course of amikacin plus cefoxitin or imipenem; might require surgical debridement. Base regimen on in vitro susceptibility testing (50% are amikacin resistant)  Serious disease, clarithromycin, amikacin, and cefoxitin on the basis of susceptibility testing; might require surgical resection  Catheter removal and tobramycin (initially) plus clarithromycin Tobramycin and ciprofloxacin or linezolid (initially) plus  clarithromycin |

\*Doxycycline should not be given to children younger than 8 yr of age unless the benefits of therapy are greater than the risks of dental staining. Only 50% of isolates of *Mycobacterium marinum* are susceptible to doxycycline.

*From American Thoracic Society/Infectious Disease Society of America Statement: Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 175:367-416, 2007.*

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| **Table 215-1** | Groups at High Risk for Acquiring Tuberculosis Infection and Developing Disease in Countries with Low Incidence |
| RISK FACTORS FOR TUBERCULOSIS INFECTION  Children exposed to high-risk adults  Foreign-born persons from high-prevalence countries Homeless persons  Persons who inject drugs  Present and former residents or employees of correctional institutions, homeless shelters, and nursing homes  Healthcare workers caring for high-risk patients (if infection control is not adequate) | |
| RISK FACTORS FOR PROGRESSION OF LATENT TUBERCULOSIS INFECTION TO TUBERCULOSIS DISEASE  Infants and children ≤4 yr of age, especially those <2 yr of age Adolescents and young adults  Persons coinfected with HIV  Persons with skin test conversion in the past 1-2 yr  Persons who are immunocompromised, especially in cases of malignancy and solid organ transplantation, immunosuppressive medical treatments including anti–tumor necrosis factor therapies, diabetes mellitus, chronic renal failure, silicosis, and malnutrition | |
| RISK FACTORS FOR DRUG-RESISTANT TUBERCULOSIS  Personal or contact history of treatment for tuberculosis Contacts of patients with drug-resistant tuberculosis  Birth or residence in a country with a high rate of drug resistance Poor response to standard therapy  Positive sputum smears (acid-fast bacilli) or culture ≥2 mo after initiating appropriate therapy | |

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TST preferred, IGRA acceptable

* Children <5 yr of age\*

IGRA preferred, TST acceptable

* Children >5 yr of age who have received the BCG vaccine
* Children >5 yr of age who are unlikely to return for TST reading TST and IGRA should be considered when:
* The initial and repeat IGRA are indeterminate
* The initial test (TST or IGRA) is negative and:
  + Clinical suspicion for tuberculosis disease is moderate to high†
  + Risk of progression and poor outcome is high†
* The initial TST is positive and:
  + >5 yr of age and history of BCG vaccination
  + Additional evidence needed to increase compliance
  + Nontuberculous mycobacterial disease is suspected

Recommendations for Use of the Tuberculin Skin Test and an Interferon-γ Release Assay in Children

**Table 215-4**

\*These definitions apply regardless of previous bacille Calmette-Guérin (BCG) immunization; erythema at TST site does not indicate a positive test result.

Tests should be read at 48-72 hr after placement.

†Evidence by physical examination or laboratory assessment that would include tuberculosis in the working differential diagnosis (e.g., meningitis).

‡Including immunosuppressive doses of corticosteroids or tumor necrosis

factor-α antagonists.

HIV, human immunodeficiency virus; TST, tuberculin skin test.

\*Positive result of either test is considered significant in these groups.

†IGRAs should not be used in children younger than 2 yr of age unless tuberculosis disease is suspected. In children 2-4 yr of age, there are limited data about the usefulness of IGRAs in determining tuberculosis infection, but IGRA testing can be performed if tuberculosis disease is suspected.

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| **Table 215-3** | Definitions of Positive Tuberculin Skin Test Results in Infants, Children, and Adolescents\* |
| INDURATION **≥**5 MM  Children in close contact with known or suspected contagious people with tuberculosis disease  Children suspected to have tuberculosis disease:   * Findings on chest radiograph consistent with active or previously tuberculosis disease * Clinical evidence of tuberculosis disease†   Children receiving immunosuppressive therapy‡ or with immunosuppressive conditions, including HIV infection | |
| INDURATION **≥**10 MM  Children at increased risk of disseminated tuberculosis disease:   * Children younger than 4 yr of age * Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition (see Table 215-2)   Children with increased exposure to tuberculosis disease:   * Children born in high-prevalence regions of the world * Children often exposed to adults who are HIV infected, homeless, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized, or migrant farm workers * Children who travel to high-prevalence regions of the world | |
| INDURATION **≥**15 MM  Children ≥4 yr of age without any risk factors | |

IGRA indicates interferon-γ release assay; TST, tuberculin skin test.

|  |  |
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| **Table 215-2** | Tuberculin Skin Test Recommendations for Infants, Children, and Adolescents\* |
| CHILDREN FOR WHOM IMMEDIATE TST OR IGRA IS INDICATED†:   * Contacts of people with confirmed or suspected contagious tuberculosis (contact investigation) * Children with radiographic or clinical findings suggesting tuberculosis disease * Children immigrating from countries with endemic infection (e.g., Asia, Middle East, Africa, Latin America, countries from the former Soviet Union), including international adoptees * Children with travel histories to countries with endemic infection and substantial contact with indigenous people from such countries‡ * Children who should have annual TST or IGRA:   + Children infected with HIV | |
| CHILDREN AT INCREASED RISK FOR PROGRESSION OF LTBI TO TUBERCULOSIS DISEASE  Children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, and congenital or acquired immunodeficiencies deserve special consideration. Without recent exposure, these children are not at increased risk of acquiring tuberculosis infection. Underlying immunodeficiencies associated with these conditions theoretically would enhance the possibility for progression to severe disease. Initial histories of potential exposure to tuberculosis should be included for all of these patients. If these histories or local epidemiologic factors suggest a possibility of exposure, immediate and periodic TST should be considered. An initial TST or IGRA should be performed before initiation of immunosuppressive therapy, including prolonged steroid administration, use of tumor necrosis factor-**α** antagonists, or immunosuppressive therapy in any child requiring these treatments. | |

\*Bacille Calmette-Guérin immunization is not a contraindication to a TST.

†Beginning as early as 3 mo of age.

‡If the child is well and has no history of exposure, the TST or IGRA should be delayed up to 10 wk after return.

HIV, human immunodeficiency virus; IGRA indicates interferon-γ release assay; LTBI, latent tuberculosis infection; TST, tuberculin skin test.

*From American Academy of Pediatrics:* Red book: 2012 report of the Committee on Infectious Diseases*, ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 740.*

**Chapter 215** ◆ Tuberculosis *(Mycobacterium tuberculosis)* **1457**

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| **Table 215-6** | Less-Commonly Used Drugs for Treating Drug-Resistant Tuberculosis in Infants, Children, and Adolescents\* | | | | |
| **DRUGS** | | **DOSAGE, FORMS** | **DAILY DOSAGE, mg/kg** | **MAXIMUM DOSE** | **ADVERSE REACTIONS** |
| Amikacin† | | Vials: 500 mg, 1 g | 15-30 (IV or IM  administration) | 1 g | Auditory and vestibular toxic effects, nephrotoxic effects |
| Capreomycin† | | Vials: 1 g | 15-30 (IM administration) | 1 g | Auditory and vestibular toxicity and nephrotoxic effects |
| Cycloserine | | Capsules: 250 mg | 10-20, given in 2 divided doses | 1 g | Psychosis, personality changes, seizures, rash |
| Ethionamide | | Tablets: 250 mg | 15-20, given in 2-3 divided doses | 1 g | Gastrointestinal tract disturbances, hepatotoxic effects, hypersensitivity reactions, hypothyroidism |
| Kanamycin | | Vials:  75 mg/2 mL  500 mg/2 mL  1 g/3 mL | 15-30 (IM or IV  administration) | 1 g | Auditory and vestibular toxic effects, nephrotoxic effects |
| Levofloxacin‡ | | Tablets:  250 mg  500 mg  750 mg  Vials: 25 mg/mL | Adults: 750-1000 mg (once daily)  Children: 15 mg/kg daily | 1 g | Theoretic effect on growing cartilage, gastrointestinal tract disturbances, rash, headache, restlessness, confusion |
| Ofloxacin | | Tablets: 200 mg  300 mg  400 mg Vials:  20 mg/mL  40 mg/mL | Adults and adolescents: 800 mg  Children 15-20 mg/kg daily | 800 mg | Arthropathy, arthritis |
| Moxifloxacin | | Tablets: 400 mg  IV solution: 400 mg/250 mL in 0.8% saline | Adults and adolescents: 400 mg  Children: 7.5-10 mg/kg daily | 400 mg | Arthropathy, arthritis |
| Paraaminosalicylic acid (PAS) | | Packets: 3 g | 200-300 (2-4 times a day) | 10 g | Gastrointestinal tract disturbances, hypersensitivity, hepatotoxic effects |
| Streptomycin† | | Vials:  1 g  4 g | 20-40 (IM administration) | 1 g | Auditory and vestibular toxic effects, nephrotoxic effects, rash |

\*These drugs should be used in consultation with a specialist in tuberculosis.

†Dose adjustment in renal insufficiency.

‡Levofloxacin currently is not approved for use in children younger than 18 yr of age; its use in younger children necessitates assessment of the potential risks and benefits.

*From American Academy of Pediatrics:* Red book: 2012 report of the Committee on Infectious Diseases*, ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 748.*

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| **Table 215-5** | Commonly Used Drugs for the Treatment of Tuberculosis in Infants, Children, and Adolescents | | | | |
| **DRUG** | **DOSAGE FORMS** | **DAILY DOSAGE,**  **mg/kg** | **TWICE A WEEK**  **DOSAGE, mg/kg PER DOSE** | **MAXIMUM DOSE** | **ADVERSE REACTIONS** |
| Ethambutol | Tablets: 100 mg  400 mg | 20 | 50 | 2.5 g | Optic neuritis (usually reversible), decreased red-green color discrimination, gastrointestinal tract disturbances, hypersensitivity |
| Isoniazid\* | Scored tablets: 100 mg  300 mg  Syrup: 10 mg/mL | 10-15† | 20-30 | Daily, 300 mg  Twice a week, 900 mg | Mild hepatic enzyme elevation, hepatitis,† peripheral neuritis, hypersensitivity |
| Pyrazinamide\* | Scored tablets: 500 mg | 30-40 | 50 | 2 g | Hepatotoxic effects, hyperuricemia, arthralgias, gastrointestinal tract upset |
| Rifampin\* | Capsules:  150 mg  300 mg  Syrup formulated from capsules | 10-20 | 10-20 | 600 mg | Orange discoloration of secretions or urine, staining of contact lenses, vomiting, hepatitis, influenza-like reaction, thrombocytopenia, pruritus; oral contraceptives may be ineffective |

\*Rifamate is a capsule containing 150 mg of isoniazid and 300 mg of rifampin. Two capsules provide the usual adult (i.e., person weighing >50 kg) daily doses of each drug. Rifater, in the United States, is a capsule containing 50 mg of isoniazid, 120 mg of rifampin, and 300 mg of pyrazinamide. Isoniazid and rifampin also are available for parenteral administration.

†When isoniazid in a dosage exceeding 10 mg/kg per day is used in combination with rifampin, the incidence of hepatotoxic effects may be increased.

*From American Academy of Pediatrics:* Red book: 2012 report of the Committee on Infectious Diseases*, ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 746.*

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| **Table 216-1** | NHDP Recommended Multidrug Therapy Regimens for Hansen Disease in the United States | | | |
| **TYPE OF LEPROSY ANTIMICROBIAL THERAPY** | | **ADULT DOSING (GIVEN ORALLY)** | **PEDIATRIC DOSING\* (GIVEN ORALLY)** | **DURATION OF THERAPY** |
| MULTIBACILLARY LEPROSY (LL, BL, BB)  Dapsone *and* Rifampin *and* Clofazimine | | 100 mg/day  600 mg/day  50 mg/day | 1 mg/kg/day  10-20 mg/kg/day  1 mg/kg/day† | 24 months  24 months  24 months |
| PAUCIBACILLARY LEPROSY (TT, BT)  Dapsone *and*  Rifampin | | 100 mg/day  600 mg/day | 1-2 mg/kg/day  10-20 mg/kg/day | 12 months  12 months |

NHDP multidrug therapy therapy is daily and of longer duration than World Health Organization recommended regimen.

\*Daily pediatric mg/kg dose should not exceed adult daily maximum.

†Clofazimine is only available through NHDP Investigational New Drug (IND) program; minimum formulation is 50 mg and capsules should not be cut. Alternative dosing includes: clofazimine 2 mg/kg every other day *or* clarithromycin 7.5 mg/kg/day.

BB, borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; NHDP, National Hansen’s Disease Program; TT, tuberculoid.

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| **Table 216-2** | World Health Organization Recommended Multidrug Therapy Regimens for Hansen Disease | | |
| **TYPE OF LEPROSY** |  | **Antimicrobial Therapy**  **MONTHLY (SUPERVISED) DAILY (SELF-ADMINISTERED)** | **DURATION OF THERAPY** |
| Multibacillary (LL, BL, BB) | Adult Pediatric\* | Rifampicin 600 mg *and* clofazimine 300 mg Dapsone 100 mg *and* clofazimine 50 mg Rifampicin 450 mg *and* clofazimine 150 mg Dapsone 50 mg *and* clofazimine 50 mg  *every other day* | 12-24 months |
| Paucibacillary (TT, BT) | Adult Pediatric\* | Rifampicin 600 mg Dapsone 100 mg  Rifampicin 450 mg Dapsone 50 mg | 6-12 months  6 months |
| Paucibacillary (single lesion)† |  | Rifampicin 600 mg *and* ofloxacin 400 mg  *and* minocycline 100 mg | One time, single dose |

\*In children younger than 10 yr of age, dosages of multidrug therapy should be in mg/kg, not to exceed the adult daily maximum: rifampicin 10 mg/kg once monthly, dapsone 2 mg/kg/day, clofazimine 1 mg/kg on alternate days.

†Paucibacillary single-lesion, one-time single-dose therapy may be less effective than the 6 mo paucibacillary multidrug therapy regimen. BB, borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; TT, tuberculoid.

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| **Table 217-1** | Diseases Caused by Nontuberculous Mycobacterial Species | | |
| **CLINICAL DISEASE** | | **COMMON SPECIES** | **LESS-COMMON SPECIES** |
| Cutaneous infection | | *Mycobacterium chelonae, Mycobacterium fortuitum, Mycobacterium abscessus, Mycobacterium marinum* | *Mycobacterium ulcerans*\* |
| Lymphadenitis | | MAC | *Mycobacterium kansasii, Mycobacterium haemophilum, Mycobacterium malmoense*† |
| Otologic infection | | *M. abscessus*, MAC | *M. fortuitum* |
| Pulmonary infection | | MAC, *M. kansasii, M. abscessus* | *Mycobacterium xenopi, Mycobacterium malmoense,*† *Mycobacterium szulgai, M. fortuitum, Mycobacterium simiae* |
| Catheter-associated infection | | *M. chelonae, M. fortuitum* | *M. abscessus* |
| Skeletal infection | | MAC, *M. kansasii, M. fortuitum* | *M. chelonae, M. marinum, M. abscessus, M. ulcerans*\* |
| Disseminated | | MAC | *M. kansasii, Mycobacterium genavense,*  *M. haemophilum, M. chelonae* |

\*Endemic in West Africa and Australia, minor foci in East Asia and Latin America.

†Found primarily in Northern Europe.

MAC, *Mycobacterium avium* complex.

*From American Academy of Pediatrics:* Red book: 2012 report of the Committee on Infectious Diseases*, ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 761.*

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EIA or CIA

A B

RPR

+

*Syphilis (past or present)§*

RPR

—

EIA/CIA

†

–

EIA/CIA

+

Quantitative RPR or other nontreponemal test

TP-PA

—

*Syphilis unlikely ¶*

TP-PA

+

*Syphilis (past or present)§*

TP-PA

**– Treponemal test** Biologic false positive (see text for significance)

**+ Treponemal test** Syphilis new case or previously treated case

**– Nontreponemal test** No Syphilis or very recent infection testing concludes

**+ Nontreponemal test**

Treponemal test

EIA/CIA, TP-PA, TP-HA, or FTA-ABS

**Figure 218-9 A,** Traditional laboratory testing algorithm for syphilis. **B,** CDC-recommended algorithm for reverse sequence syphilis screening (treponemal test screening followed by nontreponemal test confirmation). Despite these recommendations for reverse sequence screening, the CDC continues to recommend the traditional algorithm with reactive nontreponemal tests confirmed by treponemal testing. *EIA/CIA*, enzyme immunoassay/chemiluminescence immunoassay; *FTA-ABS*, fluorescent treponemal antibody absorption; *RPR*, rapid plasma reagin; *TP-HA*, *Trepo- nema pallidum* hemagglutination; *TP-PA*, Treponema pallidum particle agglutination; *VDRL*, Venereal Disease Research Laboratory. \*If nontrepo- nemal test is positive qualitatively, a titer is then quantitated. †If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units intramuscularly in a single dose. §Evaluate clinically, determine whether treated for syphilis in the past, assess risk for infection, and administer therapy according to CDC’s 2010 STD Treatment Guidelines (available at [http://www.cdc.gov/std/treatment/2010).](http://www.cdc.gov/std/treatment/2010)) ¶If at risk for syphilis, repeat RPR in several weeks. *(****A*** *based on data from Workowski KA, Berman S; Centers for Diseases Control and Prevention [CDC]: Sexually trans- mitted diseases treatment guidelines, 2010. MMWR Recomm Rep 59[RR-12]:1-110, 26-29, 2010;* ***B*** *from Centers for Disease Control and Prevention [CDC]: Discordant results from reverse sequence syphilis screening—five laboratories, United States, 2006-2010. MMWR Morb Mortal Wkly Rep 60(5):133-137, 2011.)*

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| **Table 234-1** | Dosing of Antifungal Agents in Infants\* and Number of Infants Younger Than  1 Yr of Age Studied with Reported Pharmacokinetic Parameters | | |
| **DRUG** | | **INFANTS STUDIED** | **SUGGESTED DOSE** |
| Amphotericin B deoxycholate | | 27 | 1 mg/kg/day |
| Amphotericin B lipid complex | | 28 | 5 mg/kg/day |
| Liposomal amphotericin B | | 17 | 5 mg/kg/day |
| Amphotericin B colloidal dispersion | | 0 | 5 mg/kg/day |
| Fluconazole† | | 65 | 12 mg/kg/day |
| Micafungin‡ | | 120 | 10 mg/kg/day |
| Caspofungin§ | | 22 | 50 mg/m2/day |
| Anidulafungin‡ | | 15 | 1.5 mg/kg/day |

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| **Table 234-2** | Dosing of Antifungal Agents in Children Older Than 1 Year of Age for Treatment of Invasive Disease | |
| **DRUG** | | **SUGGESTED DOSAGE** |
| Amphotericin B deoxycholate | | 1 mg/kg/day |
| Amphotericin B lipid complex | | 5 mg/kg/day |
| Liposomal amphotericin B | | 5 mg/kg/day |
| Amphotericin B colloidal dispersion | | 5 mg/kg/day |
| Fluconazole† | | 12 mg/kg/day |
| Voriconazole | | 8 mg/kg every 12 hr |
| Micafungin\* | | 2-4 mg/kg/day |
| Caspofungin | | 50 mg/m2/day |
| Anidulafungin | | 1.5 mg/kg/day |

\*Voriconazole dosing has not been investigated in the nursery.

RPR or VDRL

(**Nontreponemal test\***)

†A loading dose of 25 mg/kg of fluconazole is necessary to achieve therapeutic serum concentrations in the early days of therapy.

‡Micafungin has been studied in infants <120 days of life at this dosage.

§Caspofungin and anidulafungin should generally be avoided because dosing

sufficient to penetrate brain tissue has not been studied.

\*Use adult dosages in children older than 8 yr of age.

Loading doses should be used for fluconazole (25 mg/kg), voriconazole

†

(9 mg/kg q 12 × 24 hr), caspofungin (70 mg/m2), and anidulafungin (3 mg/kg).

Nonreactive maternal treponemal test

Reactive maternal RPR/VDRL

No evaluation No treatment

No evaluation; Treatment (Option 2)

Evaluation and Treatment (Option 1)

Treatment (Option 1)

Treatment

False-positive reaction: no further evalution

Reactive maternal treponemal test

Maternal treatment:

* none, OR
* undocumented, OR
* 4 wk or less before delivery, OR
* nonpenicillin drug, OR
* maternal evidence of reinfection/relapse (fourfold or greater increase in maternal titers)

Maternal penicillin treatment during pregnancy AND more than 4 weeks before delivery, AND no evidence of maternal reinfection or relapse

Adequate maternal treatment before pregnancy with stable low titer (serofast), AND infant examination normal; if infant examination is abnormal, proceed with evaluation

Evaluate

Infant physical examination normal; evaluation normal; infant RPR/VDRL

Infant physical examination abnormal; OR evaluation abnormal or incomplete; OR

Infant RPR/VDRL fourfold or greater than maternal RPR/VDRL titer

Infant RPR/VDRL same or less than fourfold the maternal RPR/VDRL titer

same or less than fourfold the maternal RPR/VDRL

titer

RPR/VDRL at least fourfold greater than maternal RPR/VDRL titer

Infant physical

examination abnormal

Infant physical

examination normal

**Figure 218-11** Algorithm for evaluating and treating infants born to mothers with reactive serologic tests for syphilis. *(From American Academy of Pediatrics:* Red book: 2012 report of the Committee on Infectious Diseases*, ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics,* Fig. 3-7*, p. 695.)*

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| **Table 233-1** Suggested Dosing of | | Antifungal Agents in Children and Neonates | |
| **DRUG** | **FORMULATIONS** | **SUGGESTED PEDIATRIC DOSAGE** | **COMMENTS** |
| Amphotericin B deoxycholate | IV | 1 mg/kg/day | Generally less toxicity in children than adults; do not start with smaller test doses |
| Lipid amphotericin B formulations | IV | 5 mg/kg/day | Generally all lipid formulations are dosed the same; there is no clear indication of one formulation over another for clinical efficacy |
| Fluconazole | IV, PO | 12 mg/kg/day | Loading dose (25 mg/kg) is suggested based on pharmacokinetic simulations, but insufficiently studied |
| Itraconazole | IV, PO | 2.5 mg/kg/dose bid | Divide dosage twice daily in children; follow trough levels |
| Voriconazole | IV, PO | 8 mg/kg/dose bid IV maintenance; 9 mg/kg/ dose bid oral maintenance | Linear pharmacokinetics in children requires higher dosing than in adults; 9 mg/kg/dose bid IV loading, followed by maintenance dosing; follow trough levels |
| Posaconazole | PO | 12-24 mg/kg/day divided tid | Dosage unclear in children at present  In adults, max dosage is 800 mg/day, and optimally divide this into 2 or 3 doses; follow trough levels |
| Micafungin | IV | 2-10 mg/kg/day | Highest dosages in neonates (10 mg/kg/day), and lower dosages in children; older than 8 yr of age, use adult dosage |
| Anidulafungin | IV | 1.5 mg/kg/day | Loading dose of 3 mg/kg/day |
| Caspofungin | IV | 50 mg/m2/day | Load with 70 mg/m2/day, then 50/mg/m2/day as maintenance dosage |

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| **Table 218-2** | Clues That Suggest a Diagnosis of Congenital Syphilis\* |
| **EPIDEMIOLOGIC BACKGROUND CLINICAL FINDINGS** | |
| Untreated early syphilis in the mother Osteochondritis, periostitis  Untreated latent syphilis in the mother Snuffles, hemorrhagic rhinitis An untreated mother who has contact with a known Condylomata lata  syphilitic during pregnancy Bullous lesions, palmar or plantar rash Mother treated for syphilis during pregnancy with a drug Mucous patches  other than penicillin Hepatomegaly, splenomegaly Mother treated for syphilis during pregnancy without Jaundice  follow-up to demonstrate 4-fold change in titer Nonimmune hydrops fetalis Mother coinfected with HIV Generalized lymphadenopathy  Central nervous system signs; elevated cell count or protein in cerebrospinal fluid Hemolytic anemia, diffuse intravascular coagulation, thrombocytopenia Pneumonitis  Nephrotic syndrome  Placental villitis or vasculitis (unexplained enlarged placenta) Intrauterine growth restriction | |

\*Arranged in decreasing order of confidence of diagnosis.

*Modified from Remington JS, Klein JO, Wilson CB, et al, editors:* Infectious diseases of the fetus and newborn infant, *ed 6. Philadelphia, 2006, WB Saunders, p. 556.*

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| **Table 218-3** | Recommended Management of Neonates (≤1 Month of Age) Born to Mothers with Serologic Tests for Syphilis | | |
| **CLINICAL STATUS** | | **EVALUATION (IN ADDITION TO PHYSICAL EXAMINATION AND QUANTITATIVE NONTREPONEMAL TESTING)** | **ANTIMICROBIAL THERAPY**\* |
| Proven or highly probable disease† | | CSF analysis for VDRL, cell count, and protein CBC and platelet count  Other tests as clinically indicated (e.g.,  long-bone radiography, liver function tests, ophthalmologic examination) | Aqueous crystalline penicillin G, 100,000- 150,000 units/kg/day, administered as 50,000 units/kg/dose IV q12hr during the 1st 7 days of life and 18 hr thereafter for a total of 10 days  *or*  Penicillin G procaine, 50,000 units/kg/day IM in a single dose × 10 days |
| NORMAL PHYSICAL EXAMINATION AND SERUM QUANTITATIVE NONTREPONEMAL TITER **≤**4 TIMES THE MATERNAL TITER:   1. (i) Mother was not treated or inadequately CSF analysis for VDRL, cell count, and protein§ Aqueous crystalline penicillin G IV × 10 days§ treated or has no documented treatment; CBC and platelet count§ *or*   (ii) mother was treated with erythromycin or Long-bone radiography§ Penicillin G procaine‡ 50,000 units/kg IM in a other nonpenicillin regimen; (iii) mother single dose × 10 days§  received treatment ≤4 wk before delivery; *or*  (iv) maternal evidence of reinfection or Penicillin G benzathine‡ 50,000 units/kg IM  relapse (<4-fold decrease in titers) in a single dose§   1. (i) Adequate maternal therapy given >4 wk None Clinical, serologic follow-up, and penicillin G   before delivery; (ii) mother has no evidence benzathine 50,000 units/kg IM in a single  of reinfection or relapse dose   1. Adequate therapy before pregnancy and None None¶ mother’s nontreponemal serologic titer   remained low and stable during pregnancy and at delivery | | | |

\*If more than 1 day of therapy is missed, the entire course should be restarted.

†Abnormal physical examination, serum quantitative nontreponemal titer that is 4-fold greater than the mother’s titer, or positive result of darkfield or fluorescent antibody test of body fluid(s).

‡Penicillin G benzathine and penicillin G procaine are approved for IM administration only.

§A complete evaluation (CSF analysis, bone radiography, CBC) is not necessary if 10 days of parenteral therapy is administered, but it may be useful to support a diagnosis of congenital syphilis. If a single dose of penicillin G benzathine is used, then the infant must be evaluated fully, results of the full evaluation must be normal, and follow-up must be certain. If any part of the infant’s evaluation is abnormal or not performed or if the CSF analysis is uninterpretable, the 10-day course of penicillin is required.

Some experts would not treat the infant but would provide close serologic follow-up.

¶Some experts would treat with penicillin G benzathine, 50,000 units/kg, as a single IM injection, if follow-up is uncertain. CBC, complete blood cell count; CSF, cerebrospinal fluid; VDRL, Venereal Disease Research Laboratory.

*From American Academy of Pediatrics:* Red book: 2009 report of the Committee on Infectious Diseases*, 28/e. Elk Grove Village, IL, 2009, American Academy of*

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| **Table 218-4** | Recommended Treatment for Syphilis in Patients Older Than 1 Month of Age |
| **STATUS CHILDREN ADULTS** | |
| Congenital syphilis Aqueous crystalline penicillin G 200,000-300,000  units/kg/day IV administered as 50,000 units/ kg q4-6hr × 10 days\* | |
| Primary, secondary, and early Penicillin G benzathine,‡ 50,000 units/kg, IM, up Penicillin G benzathine,‡ 2.4 million units IM in a single dose latent syphilis† to the adult dose of 2.4 million units in a *or*  single dose *If allergic to penicillin and not pregnant,* doxycycline 100 mg PO bid × 14 days  *or*  Tetracycline 500 mg PO qid × 14 days | |
| Late latent syphilis§ or syphilis Penicillin G benzathine,‡ 50,000 units/kg IM Penicillin G benzathine‡ 7.2 million units total administered of unknown duration up to the adult dose of 2.4 million units, as 3 doses of 2.4 million units IM, each at 1 wk intervals  administered as 3 single doses at 1 wk *or*  intervals (total 150,000 units/kg, up to the *If allergic to penicillin and not pregnant,* doxycycline adult dose of 7.2 million units) 100 mg PO bid × 4 wk  *or*  Tetracycline 500 mg PO qid × 4 wk | |
| Tertiary syphilis Penicillin G benzathine‡ 7.2 million units total, administered as 3 doses of 2.4 million units IM at 1 wk intervals  *If allergic to penicillin and not pregnant, same as for late latent syphilis* | |
| Neurosyphilis Aqueous crystalline penicillin G 200,000-300,000 Aqueous crystalline penicillin G 18-24 million units/day units/kg/day q4-6hr × 10-14 days in doses not administered as 3-4 million units IV q4hr × 10-14 days¶ to exceed the adult dose *or*  Penicillin G procaine,‡ 2.4 million units IM once daily *plus*  probenecid 500 mg PO qid, both × 10-14 days¶ | |

\*If the patient has no clinical manifestations of disease, the CSF examination is normal, and the CSF VDRL result is negative, some experts would treat with up to

3 weekly doses of penicillin G benzathine 50,000 units/kg IM. Some experts also suggest giving these patients a single dose of penicillin G benzathine 50,000 units/kg IM after the 10-day course of IV aqueous penicillin.

†Early latent syphilis is defined as being acquired within the preceding year.

‡Penicillin G benzathine and penicillin G procaine are approved for IM administration only.

§Late latent syphilis is defined as syphilis beyond 1 year’s duration. Patients who are allergic to penicillin should be desensitized.

¶Some experts administer penicillin G benzathine 2.4 million units IM, once per week for up to 3 wk after completion of these neurosyphilis treatment regimens. CSF, cerebrospinal fluid; VDRL, Venereal Disease Research Laboratory.

*From American Academy of Pediatrics:* Red book: 2012 report of the Committee on Infectious Diseases*, ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 698, Table 3.72.*

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| **Table 222-2** | Recommended Treatment of Lyme Disease |
| **DRUG PEDIATRIC DOSING** | |
| Amoxicillin 50 mg/kg/day in 3 divided doses (max: 1,500 mg/day)  Doxycycline 4 mg/kg/day in 2 divided doses  (max: 200 mg/day) (see text regarding doxycycline use in children)  Cefuroxime axetil 30 mg/kg/day in 2 divided doses (max: 1,000 mg/day)  Ceftriaxone (IV)\*† 50-75 mg/kg/day once daily  (max: 2,000 mg/day) | |
| RECOMMENDED THERAPY BASED ON CLINICAL MANIFESTATION  Erythema migrans Oral regimen, 14-21 days Meningitis Ceftriaxone, 10-28 days  Cranial nerve palsy Oral regimen, 14-21 days (see text regarding  possible need for lumbar puncture)  Cardiac disease Oral regimen or ceftriaxone, 14-21 days (see text for specifics)  Arthritis‡ Oral regimen, 28 days Late neurologic Ceftriaxone, 14-28 days  disease | |

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| **Table 222-1** | Clinical Stages | of Lyme Disease |
| **DISEASE STAGE** | **TIMING AFTER TICK BITE** | **TYPICAL CLINICAL MANIFESTATIONS** |
| Early localized | 3-30 days | Erythema migrans (single), variable constitutional symptoms (headache, fever, myalgia, arthralgia, fatigue) |
| Early  disseminated | 3-12 wk | Erythema migrans (single or multiple), worse constitutional symptoms, cranial neuritis, meningitis, carditis, ocular disease |
| Late | >2 mo | Arthritis |

\*Cefotaxime and penicillin G are alternative parenteral agents.

†Doses of 100 mg/kg/day should be used for meningitis.

‡Persistent arthritis can be treated with a second oral regimen or ceftriaxone.

*From Wormser GP, Dattwyler RJ, Shapiro ED, et al: The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America,* Clin Infect Dis *43:1089–1134, 2006.*

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| **Table 245-1** | Currently Licensed Antiviral Drugs\* | | |
| **ANTIVIRAL** | | **TRADE NAME** | **MECHANISM OF ACTION** |
| Acyclovir Adefovir Amantadine Cidofovir Famciclovir Fomivirsen | | Zovirax Hepsera Symmetrel Vistide Famvir Vitravene | Inhibits viral DNA polymerase Nucleotide reverse transcriptase inhibitor Blocks M2 protein ion channel  Inhibits viral DNA polymerase Inhibits viral DNA polymerase  Phosphorothioate oligonucleotide inhibits viral replication via antisense mechanism  Inhibits viral DNA polymerase and reverse transcriptase at pyrophosphate-binding site  Inhibits viral DNA polymerase Inhibits viral DNA polymerase  Produces multiple effector proteins that exert antiviral effects; also directly interacts with immune system components  Not established  Inhibits viral DNA polymerase and reverse transcriptase Neuraminidase inhibitor; interference with  deaggregation and release of viral progeny Same as interferon  Inhibits viral DNA polymerase Interference with viral messenger RNA Blocks M2 protein ion channel  Inhibits viral DNA polymerase Same as acyclovir  Same as ganciclovir  Inhibits viral DNA polymerase (and to lesser extent, cellular DNA polymerase)  Neuraminidase inhibitor; interference with deaggregation and release of viral progeny |
| Foscarnet | | Foscavir |
| Ganciclovir Idoxuridine Interferon-α  Interferon-α2b plus ribavirin Lamivudine  Oseltamivir | | Cytovene Herplex  Intro-A (interferon-α2b) Roferon-A (interferon-α2a) Infergen (interferon alfacon-1) Rebetron  Epivir Tamiflu |
| Pegylated interferon Penciclovir  Ribavirin Rimantadine Trifluridine Valacyclovir Valganciclovir Vidarabine | | PEG-Intron (α2b), Pegasys (α2a) Denavir  Virazole, Rebetol, Copegus Flumadine  Viroptic Valtrex Valcyte ara-A |
| Zanamivir | | Relenza |
| FDA-APPROVED COMBINATION THERAPIES  Interferon-α2b + ribavirin Rebetron (Intron-A plus Rebetol)  Interferon-α2a + ribavirin Roferon-A + ribavirin Pegylated interferon-α2b + ribavirin PEG-Intron + Rebetol Pegylated interferon-α2a + ribavirin Pegasys + Copegus | | | |

\*See Chapter 276 for antiretroviral drugs.

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| **Table 246-2** | Recommendations for Measles Immunization | |
| **CATEGORY** | | **RECOMMENDATIONS** |
| Unimmunized, no history of measles (12-15 mo of age) | | A 2 dose schedule (with MMR) is recommended  The 1st dose is recommended at 12-15 mo of age; the 2nd is recommended at 4-6 yr of age |
| Children 6-11 mo of age in epidemic situations or prior to international travel | | Immunize with MMR vaccine, but this dose is not considered valid, and 2 valid doses administered on or after the 1st birthday are required, The 1st valid dose should be administered at  12-15 mo of age. The 2nd valid dose is recommended at least 28 days later and is given at 4 through 6 yr of age |
| Students in kindergarten or elementary, middle, and high school who have received 1 dose of measles vaccine at 12 mo of age or older | | Administer the 2nd dose |
| Students in college and other post–high school institutions who have received 1 dose of measles vaccine at ≥12 mo of age | | Administer the 2nd dose |
| History of immunization before the 1st birthday | | Do not consider valid and immunize (2 doses) |
| History of receipt of inactivated measles vaccine or unknown type of vaccine, 1963-1967 | | Do not consider valid and immunize (2 doses) |
| Further attenuated or unknown vaccine given with Ig | | Do not consider valid and immunize (2 doses) |
| Allergy to eggs | | Immunize; no reactions likely |
| Neomycin allergy, nonanaphylactic | | Immunize; no reactions likely |
| Severe hypersensitivity (anaphylaxis) to neomycin or gelatin | | Avoid immunization |
| Tuberculosis | | Immunize; if patient has untreated tuberculosis disease, start antituberculosis therapy before immunizing |
| Measles exposure | | Immunize and/or give Ig, depending on circumstances |
| HIV-infected | | Immunize (2 doses) unless severely immunocompromised, and give Ig if exposed to measles |
| Personal or family history of seizures | | Immunize; advise parents of slightly increased risk of seizures |
| Ig or blood recipient | | Immunize at the appropriate interval (see Table 246-3) |

Ig, immunoglobulin; MMR, measles-mumps-rubella vaccine.

*From American Academy of Pediatrics:* Red book: 2012 report of the Committee on Infectious Diseases*, ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 494.*

**Chapter 245** ◆ Principles of Antiviral Therapy **1539**

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| **Table 245-2** | Antiviral Therapies for Non-HIV Clinical Conditions | | |
| **VIRUS** | **CLINICAL SYNDROME** | **ANTIVIRAL AGENT OF CHOICE** | **ALTERNATIVE ANTIVIRAL AGENTS** |
| Influenza A | Treatment Prophylaxis | Oseltamivir (>1 yr old) Oseltamivir (>1 yr old) | Rimantadine Amantadine Amantadine Rimantadine Zanamivir (>7 yr old) |
| Influenza B | Treatment | Oseltamivir | Zanamivir (>7 yr old) |
| Respiratory Bronchiolitis or pneumonia in high-risk host Ribavirin aerosol syncytial virus | | | |
| Cytomegalovirus (CMV) | Congenital CMV infection  Retinitis in AIDS patients  Pneumonitis, colitis; esophagitis in immunocompromised patients | Ganciclovir (IV)  Valganciclovir  Ganciclovir (IV) | Valganciclovir (if oral therapy appropriate; long-term oral valganciclovir investigational but may improve developmental and hearing outcomes)  Ganciclovir Cidofovir Foscarnet  Ganciclovir ocular insert Foscarnet  Cidofovir Valganciclovir |
| Herpes simplex virus (HSV) | Neonatal herpes  Suppressive therapy following neonatal herpes with central nervous system involvement  HSV encephalitis  HSV gingivostomatitis  First episode genital infection  Recurrent genital herpes Suppression of genital herpes  Cutaneous HSV (whitlow, herpes gladiatorum) Eczema herpeticum  Mucocutaneous infection in immunocompromised host (mild)  Mucocutaneous infection in immunocompromised host (moderate to severe)  Prophylaxis in bone marrow transplant recipients  Acyclovir-resistant HSV Keratitis or keratoconjunctivitis | Acyclovir (IV) Acyclovir (PO)  Acyclovir (IV) Acyclovir (PO) Acyclovir (PO)  Acyclovir (PO) Acyclovir (PO)  Acyclovir (PO) Acyclovir (PO) Acyclovir (IV)  Acyclovir (IV) Acyclovir (IV)  Foscarnet Trifluridine | Acyclovir (IV) Valacyclovir Famciclovir  Acyclovir (IV) (severe disease) Valacyclovir  Famciclovir Valacyclovir Famciclovir Penciclovir (topical)  Acyclovir (IV) (severe disease)  Acyclovir (PO) (if outpatient therapy acceptable)  Valacyclovir Famciclovir Cidofovir Vidarabine |
| Varicella-zoster virus | Chickenpox, healthy child  Chickenpox, immunocompromised child Zoster (not ophthalmic branch of trigeminal  nerve), healthy child  Zoster (ophthalmic branch of trigeminal nerve), healthy child  Zoster, immunocompromised child | Supportive care Acyclovir (IV) Supportive care  Acyclovir (IV) Acyclovir (IV) | Acyclovir (PO) Acyclovir (PO)  Valacyclovir |

*Modified from Kimberlin DW: Antiviral therapies in children: Has their time arrived?* Pediatr Clin North Am *52:837–867, 2005.*

**Chapter 246** ◆ Measles **1547**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 246-3** | Suggested Intervals Between Immunoglobulin Administration and Measles Immunization\* | | | | |
| **INDICATION FOR IMMUNOGLOBULIN** | | **Dose** | | | |
| **ROUTE** | **UNITS (U) OR MILLILITERS (mL)** | **mg IgG/kg** | **INTERVAL**  **(mo)†** |
| Tetanus (as tetanus Ig) | | IM | 250 U | 10 | 3 |
| Hepatitis A prophylaxis (as Ig): Contact prophylaxis International travel | | IM IM | 0.02 mL/kg  0.06 mL/kg | 3.3  10 | 3  3 |
| Hepatitis B prophylaxis (as hepatitis B Ig) | | IM | 0.06 mL/kg | 10 | 3 |
| Rabies prophylaxis (as rabies Ig) | | IM | 20 IU/kg | 22 | 4 |
| Varicella prophylaxis (as VariZIG) | | IM | 125 U/10 kg  (maximum 625 U) | 20-40 | 5 |
| Measles prophylaxis (as Ig): Standard Immunocompromised host | | IM IM | 0.25 mL/kg  0.50 mL/kg | 40  80 | 5  6 |
| Respiratory syncytial virus prophylaxis (palivizumab monoclonal antibody)‡ | | IM | — | 15 mg/kg (monoclonal) | None |
| Cytomegalovirus immune globulin | | IV | 3 mL/kg | 150 | 6 |
| Blood transfusion: Washed RBCs  RBCs, adenine-saline added Packed RBCs  Whole blood  Plasma or platelet products | | IV IV IV IV IV | 10 mL/kg  10 mL/kg  10 mL/kg  10 mL/kg  10 mL/kg | Negligible 10  20-60  80-100  160 | 0  3  5  6  7 |

##### Continued

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 246-3** | Suggested Intervals Between Immunoglobulin Administration and Measles Immunization\*—cont’d | | | | |
| **INDICATION FOR IMMUNOGLOBULIN** | | **Dose** | | | |
| **ROUTE** | **UNITS (U) OR MILLILITERS (mL)** | **mg IgG/kg** | **INTERVAL**  **(mo)†** |
| Replacement (or therapy) of immune deficiencies (as IVIG) | | IV | — | 300-400 | 8 |
| ITP (as IVIG) | | IV | — | 400 | 8 |
| ITP | | IV | — | 1,000 | 10 |
| ITP or Kawasaki disease | | IV | — | 1,600-2,000 | 11 |

\*Immunization in the form of measles-mumps-rubella (MMR), measles-mumps-rubella-varicella (MMRV), or monovalent measles vaccine.

†These intervals should provide sufficient time for decreases in passive antibodies in all children to allow for an adequate response to measles vaccine. Physicians should not assume that children are fully protected against measles during these intervals. Additional doses of Ig or measles vaccine may be indicated after exposure to measles (see text).

‡Monoclonal antibodies, such as palivizumab, do not interfere with the immune response to vaccines.

Ig, immunoglobulin; IgG, immunoglobulin G; ITP, immune (formerly termed “idiopathic”) thrombocytopenic purpura; IVIG, intravenous Ig; RBCs, red blood cells.

|  |  |  |
| --- | --- | --- |
| **Table 247-2** | Clinical Manifestations of Congenital Rubella Syndrome in 376 Children Following Maternal Rubella\* | |
| **MANIFESTATION** | | **RATE (%)** |
| Deafness | | 67 |
| Ocular | | 71 |
| Cataracts | | 29 |
| Retinopathy | | 39 |
| Heart disease† | | 48 |
| Patent ductus arteriosus | | 78 |
| Right pulmonary artery stenosis | | 70 |
| Left pulmonary artery stenosis | | 56 |
| Valvular pulmonic stenosis | | 40 |
| Low birthweight | | 60 |
| Psychomotor retardation | | 45 |
| Neonatal purpura | | 23 |
| Death | | 35 |

\*Other findings: hepatitis, linear streaking of bone, hazy cornea, congenital glaucoma, delayed growth.

†Findings in 87 patients with congenital rubella syndrome and heart disease who underwent cardiac angiography.

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|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table 249-1** Differential Diagnosis of Acute Flaccid Paralysis | | | | | | |
| **SITE, CONDITION,**  **FACTOR, OR AGENT CLINICAL FINDINGS** | **ONSET OF PARALYSIS** | **PROGRESSION OF PARALYSIS** | **SENSORY SIGNS AND SYMPTOMS** | **REDUCTION OR ABSENCE OF DEEP TENDON REFLEXES** | **RESIDUAL PARALYSIS** | **PLEOCYTOSIS** |
| ANTERIOR HORN CELLS OF SPINAL CORD  Poliomyelitis (wild and Paralysis vaccine-associated  paralytic poliomyelitis)  Nonpolio enteroviruses Hand-foot-and-mouth disease,  aseptic meningitis, acute hemorrhagic conjunctivitis, possibly idiopathic epidemic flaccid paralysis  West Nile virus Meningitis encephalitis | Incubation period 7-14 days (range: 4-35 days)  As in poliomyelitis  As in poliomyelitis | 24-48 hr to onset of full paralysis; proximal → distal, asymmetric  As in poliomyelitis  As in poliomyelitis | No  No  No | Yes  Yes  Yes | Yes  Yes  Yes | Aseptic meningitis (moderate polymorphonuclear leukocytes at 2-3 days)  As in poliomyelitis  Yes |
| OTHER NEUROTROPIC VIRUSES  Rabies virus  Varicella-zoster virus Exanthematous vesicular  eruptions  Japanese encephalitis virus | Month–year  Incubation period 10-21 days  Incubation period 5-15 days | Acute, symmetric, ascending  Acute, symmetric, ascending  Acute, proximal, asymmetric | Yes Yes  ± | Yes  ±  ± | No  ±  ± | ±  Yes Yes |
| GUILLAIN-BARRÉ SYNDROME  Acute inflammatory Preceding infection, bilateral polyradiculoneuropathy facial weakness  Acute motor axonal Fulminant, widespread paralysis, neuropathy bilateral facial weakness,  tongue involvement | Hours to 10 days Hours to 10 days | Acute, symmetric, ascending (days to 4 wk)  1-6 days | Yes No | Yes Yes | ±  ± | No No |

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**Chapter 249** ◆ Polioviruses **1559**

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| --- | --- | --- | --- | --- | --- | --- |
| ACUTE TRAUMATIC SCIATIC NEURITIS  Intramuscular gluteal Acute, asymmetric injection  Acute transverse myelitis Preceding *Mycoplasma*  *pneumoniae, Schistosoma*, other parasitic or viral infection  Epidural abscess Headache, back pain, local spinal tenderness, meningismus  Spinal cord compression; trauma | Hours to 4 days  Acute, symmetric hypotonia of lower limbs  Complete  Complete | Complete, affected limb  Hours to days  Hours to days | Yes | Yes | ± | No |
| Yes | Yes, early | Yes | Yes |
| Yes | Yes | ± | Yes |
| Yes | Yes | ± | ± |
| NEUROPATHIES  Exotoxin of In severe cases, palatal paralysis,  *Corynebacterium* blurred vision  *diphtheriae*  Toxin of *Clostridium* Abdominal pain, diplopia, loss  *botulinum* of accommodation, mydriasis  Tick bite paralysis Ocular symptoms | Incubation period 1-8 wk (paralysis 8-12 wk after onset of illness)  Incubation period 18-36 hr  Latency period 5-10 days | Rapid, descending, symmetric  Acute, symmetric, ascending | Yes  ±  No | Yes  No Yes |  | ±  No No |
| DISEASES OF THE NEUROMUSCULAR JUNCTION  Myasthenia gravis Weakness, fatigability, diplopia,  ptosis, dysarthria |  | Multifocal | No | No | No | No |
| DISORDERS OF MUSCLE  Polymyositis Neoplasm, autoimmune disease  Viral myositis | Subacute, proximal →  distal Pseudoparalysis | Weeks to months Hours to days | No No | Yes No |  | No No |
| METABOLIC DISORDERS  Hypokalemic periodic paralysis | Proximal limb, respiratory muscles | Sudden postprandial | No | Yes | ± | No |
| INTENSIVE CARE UNIT WEAKNESS  Critical illness Flaccid limbs and respiratory  polyneuropathy weakness | Acute, following systemic inflammatory response syndrome/sepsis | Hours to days | ± | Yes | ± | No |

*Modified from Marx A, Glass JD, Sutter RW: Differential diagnosis of acute flaccid paralysis and its role in poliomyelitis surveillance,* Epidemiol Rev *22:298–316, 2000.*

**1602 Part XVII** ◆ Infectious Diseases

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| --- | --- | --- | --- |
| **Table 258-3** | Centers for Disease Control and Prevention Recommended Dosage and Schedule of Influenza Antiviral Medications for Treatment and Chemoprophylaxis | | |
| **ANTIVIRAL AGENT** | **USE** | **CHILDREN** | **ADULTS\*** |
| Oseltamivir (Tamiflu) | Treatment (5 days)  Chemoprophylaxis (7 days) | If child is younger than 1 yr old†:  3 mg/kg/dose twice daily‡  If child is 1 yr or older, dose varies by child’s weight:  15 kg or less, the dose is 30 mg twice a day  >15-23 kg, the dose is 45 mg twice a day  >23-40 kg, the dose is 60 mg twice a day  >40 kg, the dose is 75 mg twice a day  If child is younger than 3 mo old, use of oseltamivir for chemoprophylaxis is not recommended unless situation is judged critical because of limited data in this age group  If child’s age is 3 mo or older and younger than 1 yr old†:  3 mg/kg/dose once daily‡  If child is 1 yr or older, dose varies by child’s weight:  15 kg or less, the dose is 30 mg once a day  >15-23 kg, the dose is 45 mg once a day  >23-40 kg, the dose is 60 mg once a day  >40 kg, the dose is 75 mg once a day | 75 mg twice daily  75 mg once daily |
| Zanamivir¶ (Relenza) | Treatment (5 days)  Chemoprophylaxis (7 days) | For children age 7 yr and older:  10 mg (two 5-mg inhalations) twice daily  For children age 5 yr and older:  10 mg (two 5-mg inhalations) once daily | 10 mg (two 5-mg inhalations) twice daily  10 mg (two 5-mg inhalations) once daily |

Current for 2013-2014 influenza season, United States.

\*Intravenous peramivir (Rapivab) was approved on December 19, 2014, for use in the treatment of acute uncomplicated influenza in people 18 years and older.

†Oral oseltamivir is approved by the FDA for treatment of acute uncomplicated influenza with twice-daily dosing in persons older than 14 days of age, and for prophylaxis with once-daily dosing in persons 1 yr and older. Although not part of the FDA-approved indications, use of oral oseltamivir for treatment of influenza in infants younger than 14 days old, and for prophylaxis in infants 3 mo to 1 yr of age, is recommended by the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics.

‡This is the FDA-approved oral and CDC-recommended oseltamivir treatment dose for infants 14 days and older and less than 1 yr old, and provides oseltamivir

exposure in children similar to that achieved by the approved dose of 75 mg orally twice daily for adults, as shown in 2 studies of oseltamivir pharmacokinetics. The American Academy of Pediatrics recommends an oseltamivir treatment dose of 3.5 mg/kg orally twice daily for infants ages 9-11 mo for the 2013-2014 season, on the basis of data that indicated that the higher dose of 3.5 mg/kg was needed to achieve the protocol-defined targeted exposure for this cohort as defined in the Collaborative Antiviral Study Group (CASG) 114 study. It is unknown whether this higher dose will improve efficacy or prevent the development of antiviral resistance. However, there is no evidence that the 3.5 mg/kg dose is harmful or causes more adverse events to infants in this age group.

¶Inhaled zanamivir is approved for treatment of acute uncomplicated influenza with twice-daily dosing in persons age 7 yr and older, and for prophylaxis with

once-daily dosing in persons age 5 yr and older.

*Adapted from Centers for Disease Control and Prevention (CDC):* Influenza antiviral medications: summary for clinicians*. Available at* [*http://www.cdc.gov/flu/*](http://www.cdc.gov/flu/) *professionals/antivirals/summary-clinicians.htm. For current details, consult annually updated recommendations at* [*http://www.cdc.gov/flu*](http://www.cdc.gov/flu)

|  |  |
| --- | --- |
| **Table 255-1** | Findings in Infants with Symptomatic Congenital Cytomegalovirus Infection Identified Through Newborn Screening Program\* |
| **PERCENTAGE (%) OF INFANTS** | |
| CLINICAL FINDINGS  Prematurity (<37 wk) 24  Jaundice (direct bilirubin >2 mg/dL) 42  Petechiae 54  Hepatosplenomegaly 19  Purpura 3  Microcephaly 35  Small gestational age 28   1. Clinical finding 41 2. Clinical findings 59 | |
| LABORATORY FINDINGS  Elevated alanine aminotransferase (>80 IU/mL) 71  Thrombocytopenia (<100,000/μL) 43  Direct hyperbilirubinemia (>2 mg/dL) 54  Head CT abnormalities 42 | |

\*Findings in 70 infants with symptomatic congenital CMV infection identified during the newborn screening program for infants with congenital CMV infection performed at the University of Alabama Hospitals over an approximate 20 yr interval.

**Chapter 274** ◆ Rabies **1643**

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 250-2** | Differential Diagnosis of Enterovirus Infections | | |
| **CLINICAL MANIFESTATION** | | **BACTERIAL PATHOGENS** | **VIRAL PATHOGENS** |
| Nonspecific febrile illness | | *Streptococcus pneumoniae, Haemophilus influenzae* type b, *Neisseria meningitidis* | Influenza viruses, human herpesviruses 6 and 7, human parechoviruses |
| Exanthems/enanthems | | Group A streptococcus, *Staphylococcus aureus*, *N. meningitidis* | Herpes simplex virus, adenoviruses, varicella-zoster virus, Epstein-Barr virus, measles virus, rubella virus, human herpesviruses 6 and 7, human parechoviruses |
| Respiratory illness/conjunctivitis | | *S. pneumoniae, H. influenzae* (nontypeable and type b), *N. meningitidis, Mycoplasma pneumoniae, Chlamydia pneumoniae* | Adenoviruses, influenza viruses, respiratory syncytial virus, parainfluenza viruses, rhinoviruses, human metapneumovirus, coronaviruses |
| Myocarditis/pericarditis | | *S. aureus, H. influenzae* type b, *M. pneumoniae* | Adenoviruses, influenza virus, parvovirus, cytomegalovirus |
| Meningitis/encephalitis | | *S. pneumoniae, H. influenzae* type b,  *N. meningitidis, Mycobacterium tuberculosis*, *Borrelia burgdorferi, M. pneumoniae*, *Bartonella henselae, Listeria monocytogenes* | Herpes simplex virus, West Nile virus, influenza viruses, adenoviruses, Epstein-Barr virus, mumps virus, lymphocytic choriomeningitis virus, arboviruses, human parechoviruses |
| Neonatal infections | | Group B streptococcus, Gram-negative enteric bacilli, *L. monocytogenes, Enterococcus* | Herpes simplex virus, adenoviruses, cytomegalovirus, rubella virus, human parechoviruses |

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 274-1** | Rabies Postexposure Prophylaxis Guide | | |
| **ANIMAL TYPE** | | **EVALUATION AND DISPOSITION OF ANIMAL** | **POSTEXPOSURE PROPHYLAXIS RECOMMENDATIONS** |
| Dogs, cats, and ferrets | | Healthy and available for 10 days of observation Rabid or suspected of being rabid†  Unknown (escaped) | Prophylaxis only if animal shows signs of rabies\* Immediate immunization and RIG  Consult public health officials for advice |
| Bats, skunks, raccoons, foxes, and most other carnivores; woodchucks | | Regarded as rabid unless geographic area is known to be free of rabies or until animal proven negative by laboratory tests† | Immediate immunization and RIG |
| Livestock, rodents, and lagomorphs (rabbits, hares, and pikas) | | Consider individually | Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice and other rodents, rabbits, hares, and pikas almost never require antirabies treatment |

\*During the 10-day observation period, at the first sign of rabies in the biting dog, cat, or ferret, treatment of the exposed person with RIG (human) and vaccine should be initiated. The animal should be euthanized immediately and tested.

†The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended. Immunization is discontinued if immunofluorescent test result for the animal is negative.

RIG, rabies immunoglobulin.

*From American Academy of Pediatrics:* Red book 2012: report of the Committee on Infectious Diseases*, ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

Bite, scratch, or mucous membrane contact from a mammal

No

Domestic animals: dogs, cats, ferrets Wildlife: bats, raccoons, skunks, foxes, coyotes

In some locations: livestock

Yes

Yes

No PEP

No Squirrels, hamsters, gerbils, chipmunks, rat, mice, rabbits

No

Yes

Dog, cat, ferret

Yes Yes No

Yes No

No

PEP

PEP

Consult local health officials. Quarantine animal for 10 days.

Signs of rabies?

Yes No

Contact health department for testing.

Testing positive?

PEP

PEP

No

PEP

Yes No

Animal available for testing?

Animal available for observation?

No

Consult local health officials

**Figure 274-1** Algorithm for evaluating a child for rabies postexposure prophylaxis. This and any other algorithm should be used in concert with local epidemiologic information regarding the incidence of animal rabies in any given location.

**Chapter 276** ◆ Acquired Immunodeficiency Syndrome (Human Immunodeficiency Virus) **1651**

Bacterial infections, multiple or recurrent\* Candidiasis of bronchi, trachea, or lungs Candidiasis of esophagus

Cervical cancer, invasive†

Coccidioidomycosis, disseminated or extrapulmonary Cryptococcosis, extrapulmonary

Cryptosporidiosis, chronic intestinal (>1 mo duration)

Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 mo

Cytomegalovirus retinitis (with loss of vision) Encephalopathy attributed to HIV‡

Herpes simplex: chronic ulcers (>1 mo duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 mo)

Histoplasmosis, disseminated or extrapulmonary Isosporiasis, chronic intestinal (>1 mo duration) Kaposi sarcoma

Lymphoma, Burkitt (or equivalent term) Lymphoma, immunoblastic (or equivalent term) Lymphoma, primary, of brain

*Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary

*Mycobacterium tuberculosis* of any site, pulmonary,† disseminated, or extrapulmonary

Mycobacterium, other species or unidentified species, disseminated or extrapulmonary

*Pneumocystis jiroveci* (previously known as *Pneumocystis carinii*) pneumonia

Pneumonia, recurrent†

Progressive multifocal leukoencephalopathy *Salmonella* septicemia, recurrent Toxoplasmosis of brain, onset at age >1 mo Wasting syndrome attributed to HIV‡

Stage 3—Defining Opportunistic Illnesses in HIV Infection

**Table 276-2**

|  |  |
| --- | --- |
| **Table 276-3** | Laboratory Diagnosis of HIV Infection |
| **TEST** | **COMMENT** |
| HIV DNA PCR | Preferred test to diagnose HIV-1 subtype B infection in infants and children younger than 18 mo of age; highly sensitive and specific by 2 wk of age and available; performed on peripheral blood mononuclear cells. False negatives can occur in non-B subtype HIV-1 infections |
| HIV culture | Expensive, not easily available, requires up to 4 wk to do test; not recommended |
| HIV RNA PCR | Preferred test to identify non-B subtype HIV-1infections. Similar sensitivity and specificity to HIV DNA PCR in infants and children younger than 18 mo of age, but  DNA PCR is generally preferred because of greater clinical experience with that assay |

\*Only among children aged <6 yr.

†Only among adults, adolescents, and children aged≥6 yr.

‡Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table 276-1** | HIV Infection Stage\* Based on Age-Specific CD4+ T-Lymphocyte Count or CD4+ T-Lymphocyte Percentage of Total Lymphocytes | | | |
| **Stage** | | **Age on Date of CD4+ T-Lymphocyte Test** | | |
| **<1 Yr** | **1-5 Yr**  **CELLS/µL %** | ≥**6 Yr** |
| **CELLS/µL %** | **CELLS/µL %** |
| 1 ≥1,500 ≥34 ≥1,000 ≥30 ≥500 ≥26 | | | | |
| 2 750-1,499 26-33 500-999 22-29 200-499 14-25 | | | | |
| 3 <750 <26 <500 <22 <200 <14 | | | | |

\*Stage is based primarily on the CD4+ T-lymphocyte count. The CD4+ T-lymphocyte count takes precedence over the CD4+ T-lymphocyte percentage, and the percentage is considered only if the count is missing.

*From Centers for Disease Control and Prevention: Revised surveillance case definition for HIV infection—United States, 2014. MMWR 63(No RR-3):1-10, 2014.*

**Chapter 276** ◆ Acquired Immunodeficiency Syndrome (Human Immunodeficiency Virus) **1655**

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 276-4** Summary of Antiretroviral Therapies Available in 2014 | | | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **DOSING** | **SIDE EFFECTS** | **COMMENTS** |
| NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS | | Class adverse effects: Lactic acidosis with hepatic steatosis |  |
| Abacavir (ABC) | Children: ≥3 mo to 13 yr: | Common: nausea, vomiting, anorexia, fever, headache, diarrhea, rash  Less common: hypersensitivity, lactic acidosis with hepatic steatosis, pancreatitis, elevated triglycerides, myocardial infarction | Can be given with food  Genetic screening for HLAB\*5701 is recommended prior to initiation of ABC-containing treatment. If test is positive avoid ABC. Do not restart  ABC in patients who had hypersensitivity-like symptoms (e.g., flu-like symptoms) |
| Ziagen, ABC | 8 mg/kg bid (maximum dose |
| Tablet: 300 mg | 300 mg bid) |
| Oral solution: 20 mg/mL | >30 kg: 300 mg bid |
| Trizivir: combination of zidovudine | Children with viral load <40 |
| (ZDV), lamivudine, ABC (300, 150, | copies/mm3:16 mg/kg once |
| 300 mg) | daily (max 600 mg) |
| Epzicom: combination of lamivudine, | Adolescents >16 yr and adults: |
| ABC (300, 600 mg) | 600 mg once daily Trizivir |
|  | (>40 kg): 1 tablet bid |
|  | Epzicom (>16 yr of age): |
|  | 1 tablet bid |
| Didanosine Videx, ddI  Powder for oral solution (prepared with solution containing antacid): 10 mg/mL | 2 wk to <3 mo: 50 mg/m2 bid  3-8 mo: 100 mg/m2 bid  >8 mo: 120 mg/m2 (maximum 200 mg per dose) bid  Adolescents (>13 yr) and adults  <60 kg: 250 mg once daily  >60 kg: 400 mg once daily (to increase adherence)  If combined with tenofovir  <60 kg–200 mg once daily  >60 kg–250 mg once daily | Common: diarrhea, abdominal pain, nausea, vomiting  Less common: pancreatitis, peripheral neuropathy, electrolyte abnormalities, lactic acidosis with  hepatic steatosis, hepatomegaly, retinal depigmentation | Food decreases bioavailability up to 50%. Take 30 min before  or 2 hr after meal. Tablets dissolved in water are stable for 1 hr (4 hr in buffered solution)  Drug interactions: antacids/gastric acid antagonists may increase bioavailability; possible decreased absorption of fluoroquinolones, ganciclovir, ketoconazole, itraconazole, dapsone, and some protease inhibitors. Combination with d4T enhances toxicity, also common if combined with tenofovir  Same as for ddI |
| Videx EC  Capsule, delayed release: 125, 200,  250, 400 mg  Generic: 200, 250, 400 mg | Children: not established  20-25 kg: 200 mg once daily  25-60 kg: 250 mg once daily  ≥60 kg: 400 mg once daily | Same as for ddI |
| Emtricitabine | Infants: 0-3 mo: 3 mg/kg once | Common: headache, insomnia, diarrhea, nausea, skin discoloration  Less common: lactic acidosis with hepatic steatosis, neutropenia | Closely monitor patients with hepatitis B coinfection  Can be given without regard to food. Oral solution should be refrigerated if temperature above 25°C (77°F) |
| Emtriva, FTC | daily |
| Capsules: 200 mg | Children ≥3 mo to 17 yr: 6 mg/ |
| Oral solution: 10 mg/mL | kg (maximum 240 mg) once |
| Truvada: combination FTC, tenofovir | daily |
| disoproxil fumarate (TDF) (200, | >33 kg, adolescent and adult: |
| 300 mg) | 200 mg capsule or 240 mg |
| Atripla: Combination FTC, TDF, | solution once daily |
| efavirenz (EFV) (200, 300, 600 mg) | Truvada or Atripla or Complera |
| Complera: combination of FTC, TDF, | or Stribild adult dose: 1 tablet |
| rilpivirine (RPV) (200, 300, 25mg) | once daily |
| Stribild: combination of FTC, |  |
| TDF, elvitegravir (EVG), |  |
| cobicistat (COBI) (200, 300, 150, |  |
| 150 mg) |  |
| Lamivudine  Epivir, Epivir HBV, 3TC  Tablet: 150 (scored), 300 mg (Epivir) 100 mg (Epivir HBV)  Solution: 5 mg/mL (Epivir HBV), 10 mg/mL (Epivir)  Combivir: combination of ZDV, lamivudine (300, 150 mg)  Trizivir and Epzicom combination (see abacavir) | Neonates (<30 days): 2 mg/kg bid  >1 mo: 4 mg/kg bid (maximum  150 mg bid)  ≥30 kg: 150 mg bid or  300 mg once daily  Children with VL <40 copies/mL: 8-10 mg/kg qd  Combivir, Trizivir (>30 kg): 1 tablet bid  Epzicom (>16 yr): 1 tablet qd | Common: headache, nausea  Less common: pancreatitis, peripheral neuropathy, lactic acidosis with hepatic steatosis, lipodystrophy | No food restrictions Combination with ZDV may  prevent ZDV resistance. Patient should be screened for hepatitis B virus (HBV) and if positive watched for HBV exacerbation when lamivudine is discontinued |
| Stavudine Zerit, d4T  Capsule: 15, 20, 30, 40 mg  Solution: 1 mg/mL | Neonates (0-13 days): 0.5 mg/kg bid  14 days to 30 kg: 1 mg/kg bid  >30 kg: 30 mg bid | Common: headache, nausea, hyperlipidemia, fat maldistribution  Less common: peripheral neuropathy, pancreatitis, lactic acidosis, hepatic steatosis | No food restrictions. Should not be administered with ZDV because of virologic antagonism. Higher incidence of lactic acidosis. Increased toxicity if combined with ddI |

*Continued*

**1656 Part XVII** ◆ Infectious Diseases

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| **Table 276-4** Summary of Antiretroviral Therapies Available in 2014—cont’d | | | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **DOSING** | **SIDE EFFECTS** | **COMMENTS** |
| Tenofovir Viread, TDF  Tablet: 150, 200, 250, 300 mg  Powder: 40 mg per 1 gr powder Truvada: combination of FTC, TDF  (200, 300 mg)  Atripla: Combination of FTC, TDF, EFV (200, 300, 600 mg)  Complera: combination of FTC, TDF, RPV (200, 300, 25 mg)  Stribild: combination of FTC, TDF, EVG, COBI (200, 300, 150, 150 mg) | 2 to <12 yr: 8 mg/kg qd  >12 yr and 35 kg, adolescent  >12 yr and 35 kg and adult: 300 mg once daily  Truvada, Atripla, Complera, and Stribild (see FTC) | Common: nausea, vomiting, diarrhea  Less common: lactic acidosis with hepatic steatosis, hepatomegaly,  reduced bone density, renal toxicity | High-fat meal increases absorption; coadministration with ddI may increase ddI toxicity, decrease atazanavir (ATV) levels (therefore boosting ATV with ritonavir is required). ATV and lopinavir (LPV) increase TDF levels and potential toxicity. Screen for HBV before TDF given, as exacerbation of hepatitis may occur when TDF is discontinued |
| Zidovudine Retrovir, AZT, ZDV Capsule: 100 mg  Tablet: 300 mg  Syrup: 10 mg/mL  Injection: 10 mg/mL  Combivir: combination of ZDV, lamivudine (300, 150 mg)  Trizivir: Combination of ZDV, lamivudine, ABC (300, 150, 300 mg) | Prophylaxis: 0-6 wk: Premature infants:  1.5 mg/kg IV every 12 hr  *or*  2 mg/kg orally every 12 hr for  2 wk (for gestational age 30 to 35 wk) or 4 wk (for gestational age <30 wk); then increase to 3 mg/kg every 12 hr to complete 6 wk (if needed)  For gestational age >35 wk:  3 mg/kg/dose IV every 12 hr  *or*  4 mg/kg orally every 12 hr  Treatment:  6 wk to 18 yr: 240 mg/m2 every  12 hr  *or*  4 kg to <9 kg: 12 mg/kg bid  9 kg to <30 kg: 9 mg/kg bid  >30 kg, adolescent and adult: 200 mg tid or 300 mg bid Combivir *or* Trizivir: 1 tablet bid | Common: bone marrow suppression (e.g., macrocytic anemia, leukopenia), headache, nausea, vomiting, anorexia  Less common: liver toxicity, lactic acidosis with hepatic steatosis, myopathy, fat redistribution | No food restrictions  Drug interactions: should not be given with d4T or doxorubicin  Rifampin may increase metabolism  Cimetidine, fluconazole, valproic acid may decrease metabolism  Ganciclovir, IFN-α, ribavirin increase ZDV toxicity |
| NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS | | Class adverse effects: Rash is mild to severe, usually within 1st 6 wk. Discontinue the drug if severe rash (with blistering, desquamation, muscle involvement, or fever) | |
| Efavirenz Sustiva, EFV  Capsule: 50, 200 mg  Tablet: 600 mg  Atripla combination of EFV, FTC, TDF (600, 200, 300 mg) | Children <3 yr: consult with expert  Children ≥3 yr:  10 to <15 kg: 200 mg qd  15 to <20 kg: 250 mg qd  20 to <25 kg: 300 mg qd  25 to <32.5 kg: 350 mg qd  32.5 to <40 kg: 400 mg qd  ≥40 kg: 600 mg qd or  370 mg/m2 body surface area  Atripla (see FTC) | Common: skin rashes, CNS abnormalities (e.g., abnormal dreams, impaired concentration, insomnia, depression, hallucination)  Less common: increased liver enzymes; potentially teratogenic | Capsules can be opened for mixing in food. Can be given without regard to food except fatty foods (because absorption is increased 50%)  Drug interactions: Efavirenz induces/inhibits CYP3A4 enzymes. Increase clearance of drugs metabolized by this pathway (e.g., antihistamines, sedatives and hypnotics, cisapride, ergot derivatives, warfarin, ethinyl estradiol) and several other ARVs (i.e., protease inhibitors). Drugs that induce CYP3A4 (e.g., phenobarbital, rifampin, rifabutin) decrease efavirenz levels.  Clarithromycin levels decrease with EFV and azithromycin should be considered |
| Etravirine (ETR), Intelence, ETR, tablet: 25, 100, 200 mg | Children <6 yr: consult with expert  16 to <20 kg: 100 mg bid  20 to <25 kg: 125 mg bid  25 to <30 kg: 150 mg bid  >30 kg, adolescent and adult: 200 mg bid | Common: nausea, rash, diarrhea  Less common: hypersensitivity reactions | Given only with food. Tablets can be dispensed in water  Inducer of CYP3A4 enzymes and inhibitor of CYP2C9 and CYP2C19, causing multiple interactions that should be checked before initiating ETR. Should not be given in combination with TPV, Fos-APV, ATZ, or other nonnucleoside reverse transcriptase inhibitors |

**Chapter 276** ◆ Acquired Immunodeficiency Syndrome (Human Immunodeficiency Virus) **1657**

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| **Table 276-4** Summary of Antiretroviral Therapies Available in 2014—cont’d | | | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **DOSING** | **SIDE EFFECTS** | **COMMENTS** |
| Nevirapine Viramune, NVP Tablet: 200 mg  Extended-release (XR) tablet: 100, 400 mg  Suspension: 10 mg/mL | Prophylaxis: For infant of woman with no antepartum ARV treatment:  2 mg/kg birth to 48 hr  2 mg/kg 48 hr after 1st dose 2 mg/kg 96 hr after 2nd dose  Treatment:  <8 yr: 200 mg/m2 once daily for 14 days; then same dose bid (maximum 200 mg per dose)  or XR 400 mg qd  >8 yr: 120-150 mg/m2 once daily for 14 days; then bid (maximum 200 mg per dose)  Adolescent and adult: 200 mg once daily for 14 days; then 200 mg bid  *or*  XR 400 mg qd | Common: skin rash, headache, fever, nausea, abnormal liver function tests  Less common: hepatotoxicity (rarely life-threatening), hypersensitivity reactions | No food restrictions  Drug interactions: induces hepatic CYP450A enzymes (including CYP3A and CYP2B6) activity and decreases protease inhibitor concentrations (e.g., IND, SQV, LPV). Should not be given with ATV. Reduces ketoconazole concentrations (fluconazole should be used as an alternative). Rifampin decreases nevirapine serum levels.  Anticonvulsants and psychotropic drugs using same metabolic pathways as NVP should be monitored. Oral contraceptives may also be affected |
| Rilpivirine Edurant, RPV Tablet: 25 mg  Complera combination of RPV, FTC, TDF (25, 200, 300 mg) | Pediatrics: consult with expert Adolescent (>18 yr) and adult:  25 mg | Headache, insomnia, rash, depression, mood changes | Given with food only  Should not be used if viral load  >100,000 copies/mm3 or drugs that induce CYP3A or with proton pump inhibitors |
| PROTEASE INHIBITORS |  | Class adverse effects: hyperglycemia, hyperlipidemia (except atazanavir), lipodystrophy, increased transaminases, increased bleeding disorders in hemophiliacs. Can  induce metabolism of ethinyl estradiol; use alternate contraception (other than estrogen-containing oral contraceptives). All undergo hepatic metabolism, mostly by CYP3A4, with many drug interactions | |
| Atazanavir Reyataz, ATV  Capsules: 100, 150, 200, 300 mg | <6 yr: consult with expert 6-18 yr:  15 to <20 kg: 150 mg +  100 RTV qd  20 to 40 kg: 200 mg +  100 RTV qd  >40 kg, adolescent and adult: 300 mg + 100 RTV qd  *or*  400 mg if unboosted with food  If given with EFV (600 mg) or TDF (300 mg): 400 mg + 100  RTV qd | Common: elevation of indirect bilirubin; headache, arthralgia, depression, insomnia, nausea, vomiting, diarrhea, paresthesias  Less common: prolongation of PR interval on electrocardiogram (ECG); rash, rarely Stevens-Johnson  syndrome, diabetes mellitus, nephrolithiasis | Administer with food to increase absorption. Review drug interactions before initiating because ATV inhibits CYP3A4, CYP1A2,CYP2C9, and UGT1A1  enzymes. Use with caution with cardiac conduction disease or liver impairment. Combination with EFV should not be used in treatment-experienced patients because it decreases ATV levels. TDF, antacids, H2-receptor antagonists, and proton-pump inhibitors decreases ATV concentrations. Patients taking buffered ddI should take it at least 2 hr before ATV |
| Darunavir Prezista, DRV  Tablets: 75, 150, 400, 600, 800 mg  Suspension: 100 mg/mL | <3 yr: consult with expert 3 to <18 yr:  10 to <15 kg: 20 mg/kg DRV +  3 mg/kg RTV  15 to <30 kg: 375 mg DRV +  50 mg RTV bid  30 to <40 kg: 450 DRV mg +  100 mg RTV bid  >40 kg, adolescent and adult: 600 mg DRV + 100 mg RTV  bid  *or* Adolescent (>12 yr and 40 kg) and adult: 800 mg  DRV + 100 mg RTV qd with food  If any DRV resistance is found: 600 mg DRV = 100 mg RTV  bid | Common: diarrhea, nausea, vomiting, abdominal pain, fatigue, headache  Less common: skin rashes (including Stevens-Johnson syndrome), lipid and liver enzyme elevations, hyperglycemia, fat maldistribution | DRV should not be given without food. Contraindicated for concurrent therapy with cisapride, ergot alkaloids, benzodiazepines, pimozide, or any major CYP3A4 substrates. Use with caution in patients taking strong CYP3A4 inhibitors, or moderate/strong CYP3A4 inducers. Adjust dose with concurrent rifamycin therapy.  Contains sulfa moiety: potential for cross-sensitivity with sulfonamide class |

*Continued*

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| **Table 276-4** Summary of Antiretroviral Therapies Available in 2014—cont’d | | | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **DOSING** | **SIDE EFFECTS** | **COMMENTS** |
| Fosamprenavir Lexiva, FPV Tablets: 700 mg  Suspension: 50 mg/mL | 6 mo to 18 yr:  <11 kg: 45 mg/kg FPV + 7 mg/ kg RTV bid  11 to <15 kg: 30 mg/kg +  3 mg/kg RTV bid  15 to <20 kg: 23 mg/kg +  3 mg/kg RTV bid  >20 kg: 18 mg/kg (max  700 mg) + 3 mg/kg (max: 100 mg) RTV bid  Adolescent >18 yr and adult: FPV 700 mg + RTV  100 mg bid  *or*  FPV 1,400 mg + RTV  200 mg qd  For protease inhibitor  (PI)-experienced, the once daily dose is not recommended | Common: nausea, vomiting, perioral paresthesias, headache, rash, lipid abnormalities  Less common: Stevens- Johnson syndrome, fat redistribution, neutropenia, elevated creatine kinase, hyperglycemia, diabetes mellitus, elevated liver enzymes, angioedema, nephrolithiasis | Should be given with food. FPV is an inhibitor of the CYP450 system and an inducer, inhibitor, and substrate of CYP3A4, which can cause multiple drug interactions. Use with caution in sulfa-allergic individuals |
| Indinavir Crixivan, IDV  Capsule: 100, 200, 400 mg | Infants: not approved  Children: 500 mg/m2 every 8 hr (max dose: 800 mg per dose) *or*  400 mg/m2 + RTV 100 mg/m2 bid  Adolescent and adult: 800 mg IDV + 100  *or*  200 mg RTV bid | Common: nausea, abdominal pain, hyperbilirubinemia, headache, dizziness, lipid abnormalities, nephrolithiasis, metallic taste  Less common: fat redistribution, hyperglycemia, diabetes mellitus, hepatitis, acute hemolytic anemia | Administer on empty stomach if given without RTV. Reduce dose (600 mg IDV every 8 hr) with mild to moderate liver dysfunction. Adequate hydration (at least 48 oz fluid/day in adults) necessary to minimize risk of nephrolithiasis. IDV is cytochrome P450 3A4 inhibitor and substrate, which can cause multiple drug interactions: rifampin reduces levels; ketoconazole, ritonavir, and other protease inhibitors increase IDV levels. Do not coadminister with EFV, astemizole cisapride, terfenadine |
| Lopinavir/Ritonavir Kaletra, LPV/r  Tablets: 100/25 mg, 200/50 mg Solution: 80/20 mg per/mL (contains  42% alcohol) | 14 days to 18 yr: 300 mg/m2 LPV  +75 mg/m2 RTV bid Adolescent (>18 yr) and adult:  400 mg LPV +100 mg RTV bid  *or*  800 mg LPV +200 mg RTV qd If taken with NVP, EFV, FPV, or  NFV:  LPV 600 mg + RTV 150 mg bid | Common: diarrhea, headache, nausea and vomiting, lipid elevation  Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation | No food restrictions. High-fat meal and flavoring of solution to increase palpability are recommended if oral solution is used. Interacts with drugs using CYP3A4, which can cause multiple drug interactions |
| Nelfinavir Viracept, NFV  Tablet: 250, 625 mg | <2 yr: not recommended Children 2-13 yr: 45-55 mg/kg  bid  Adolescents and adults: 1,250 mg bid | Common: diarrhea asthenia, abdominal pain, skin rashes, lipid abnormalities  Less common: exacerbation of liver disease, fat redistribution, hyperglycemia, diabetes mellitus, elevation of liver enzymes | Administer with a meal to optimize absorption; avoid acidic food or drink (e.g., orange juice). Tablet can be crushed or dissolved in water to administer as a solution  Drug interactions: Nelfinavir inhibits CYP3A4 activity, which may cause multiple drug interactions. Rifampin, phenobarbital, and carbamazepine reduce levels. Ketoconazole, ritonavir, indinavir, and other protease inhibitors increase levels. Do not coadminister astemizole, cisapride, terfenadine.  RTV boosting has no effect. Because of very high variation in plasma levels, TDM should be used for dose adjustment |

**Chapter 276** ◆ Acquired Immunodeficiency Syndrome (Human Immunodeficiency Virus) **1659**

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| **Table 276-4** Summary of Antiretroviral Therapies Available in 2014—cont’d | | | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **DOSING** | **SIDE EFFECTS** | **COMMENTS** |
| Ritonavir Norvir, RTV  Capsule: 100 mg  Tablet: 100 mg  Solution: 80 mg/mL (contains 43% alcohol) | Only use is to enhance other PIs; dose varies (see information for specific PI) | Common: nausea, headache, vomiting, abdominal pain, diarrhea, taste aversion, lipid abnormalities, perioral paresthesias  Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation, allergic reactions | Administration with food enhances bioavailability and reduces gastrointestinal symptoms. RTV solution should not be refrigerated  RTV is potent inhibitor of CYP3A4 and CYP2D6 and inducer of CYP3A4 and CYP1A2 that leads to many drug interactions  (e.g., protease inhibitors, antiarrhythmics, antidepressants, cisapride). Use cautiously with inhaled steroids |
| Saquinavir Invirase, SQV Hard gel: 200 mg  Film-coated tablets: 500 mg | Infants and children <2 yr: not established  SQV must be boosted with RTV  >2 yr: 5 to <15 kg: 50 mg/kg +  3 mg/kg RTV bid  15-40 kg: 50 mg/kg + 2.5 mg/kg RTV bid  >40: 50 mg/kg + 100 RTV bid Adolescent and adult: SQV  1,000 mg + 100 mg RTV bid | Common: diarrhea, abdominal pain, headache, nausea, skin rashes, lipid abnormalities  Less common: exacerbation of chronic liver disease, diabetes mellitus, pancreatitis, elevated liver transaminases, fat maldistribution, increase in both QT and PR in ECG | Administration with a high-fat meal to enhance bioavailability. Use only in combination with ritonavir boosting dose. SQV  is metabolized by CYP3A4, which may cause many drug interactions): rifampin, phenobarbital, and carbamazepine decrease serum levels. Saquinavir may decrease metabolism of calcium channel antagonists, azoles (e.g., ketoconazole), macrolides |
| Tipranavir Aptivus, TPV Capsule: 250 mg  Solution 100 mg/mL (contains 116 IU vitamin E/mL) | <2 yr: not established.  2-18 yr: 375 mg/m2 TPV + 150 mg/m2 RTV (maximum 500 mg TPV + 200 mg RTV)  bid  *or*  14 mg TPV + 6 mg RTV per kg (maximum-same) bid  Adolescent (>18 yr) and adult: 500 mg TPV +200 mg RTV bid | Common: diarrhea, nausea, vomiting, fatigue, headache, skin rashes, elevated liver enzymes, lipid abnormalities  Less common: fat redistribution, hepatitis, hyperglycemia, diabetes mellitus, intracranial hemorrhage | No food restrictions. Better tolerated with meal. TPV must be boosted with RTV. Can inhibit human platelet aggregation: use with caution in patients at risk for increased bleeding (trauma, surgery, etc.) or in patients receiving concurrent medications that may increase the risk of bleeding.  TPV is metabolized by CYP3A4, which may cause many drug interactions. Contraindicated  in patients with hepatic insufficiency or receiving concurrent therapy with amiodarone, cisapride, ergot alkaloids, benzodiazepines, pimozide. TPV contains sulfonamide moiety and caution should be taken in patients with sulfonamide allergy |
| FUSION INHIBITORS  Enfuvirtide Fuzeon, ENF  Injection: lyophilized powder of 108 mg reconstituted in 1.1 mL of sterile water delivers 90 mg/mL | <6 yr: not established Children >6 yr to 16 yr: 2 mg/  kg SQ (maximum 90 mg) bid Adolescent and adult: 90 mg  SQ bid | Common: Local injection site reactions in 98% (e.g., erythema, induration nodules, cysts, ecchymoses)  Less common: increased incidence of bacterial pneumonia, hypersensitivity, fever, nausea, vomiting, chills, elevated liver enzymes, hypotension, immune-mediated reactions (e.g., glomerulonephritis, Guillain-Barré syndrome, respiratory distress) | Must be given subcutaneously. Severity of reactions increased if given intramuscularly. Apply ice after injection and massage the area to reduce local reactions. Injection sites should be rotated |

*Continued*

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| **Table 276-4** Summary of Antiretroviral Therapies Available in 2014—cont’d | | | |
| **DRUG (TRADE NAMES, FORMULATIONS)** | **DOSING** | **SIDE EFFECTS** | **COMMENTS** |
| ENTRY INHIBITORS  Maraviroc Selzentry, MVC  Tablets: 150, 300 mg | Not approved for children or adolescents <16 yr  Adolescents >16 yr and adults: 150 mg bid if given with potent CYP3A inhibitor (e.g., protease inhibitor except TPV)  300 mg bid if given with not potent CYP3A4 inhibitors (e.g., NRTI, TPV, NVP, ENF, RAL)  600 mg bid if given with potent CYP3A4 inducer (e.g., EFV, ETR, rifampin, phenobarbital) | Common: fever, upper respiratory infection– like symptoms, rash, abdominal pain, musculoskeletal symptoms, dizziness  Less common: cardiovascular abnormalities, cholestatic jaundice, rhabdomyolysis, myositis, osteonecrosis | No food restrictions. MVC is a CYP3A4 and P-glycoprotein (Pgp) substrate, which may cause many drug interactions  Tropism assay to exclude the presence of CXCR4 HIV is required before using MVC. Caution should be used when given to patients with hepatic impairment or cardiac disease or receiving CYP3A4 or Pgp modulating drugs |
| INTEGRASE INHIBITORS  Dalutegravir Tivicay, DTG Tablet: 50 mg  Elvitegravir EVG  Only as Stribild combination of EVG, FTC, TDF, cobicistat (COBI) (150, 200, 300, 150 mg)  Raltegravir Isentress, RAL  Film-coated tablet: 400 mg Chewable tablet: 25, 100 mg  Solution: 20 mg/ml | Children <12 yr: consult with expert  >12 yr and 40 kg, adolescents, and adults: 50 mg qd  If taken with EFV, FPV, TPV, or rifampin: 50 mg bid  Children and adolescents (<18 yr): not established  Adolescent (>18 yr) and adult: 1 tablet qd  Oral solution:  3 to <4 kg: 20 mg bid  4 to <6 kg: 30 mg bid  6 to <8 kg: 40 mg bid  8 to <11 kg: 60 mg bid  11 to <14 kg: 80 mg bid  14 to <20 kg: 100 mg bid Chewable tablet:  10 to <14 kg: 75 mg bid  14 to <20 kg: 100 mg bid  20 to <28 kg: 150 mg bid  28 to <40 kg: 200 mg bid Adolescent (>12 yr ) and adult:  400 mg bid | Insomnia Headache  Common: nausea, diarrhea  Less common: increased serum creatinine, urea, and phosphate, decreased bone density; lactic acidosis, hepatomegaly with stenosis  Common: nausea, headache, dizziness, diarrhea, fatigue  Less common: abdominal pain, vomiting, itching, creatine phosphokinase elevation, myopathy, rhabdomyolysis, depression, hypersensitivity | No food restrictions  UGT1A1 and CYP450 (CYP) 3A  substrate  Should be taken 2 hr before or 6 hr after taking laxatives, sucralfate, iron or calcium supplements, or buffered medications  Administer with food  EVG is metabolized by CYP3A4 and modestly induces CYP2D6 that can cause multiple drug interactions. Cautiously use with nephrotoxic drugs. Stribild should not be used with ritonavir  No food restrictions  Film-coated tablet and chewable tablet are not interchangeable  RAL is metabolized by UGT1A1 glucuronidation, and inducers of this system (e.g., rifampin, TPV) will reduce RGV levels, whereas inhibitors (e.g., ATV) will increase it |

Antiretroviral drugs often have significant drug–drug interactions, with each other and with other classes of medicines, which should be reviewed before initiating any new medication.

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| Vaccine | Birth | 1 mo | 2 mo | 4 mo | 6 mo | 12 mo | 15 mo | 18 mo | 24 mo | 4-6 yr | 11-12 yr | 14-16 yr |
| Hepatitis B | Hep B | Hep B | |  | Hep B | | | |  |  |  |  |
| Measles, Mumps, Rubella\* |  |  |  |  |  | MMR† | MMR† |  |  |  |  |  |
| Influenza |  |  |  |  | Influenza‡ | | | | | | | |
| Pneumococcal Conjugate  and Hemophilus b |  |  | PCV  Hib | PCV  Hib | PCV  Hib | PCV  Hib | |  |  |  | Pneumococcal§ | |
| Diphtheria, Tetanus, Pertussis |  |  | DTap | DTap | DTap |  | DTap | |  |  |  |  |
| Polio (inactivated) |  |  | Polio | Polio | Polio | | | |  |  |  |  |
| Varicella |  |  |  |  |  | Varicella | |  |  |  |  |  |
| Hepatitis A |  |  |  |  |  | Hep A{} | | | |  |  |  |
| Rotavirus\* |  |  | RV¶ | RV | RV |  |  |  |  |  |  |  |

**Figure 276-4** Routine childhood immunization schedule for

HIV-infected children.

See text.

Con\*traindicated in children with AIDS or CD4+ <15%. Give 2 doses 1-3 mo apart.

Rev†accination is recommended every year. Attenuated vaccine can be used >2 yr of age only if CD4+ >15%.

Rev‡accination with pneumococcal polysaccharide vaccine (PPV) every 5 yr. Two§ doses at least 6 mo apart.

Firs{}t dose 6 through 14 wk of age and final dose no later than 8 mo 0 days of age. If using Rotarix, only 2 doses (2 and 4 m¶o) are needed.

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| **Table 276-6** Prophylaxis to Prevent First Episode of Infants and Children, United States\* | | Opportunistic Infections Among HIV-Exposed and HIV-Infected | |
| **PATHOGEN** | **Preventive Regimen** | | |
| **INDICATION** | **FIRST CHOICE** | **ALTERNATIVE** |
| STRONGLY RECOMMENDED AS STANDARD OF CARE  *Pneumocystis* HIV-infected or HIV-indeterminate pneumonia† infants aged 1-12 mo; HIV-infected  children aged 1-5 yr with CD4 count of <500 cells/μL or CD4 percentage of <15%; HIV-infected children aged 6-12 yr with CD4 count of <200 cells/μL or CD4 percentage of <15%  Malaria Living or traveling to area in which malaria is endemic | | TMP-SMX, 150/750 mg/m2 body surface area per day (max: 320/1600 mg) orally qd or bid 3 times weekly on consecutive days *or*  qd or bid orally 3 times weekly on alternate days  Same for HIV-infected and  HIV-uninfected children. Refer to <http://www.cdc.gov/malaria/>  for the most recent recommendations. Mefloquine, 5 mg/kg orally 1 time weekly  (max: 250 mg)  Atovaquone/proguanil (Malarone) qd  11-20 kg: 62.5 mg/25 mg  (1 pediatric tablet)  21-30 kg: 2 pediatric tablets  31-40 kg: 3 pediatric tablets  >40 kg: 1 adult tablet  (250 mg/100 mg) | Dapsone: age ≥1 mo: 2 mg/kg (max: 100 mg) orally qd; *or*  4 mg/kg (max: 200 mg) orally once a week  Atovaquone: age 1-3 mo and  >24 mo: 30 mg/kg orally qd; age 4-24 mo: 45 mg/kg orally qd  Aerosolized pentamidine: age  ≥5 yr: 300 mg once a month by Respirgard II (Marquest, Englewood, CO) nebulizer  Doxycycline age >8 yr: 2.2 mg/kg qd  Doxycycline, 100 mg orally qd for children >8 yr  Chloroquine, 5 mg/kg base (equal 7.5 mg/kg chloroquine phosphate) orally up to 300 mg weekly (only for regions where the parasite is sensitive) |
| *Mycobacterium tuberculosis*  Isoniazid-sensitive TST reaction ≥5 mm  *or*  Prior positive TST result without treatment  *or*  Close contact with any person who has contagious TB. TB disease must be excluded before start of treatment  Isoniazid-resistant Same as previous pathogen;  increased probability of exposure to isoniazid-resistant TB  Multidrug-resistant Same as previous pathogen; (isoniazid and increased probability of exposure rifampin) to multidrug-resistant TB  *Mycobacterium* For children age ≥6 yr with CD4  *avium* complex‡ count of <50 cells/μL; age 2-5 yr  with CD4 count of <75 cells/μL; age 1-2 yr with CD4 count of <500 cells/μL; age <1 yr with CD4 count of <750 cells/μL  Varicella-zoster Exposure to varicella or shingles with virus§ no history of varicella  *or*  Zoster or seronegative status for VZV  *or*  Lack of evidence for age-appropriate vaccination  Vaccine- Standard recommendations for  preventable HIV-exposed and HIV-infected  pathogens children | | Isoniazid, 10-15 mg/kg body weight (max: 300 mg) qd for 9 mo  *or*  20-30 mg/kg body weight (max: 900 mg) orally 2 times weekly for 9 mo  Rifampin, 10-20 mg/kg body weight (max: 600 mg) orally daily for 4-6 mo  Choice of drugs requires consultation with public health authorities and depends on susceptibility of isolate from source patient  Clarithromycin, 7.5 mg/kg (max: 500 mg) orally bid  *or*  Azithromycin, 20 mg/kg (max: 1,200 mg) orally once a week  Varicella-zoster immunoglobulin (VariZIG), 125 IU per 10 kg (max: 625 IU) IM, administered within 96 hr after exposure  Routine vaccinations (see Fig. 276-3) | Rifampin, 10-20 mg/kg body weight (max: 600 mg) orally daily for 4-6 mo  Uncertain  Azithromycin, 5 mg/kg body weight (max: 250 mg) orally qd  *or*  Children age ≥6 yr  *or*  Rifabutin, 300 mg orally qd  If VariZIG is not available and  <96 hr from exposures, acyclovir 20 mg/kg (max: 800 mg) 4 times a day for 5-7 days  *or*  IVIG, 400 mg/kg, administered once |

**Chapter 276** ◆ Acquired Immunodeficiency Syndrome (Human Immunodeficiency Virus) **1665**

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| **Table 276-6** | Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States—cont’d | | | |
| **PATHOGEN** | | **Preventive Regimen** | | |
| **INDICATION** | **FIRST CHOICE** | **ALTERNATIVE** |
| USUALLY RECOMMENDED  *Toxoplasma* Seropositive IgG to *Toxoplasma* and  *gondii* ¶ severe immunosuppression: age  <6 yr with CD4 <15%; age ≥6 yr with CD4 <100 cells/μL  Invasive bacterial Hypogammaglobulinemia (i.e., IgG infections <400 mg/dL)  Cytomegalovirus CMV antibody positivity and  severe immunosuppression (CD4 <50 cells/μL) | | | TMP-SMZ, 150/750 mg/m2 orally bid  *or*  Same dosage qd 3 times weekly on consecutive days  *or*  bid 3 times weekly on alternate days  IVIG 400 mg/kg body weight every 2-4 wk  Valganciclovir, 900 mg orally qd with food for older children who can receive adult dosing | Dapsone, age ≥1 mo: 2 mg/kg or 15 mg/m2 (max: 25 mg) orally qd  *plus*  Pyrimethamine, 1 mg/kg (max: 25 mg) orally qd  *plus*  Leucovorin, 5 mg orally twice a week  *or*  Atovaquone, age 1-3 mo and  >24 mo, 30 mg/kg orally qd;  children age 4-24 mo, 45 mg/kg orally qd with or without pyrimethamine, 1 mg/kg (or  15 mg/m2) (max: 25 mg) qd  *plus*  Leucovorin, 5 mg orally twice a week (3 days apart) |

\*Information in these guidelines might not represent FDA approval or FDA-approved labeling for products or indications. Specifically, the terms “safe” and “effective” might not be synonymous with the FDA-defined legal standards for product approval.

†Daily trimethoprim-sulfamethoxazole (TMP-SMZ) reduces the frequency of certain bacterial infections. Compared with weekly dapsone, daily dapsone is associated with lower incidence of PCP but higher hematologic toxicity and mortality. Patients receiving therapy for toxoplasmosis with sulfadiazine-pyrimethamine are protected against PCP and do not need TMP-SMZ. TMP-SMZ, dapsone-pyrimethamine, and possibly atovaquone (with or without pyrimethamine) protect against toxoplasmosis; however, data have not been prospectively collected.

‡Substantial drug interactions can occur between rifamycins (i.e., rifampin and rifabutin) and protease inhibitors and nonnucleoside reverse transcriptase inhibitors. A specialist should be consulted.

§Children routinely being administered intravenous immunoglobulin (IVIG) should receive VariZIG if the last dose of IVIG was administered more than 21 days before exposure.

As of 2007, VariZIG can be obtained only under a treatment Investigational New Drug protocol (1-800-843-7477, FFF Enterprises, Temecula, CA).

¶Protection against toxoplasmosis is provided by the preferred anti-*Pneumocystis* regimens and possibly by atovaquone.

CMV, cytomegalovirus; FDA, U.S. Food and Drug Administration; HIV, human immunodeficiency virus IgG, immunoglobulin G; IM, intramuscularly; IVIG, intravenous immunoglobulin; PCP, *Pneumocystis* pneumonia; TMP-SMZ, trimethoprim-sulfamethoxazole; TB, tuberculosis; TST, tuberculin skin test;; VZV, varicella-zoster virus.

*From Centers for Disease Control and Prevention (CDC): Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children,* MMWR Recomm Rep *58(RR-11):127–128, 2009, Table 1.*

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| **Table 276-5** | Recommendations for PCP Prophylaxis and CD4 Monitoring for HIV-Exposed Infants and HIV-Infected Children, by Age and HIV Infection Status | | |
| **AGE/HIV INFECTION STATUS** | | **PCP PROPHYLAXIS** | **CD4 MONITORING** |
| Birth to 4-6 wk, HIV exposed | | No prophylaxis | None |
| HIV infection reasonably excluded\* | | No prophylaxis | None |
| <1 yr, HIV-infected or indeterminate | | Prophylaxis regardless of CD4 count or percentage | According to local practice for initiation or follow-up of cART |
| 1-5 yr, HIV infected | | Prophylaxis if: CD4 <500 cells/μL or <15%† | According to local practice for initiation or follow-up of cART |
| >6 yr, HIV infected | | Prophylaxis if: CD4 <200 cells/μL or  <15%†‡ | According to local practice for initiation or follow-up of cART |

The National Perinatal HIV Hotline (1-888-448-8765) provides consultation on all aspects of perinatal HIV care.

\*See text.

†More frequent monitoring (e.g., monthly) is recommended for children whose CD4 counts or percentages are approaching the threshold at which prophylaxis is recommended.

‡Prophylaxis should be considered on a case-by-case basis for children who might otherwise be at risk for PCP, such as children with rapidly declining CD4 counts or percentages or children with category C conditions. Children who have had PCP should receive PCP prophylaxis until their CD4 count is >20% (for >6 yr of age) or

>25% (for 2-5 yr of age) on continuous cART.

cART, combined antiretroviral therapy; PCP, *Pneumocystis carinii* (also called *P. jirovecii* ) pneumonia.