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Chapter 13

Genetics: Metabolism and Dysmorphology

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See additional content on Expert Consult

I. METABOLISM[1-7]

A. Clinical Presentation of Metabolic Disease (Box 13.1)

1. Metabolic disease can be conceptualized into broad categories (Table 13.1).
2. When considering a particular diagnosis, a complete patient history, including details of conception, pregnancy, prenatal screening and diagnostic studies, delivery, postnatal growth, development, and a three-generation family history in the form of a pedigree (Fig. EC 13.A) should accompany a comprehensive physical examination. The family history may be remarkable for close relatives who died of similar presentations (may be mistaken for "sepsis" or "SIDS").
3. A high index of suspicion is required, as routine investigations may be unrevealing.
4. Routine newborn screening (see Section II) is meant to detect many metabolic disorders before onset of clinical symptoms, but the conditions tested for vary by state and not all countries test, so clinical suspicion should remain high if clinical picture is concerning.

B. Evaluation

1. **Initial laboratory tests:** Comprehensive metabolic panel, blood glucose, venous blood gas (VBG), ammonia (beware false-positives from tourniquets, struggling children, or sample delay), lactate, creatine kinase (CK), complete blood cell count with differential, urine ketones.
2. **Subsequent evaluation for metabolic disease:**
   a. Consult a geneticist.
   b. A basic metabolic work-up includes plasma amino acids (PAA), urine organic acids (UOA), acylcarnitine profile, quantitative (free and total) plasma carnitine, lactate/pyruvate ratio. Further specialized biochemical testing is available.
3. **Additional labs given specific circumstances:**
   a. **Metabolic acidosis**: Ammonia, lactate, b-hydroxybutyrate, acetoacetate, UOA, urinalysis with urine pH, acylcarnitine profile, quantitative (free and total) plasma carnitine (Fig. 13.1).
   b. **Hyperammonemia**: VBG, UOA, PAA, acylcarnitine profile, urine orotic acid (Fig. 13.2).

BOX 13.1

WHEN TO SUSPECT METABOLIC DISEASE[1-3]

Overwhelming illness in the neonatal period
Vomiting
Acute acidosis, anion gap
Massive ketosis
Hypoglycemia
Coagulopathy
Coma
Seizures, especially myoclonic
Hypotonia
Unusual odor of urine
Extensive dermatosis
Neutropenia, thrombocytopenia, or pancytopenia
Family history of siblings dying early

TABLE 13.1

BROAD CLASSIFICATION OF METABOLIC DISEASE[1-6]

Intoxication disorders Toxic accumulation of small molecules upstream of a defective enzyme. Tend to present early in life with nonspecific symptoms that may include recurrent vomiting, irritability, lethargy progressing to coma, organ dysfunction. Symptoms may wax and wane with intercurrent illness.	Table 13.2 Acidosis algorithm Fig. 13.1 Hyperammonemia algorithm Fig. 13.2
Disorders of reduced fasting tolerance Disorders in the body's ability to tolerate fasting, with early onset of hypoglycemia. Can present in infancy or later when trying to sleep through the night, including morning symptoms or seizures. Look for laboratory abnormalities and symptoms not usually found in typical fasting.	Table 13.3 Hypoglycemia algorithm Fig. 13.4
Disorders of complex molecules These disorders have a broad phenotypic spectrum and typical biochemical screening can be unrevealing. Features can be present at birth and/or slowly progressive affecting multiple organ systems. Often enzymatic and/or broad molecular genetic testing is needed.	Table 13.4
Mitochondrial disorders Defect in energy production through the electron transport chain. There is a broad spectrum of clinical manifestations, often involving high-energy organs including brain, muscle, and/or heart.	Table 13.5
Neurotransmitter disorders Defect in neurotransmission which can present around birth with severe infantile epileptic encephalopathy, or later with parkinsonism-dystonia, neruodevelopmental or psychiatric disorders.	Table 13.6

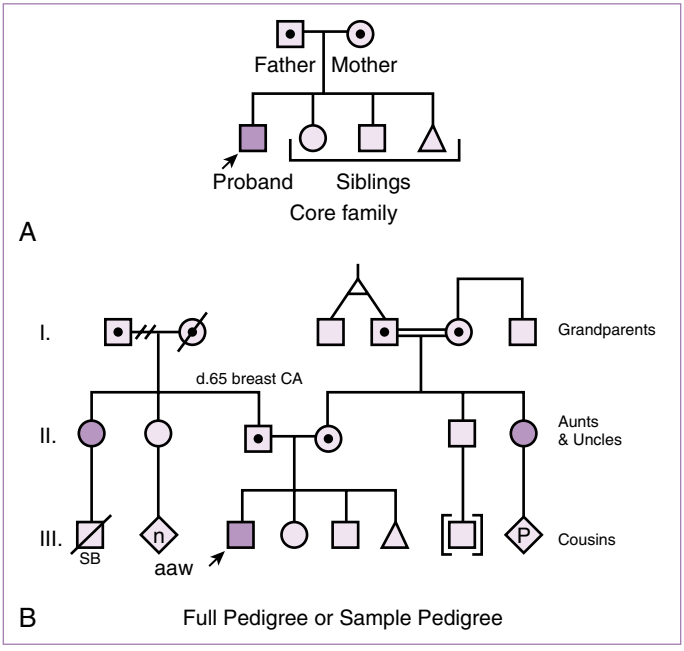

FIG. EC 13.A
Pedigree construction.

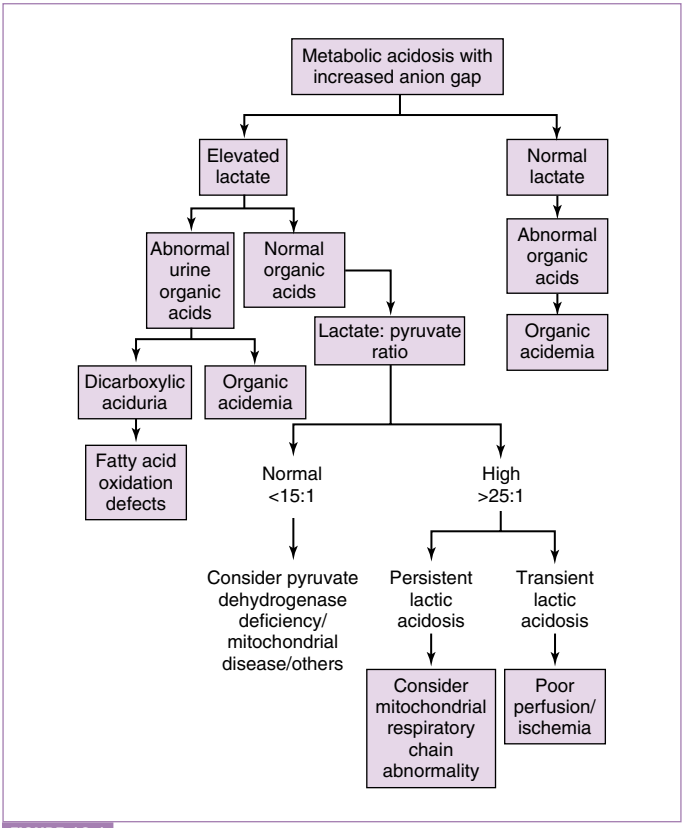

FIGURE 13.1

Evaluation of metabolic acidosis with increased anion gap. (From Burton B. Inborn errors of metabolism in infancy: a guide to diagnosis. *Pediatrics*. 1998;102:E69.)

c. **Hypoglycemia**: Samples at time of hypoglycemia—glucose, insulin, growth hormone, free fatty acids, b-hydroxybutyrate (see Chapter 10). Cortisol, fasting and postprandial lactate, urine ketones, creatine kinase, acylcarnitine profile, PAA, UOA (Fig. 13.3).

d. **Neonatal seizures:** Cerebrospinal fluid (CSF) amino acids and PAA, CSF/serum glucose ratio, serum and CSF neurotransmitters, CSF and plasma lactate, plasma very-long-chain fatty acids, UOA, serum uric acid, urine sulfites. Consider trial of pyridoxine.

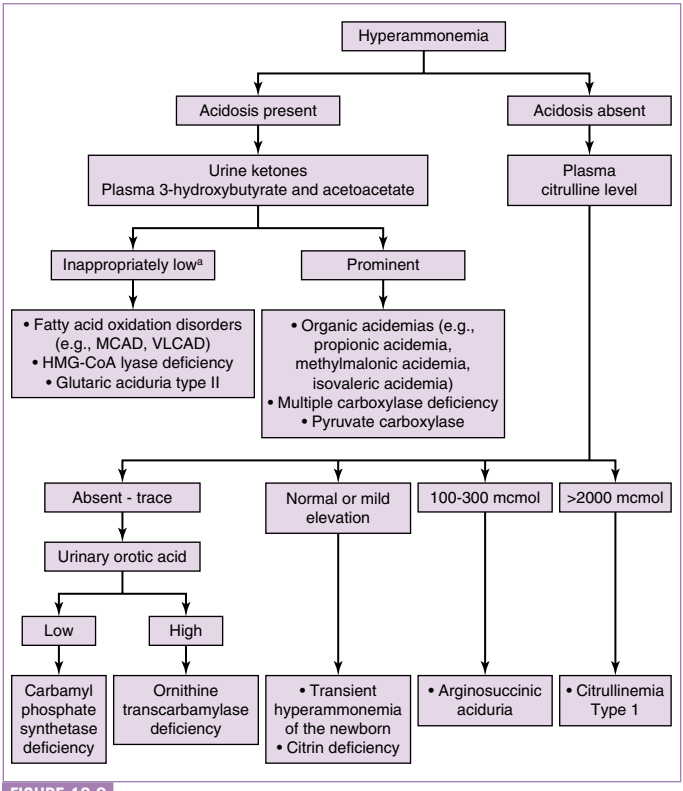

FIGURE 13.2

Evaluation of hyperammonemia.

Indicates inappropriately low urinary ketones in the setting of symptomatic hypoglycemia. *HMG-CoA*, Hydroxymethylglutaryl-CoA; *MCAD*, medium-chain acyl-CoA dehydrogenase; *VLCAD*, very-long-chain acyl-CoA dehydrogenase.

C. Categories of Metabolic Disorders

1. **Intoxication disorders** (Table 13.2)
2. **Disorders of reduced fasting tolerance** (Table 13.3)
3. **Disorders of complex molecules** (Table 13.4)
4. **Mitochondrial disorders** (Table 13.5)
5. **Neurotransmitter disorders** (Table 13.6)

D. Management of Metabolic Crisis

1. Specific acute management available in Tables 13.2–13.6.

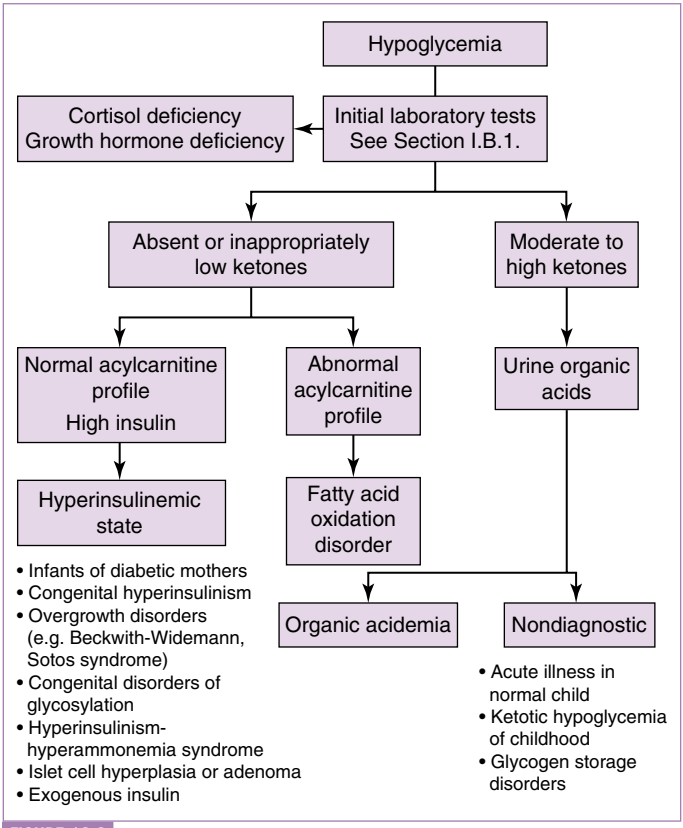

FIGURE 13.3

Evaluation of hypoglycemia. (Modified from Burton BK. Inborn errors of metabolism in infancy: a guide to diagnosis. *Pediatrics*. 1998;102:E69; and Cox GF. Diagnostic approaches to pediatric cardiomyopathy of metabolic genetic etiologies and their relation to therapy. *Prog Pediatr Cardiol*. 2007;24:15–25)

2. A general guiding principal is to provide hydration and enough glucose to meet the patient's caloric needs to stop catabolism.
   a. Use **D10% + electrolytes for age at 1.5 to 2 times maintenance rate.**
   b. Use caution in mitochondrial disorders (and do not use D10 in pyruvate dehydrogenase deficiency), because this may enhance lactic acidosis. If uncertain, measure lactate and acid-base status regularly.
3. For unknown/suspected metabolic disease, treatment should *not* be delayed during work-up.

TABLE 13.2

INTOXICATION DISORDERS[1-6]

Disorders With Selected Examples	Etiology, Clinical Presentation	Acute Management[a]	Chronic Management[a]	Diagnostic Testing[a]
Urea Cycle Disorders OTC Deficiency CPS I Deficiency Citrullinemia	Unable to metabolize proteins to energy Acute intoxication episodes of hyperammonemia, ± respiratory alkalosis	**Reversal of Catabolism** Bolus if dehydration D10 + ¼ NS to NS at 1.5–2× maintenance **Stop Intake of Offending Agents** Stop protein intake (NPO). Resume within 24–48 hrs to prevent deficiencies of essential nutrients **Toxin Removal** Removal of ammonia via sodium benzoate + sodium phenylacetate (Ammonul) with arginine IV or dialysis as indicated for ammonia >250 μmol/L	Protein-restricted diet Ammonia scavengers (e.g., sodium phenylbutyrate) Arginine supplementation (dependent on defect)	PAA Urine orotic acid Molecular testing OTC deficiency (most common, X-linked) and CPS I deficiency are not picked up on newborn **screening**
Organic Acidemias Propionic Acidemia Methylmalonic Acidemia Isovaleric Acidemia	Unable to metabolize certain amino acids and fats Acute intoxication episodes of hyperammonemia with metabolic acidosis Bone marrow suppression, cardiomyopathy	**Reversal of Catabolism,** as above **Stop Intake of Offending Agents,** as above **Toxin Removal** Carnitine in propionic, methylmalonic, and isovaleric acidemia. Glycine in isovaleric acidemia Bicarbonate if pH <7.1	Formula that restricts certain amino acids Carnitine	Acylcarnitine profile Quantitative (free and total) carnitine PAA UOA Molecular testing
Maple Syrup Urine Disease	Unable to metabolize branched-chain amino acids (BCAAs) Acute intoxication with high leucine leads to intracranial edema and coma Inappropriate urinary ketones	**Reversal of Catabolism,** as above **Stop Intake of Offending Agents** Stop protein from food and continue BCAA-free formula, valine, and isoleucine **Toxin Removal** Dialysis in extreme situations	Diet and formula that restricts BCAAs Supplementation with isoleucine and valine	PAA UOA Molecular testing

TABLE 13.2

INTOXICATION DISORDERS[1-6]—cont'd

Disorders With Selected Examples	Etiology, Clinical Presentation	Acute Management[a]	Chronic Management[a]	Diagnostic Testing[a]
Aminoacidopathies Phenylketonuria (PKU) Tyrosinemia (HT)	Unable to metabolize phenylalanine (PKU) or phenylalanine and tyrosine (HT) PKU: intellectual disability if untreated HT: liver failure, vomiting, pain crisis, hyponatremia, Fanconi syndrome	Supportive. Dextrose-based fluids are safe for use HT: Pain control and hydration during pain crisis	PKU: Phenylalanine-restricted diet; sapropterin effective in some HT: Tyrosine- and phenylalanine-restricted diet; Nitisinone	PAA HT: UOA for succinylacetone Molecular testing
Carbohydrate Disorders Galactosemia Hereditary Fructose Intolerance (HFI)	Unable to metabolize galactose (galactosemia) or fructose (HFI) Vomiting, diarrhea, liver failure, renal failure Galactosemia: risk of *Escherichia coli* sepsis	Supportive. Dextrose-based fluids are safe for use	Galactosemia: Avoidance of galactose (and lactose); Soy-based formulas HFI: Avoidance of fructose (and sucrose)	Urine reducing substances Galactosemia: erythrocyte gal-1-phosphate, galactose-1-phosphate uridyltransferase activity Molecular testing
Metal Disorders Menkes Wilson Disease Hemochromatosis	Defects in the uptake or excretion of metals Liver disease + neurologic involvement (Menkes, Wilson) + cardiomyopathy (Hemochromatosis)	Chelation therapy	Wilson: Copper avoidance, copper chelation Menkes: Copper supplementation Hemochromatosis: Phlebotomy, iron chelation	Serum copper Ceruloplasmin Iron Ferritin Transferrin Molecular Testing

[a]Management and testing should be in partnership with a genetics physician, as comprehensive details are beyond the scope of this resource.

CPS, Carbamoyl phosphate synthetase; *D10*, dextrose 10%; *IV*, intravenous; *NPO*, nil per os; *NS*, normal saline; *OTC*, ornithine transcarbamylase; *PAA*, plasma amino acids; *UOA*, urine organic acids.

TABLE 13.3

DISORDERS OF REDUCED FASTING TOLERANCE[1-6]

Disorders With Selected Examples	Etiology, Clinical Presentation	Acute Management[a]	Chronic Management[a]	Diagnostic Testing[a]
Fatty Acid Oxidation (FAO) Disorders VLCAD deficiency LCHAD deficiency MCAD deficiency	Disorders of fat metabolism Hypoketotic hypoglycemia in fasting. Can also present with rhabdomyolysis, cardiomyopathy, liver disease.	**Reversal of Fasting State** Bolus glucose if hypoglycemia D10 + ½ NS to NS at 1–1.5× maintenance **Stop Intake of Offending Agents** No IV lipids or long chain fats	Avoid prolonged fasting. Use of uncooked cornstarch for sustained anabolism. Nighttime feedings may be needed. For very-long-chain fatty acid disorders, limit intake of low-fat foods and supplement with medium-chain triglyceride oil.	Acylcarnitine profile Quantitative (free and total) carnitine UOA Urine acylglycines
Glycogen Storage Disorders GSD1a, 1b GSD II GSD III GSD IV GSD V GSD VI GSD IX	Multisystem disorders resulting from defects in the synthesis and catabolism of glycogen *Hepatic glycogenoses* (GSD Ia [von Gierke], GSD VI, GSD IX): Hepatomegaly, fasting ketotic hypoglycemia. ± hyperlipidemia, uremia, lactic acidosis *Muscle glycogenoses* (GSD V [McArdle], GSD II [Pompe]): Skeletal and cardiac muscle involvement resulting in fatigue, elevations in creatine kinase *Mixed* (GSD III [Cori], GSD IV): Fasting ketotic hypoglycemia with myopathy	**Reversal of Fasting State,** as above	Prevent long periods of fasting with use of cornstarch GSD II (Pompe): Enzyme replacement	Glucose Lactate Uric acid Lipid panel Transaminases CK Electrocardiogram Echocardiogram Enzyme activity Molecular testing

[a]Management and testing should be in partnership with a genetics physician, as comprehensive details are beyond the scope of this resource.

CK, Creatine kinase; *D10*, dextrose 10%; *GSD*, glycogen storage disease; *IV*, intravenous; *LCHAD*, long-chain L-3 hydroxyacyl-CoA dehydrogenase; *MCAD*, medium-chain acyl-CoA dehydrogenase; *NS*, normal saline; *UOA*, urine organic acids; *VLCAD*, very-long-chain acyl-CoA dehydrogenase.

TABLE 13.4

DISORDERS OF COMPLEX MOLECULES[1-6]

Disorders With Selected Examples	Etiology, Clinical Presentation	Management[a]	Diagnostic Testing[a]
Mucopolysaccharidoses MPS I (Hurler) MPS II (Hunter) MPS III (SanFillipo) MPS IV (Morquio) MPS VI (Maroteaux-Lamy)	Chronic, progressive, multisystem disorders from glycosaminoglycan accumulation Coarse facial features and organomegaly: MPS I Hurler, MPS II Hunter, MPS III SanFillipo Developmental Delay: MPS III SanFillipo Skeletal dysplasia: MPS IV Morquio	Acute management is supportive Stem cell transplantation: MPS I Enzyme replacement: MPS I, MPS II, MPS IV, MPS VI.	Skeletal survey for dysostosis multiplex Urine glycosaminoglycans Urine oligosaccharides Enzyme activity Molecular testing
Sphingolipidoses Gaucher Niemann-Pick Type A, B Tay-Sachs Krabbe Fabry	Impaired degradation of sphingolipids Progressive psychomotor retardation and neurologic problems (e.g., epilepsy, ataxia, and spasticity), hepatosplenomegaly Normal intellect: Gaucher (+ bone crises), Niemann-Pick B (+ lung disease), Fabry (+ acroparathesias, renal or cardiac disease)	Acute management is supportive Enzyme replacement: Gaucher, Fabry Stem cell transplant: Krabbe Substrate reduction with miglustat or eliglustat: Gaucher	Urine oligosaccharides Enzyme activity Molecular testing
Sterol Synthesis Disorders Smith-Lemli-Opitz Greenberg dysplasia	Multisystem disorders with dysmorphic features and variable skeletal dysplasia	Acute: Adrenal insufficiency may be present Chronic: Consider cholesterol supplementation and/or simvastatin for some disorders	Plasma sterols Serum cholesterol Molecular testing
Peroxisomal Disorders Zellweger Rhizomelic chondrodysplasia punctata (RCDP) X-Linked Adrenoleukodystrophy	Abnormal peroxisome function or synthesis Neurologic abnormalities such as hypotonia, encephalopathy, seizures, ocular findings Dysmorphic facial features: Zellweger Rhizomelia: RDCP Leukodystrophy: X-linked adrenoleukodystrophy	Acute: Stress dose corticosteroids if adrenal insufficiency Chronic: Stem cell transplant for X-linked adrenoleukodystrophy	Very-long-chain fatty acids including Phytanic and Pristanic Pipecolic acids Erythrocyte plasmalogen Molecular testing

[a]Management and testing should be in partnership with a genetics physician because comprehensive details are beyond the scope of this resource.

MPS, Mucopolysaccharidosis.

TABLE 13.5

MITOCHONDRIAL DISORDERS[1-6]

Disorders With Selected Examples	Clinical Presentation	Management[a]	Diagnostic Testing[a]
Mitochondrial Disorders MELAS MERRF Leigh Kearns-Sayre	Multisystemic disease which can include lactic acidosis, muscle weakness, cardiomyopathy, ataxia, ophthalmoplegia, neuropathy, chronic diarrhea	Acute: For MELAS, IV arginine may abort a neurologic crisis Chronic: Cocktail of antioxidants, vitamins, and cofactors	Serum & CSF lactate and pyruvate Plasma and CSF amino acids UOA Brain imaging Molecular testing Muscle biopsy

[a]Management and testing should be in partnership with a genetics physician, as comprehensive details are beyond the scope of this resource.
CSF, Cerebrospinal fluid; *IV*, intravenous; *MELAS*, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; *MERRF*, myoclonic epilepsy with ragged red fibers; *UOA*, urine organic acids.

TABLE 13.6

NEUROTRANSMITTER DISORDERS[1-6]

Disorders With Selected Examples	Clinical Presentation	Management[a]	Diagnostic Testing[a]
Neurotransmitter Disorders Nonketotic hyperglycinemia (NKH) Sulfite Oxidase Deficiency B6-dependent seizures GABA receptor mutations or metabolism defects	Infantile epileptic encephalopathy	Acute: Consider trial of pyridoxine +/- folinic acid	CSF neurotransmitters CSF glucose Urine sulfite PAA UOA Molecular testing
Dopamine Disorders Dopa-responsive dystonia Tyrosine hydroxylase deficiency	Dystonia, dyskinesia	Dopamine	CSF biogenic amines

[a]Management and testing should be in partnership with a genetics physician, as comprehensive details are beyond the scope of this resource.
CSF, Cerebrospinal fluid; *GABA*, γ-aminobutyric acid; *PAA*, plasma amino acid; *UOA*, urine organic acid.

E. Commonly Used Medications

1. Carnitine 50 mg/kg/dose intravenous (IV) every 6 hours when ill, or 100 mg/kg/day orally (PO) divided every 8 hours when well. For dosing in primary carnitine deficiency, see Formulary.
2. Sodium phenylacetate (10%) + sodium benzoate (10%) (Ammonul) should be combined with arginine HCl in a 25 to 35 mL/kg 10% dextrose solution and administered through a central venous catheter to treat acute hyperammonemia in a urea cycle patient.
   a. For a child less than 20 kg, the dose is 250 mg/kg sodium phenylacetate and 250 mg/kg sodium benzoate.
   b. For a child greater than 20 kg, the dose is 5.5 g/m^2 sodium phenylacetate and 5.5 g/m^2 sodium benzoate.

   c. The dose of arginine HCl is 200 to 600 mg/kg, depending on the diagnosis.
      (1) 200 mg/kg for carbamylphosphate synthase (CPS) deficiency and ornithine transcarbamylase (OTC) deficiency.
      (2) 600 mg/kg for citrullinemia and argininosuccinate lyase (ASL) deficiency.
   d. Administer as a loading dose over 90 to 120 minutes, followed by an equivalent dose as a maintenance infusion over 24 hours.
3. Arginine HCl for MELAS stroke-like episode: bolus of 0.5 g/kg given within 3 hours of symptom onset, followed by an additional 0.5 g/kg administered as a continuous infusion for 24 hours for the next 3 to 5 days.[9] (MELAS: mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes)
4. Sodium benzoate for nonketotic hyperglycinemia (NKH): start with 500 mg/kg/day added to a 24-hour supply of formula or divided at least 4 times daily and consult a biochemical geneticist.[10]

II. NEWBORN METABOLIC SCREENING[7]

A. Timing

1. First screen should be performed within the first 48 to 72 hours of life (at least 24 hours after initiation of feeding).
2. Second screen (requested in some states) should be performed after 7 days of age.
3. Preterm infants: Perform initial screen at birth (to collect sample before transfusions), another at age 48 to 72 hours, a third at age 7 days, and a final at age 28 days or before discharge (whichever comes first).

B. Abnormal Result

1. Requires immediate follow-up and confirmatory testing; consult a geneticist.
2. ACT Sheets and Confirmatory Algorithms are available for more information on how to proceed with specific abnormalities: https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx (search ACT sheets).

C. Results Affected by Transfusion

Note: Repeat newborn metabolic screen 3 months after last transfusion.

1. Biotinidase enzyme activity
2. Galactose-1-phosphate uridyltransferase (GALT) activity
3. Hemoglobinopathy evaluation

III. DYSMORPHOLOGY[7,11-14]

A. History

Pertinent history includes pregnancy course, prenatal exposures, type of conception (natural or assisted), perinatal history, developmental milestones, and review of systems.

B. Family History

1. Three-generation pedigree focused on both medical and developmental histories (see Fig. EC 13.A).
2. Helpful mnemonics include:
   a. SIDE mnemonic[15]: Anything SIMILAR in the family? Anything INHERITED through the family? Any premature, unexplained DEATHS? Any EXTRAORDINARY events?
   b. SCREEN mnemonic[16]: SOME CONCERNS about conditions running in the family? REPRODUCTION—any issues with pregnancy infertility, or birth defects? EARLY disease, death, or disability? ETHNICITY? NONGENETIC—any other risk factors?
   c. Rule of Too/Two[13]:
      (1) Too: tall? short? many? few? early? young? different?
      (2) Two: cancers? generations? in the family? birth defects?
3. **Patterns of inheritance:** See Online Content for discussion of different patterns of inheritance.

C. Physical Examination

1. **Major anomalies:** Structural anomalies that are found in less than 5% of the population and may cause significant cosmetic or functional impairment, often requiring medical or surgical management.
2. **Minor anomalies**[11,12,14,17]: Structural anomalies that are found in greater than 5% of the population with little or no cosmetic or functional significance to the patient.
3. Examples of major and minor anomalies (Table 13.7). Three or more minor anomalies may be a nonspecific indicator of occult or major anomaly.

D. Work-up

1. **Imaging to evaluate for major anomalies**
   a. Head ultrasound (US) or brain magnetic resonance imaging (MRI)
   b. Echocardiogram
   c. Complete abdominal US
   d. Skeletal survey with radiographs composed of: AP views of skull, chest/ribs, upper extremities and hands, lower extremities and feet; lateral views of skull, complete spine, chest, and odontoid view.
2. **Dilated eye exam**
3. **Hearing evaluation**
4. **Genetic testing:** See Fig. 13.4 and Table 13.8. The patient should be referred to genetics for a dysmorphology evaluation and appropriate testing.

TABLE 13.7

EXAMPLES OF DYSMORPHOLOGY EXAM FINDINGS[11-14,17]

	Major Anomalies	Minor Anomalies
General	Growth <3rd percentile	Short or tall stature
Head	Structural brain abnormalities (e.g., holoprosencephaly, schizencephaly), craniosynostosis	Asymmetric head shape, micrognathia, prominent metopic ridge, widows peak
Eyes	Anophthalmia, cataracts, coloboma	Palpebral fissures, epicanthal folds, hypertelorism or hypotelorism, telecanthus, epicanthus, ptosis
Ears, Nose, Throat	Cleft lip/palate, tracheal-esophageal fistula	Periauricular pits/tags, overfolded helix, everted ears, low set ears, microtia, abnormal nasal bridge, branchial cleft cysts
Chest/Lungs	Congenital diaphragmatic hernia, situs inversus	Inverted nipples, accessory nipples, pectus excavatum or carinatum
Heart	Congenital heart defects (e.g., tetralogy of Fallot, coarctation of aorta, atrial or ventricular septal defects)	Patent ductus arteriosus, valvular abnormalities
Abdomen	Omphalocele, gastroschisis, intestinal atresia	Umbilical hernia
Genitourinary	Ambiguous genitalia, horseshoe kidney	Hypogonadism, pelvic kidney, shawl scrotum, labial hypoplasia
Musculoskeletal	Skeletal dysplasia, spina bifida	Clubfeet, bowing, syndactyly of two digits, post axial polydactyly, 5th finger clinodactyly, hypoplastic nails, short metacarpals or metatarsals
Skin	Cutis aplasia	Striae, café au lait spots, atypical skin creases, transverse palmar crease, nevus simplex, congenital dermal melanocytosis

IV. PATTERNS OF DYSMORPHOLOGIC CONDITIONS[11,14]

This section is not comprehensive; it covers some common reasons to seek a genetics consult. These conditions will often be managed by a multidisciplinary team.

A. Cardiac Disorders

1. **Congenital heart disease**: Investigation for co-occurring anomalies with abdominal US. Chromosome microarray testing indicated, including for 22q11 deletion syndrome. Table 13.9.
2. **Cardiomyopathy**: Can be from inborn errors of metabolism, channelopathies, mutations in genes important for sarcomere and desmosome production/function, or other single gene disorders.
3. **Long QT disorders**: Many single gene disorders.

B. Ciliopathies

1. **Nonmotile ciliopathies**: Defects in primary (nonmotile) ciliary function. Cystic renal disease, brain malformations (molar tooth sign), retinal

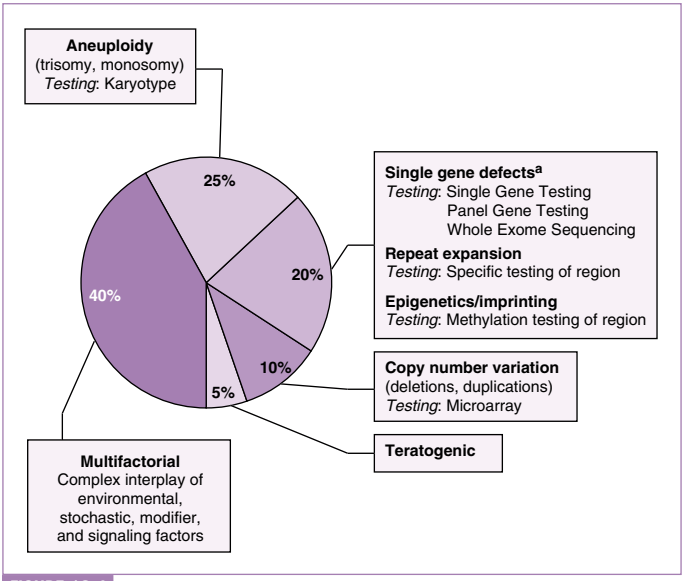

FIGURE 13.4

Etiologies of dysmorphic features.[29]

[a]Whole exome sequencing can only reliably detect single base pair changes and insertions/deletions of less than 20 base pairs.

degeneration, liver congenital hepatic fibrosis, polydactyly, skeletal dysplasia, obesity. **Examples**: Cystic kidneys as a result of heritable polycystic kidney disease; neurodevelopmental ciliopathies such as Joubert syndrome or Bardet-Biedl syndrome.

2. **Primary ciliary dyskinesias**: Defects in motile cilia. Recurrent respiratory infections (chronic sinopulmonary disease), infertility, situs inversus. **Examples**: More than 30 genes known to cause primary ciliary dyskinesia. When situs inversus is present, it is referred to as Kartagener syndrome.
3. **Evaluation**: Evaluation for potentially affected organ systems, including abdominal US, echocardiogram, brain MRI, and complete retinal evaluation with ophthalmology. Skeletal survey if limb defects. CMP to evaluate kidney and liver function. Unless a specific disorder suspected, broad genetic testing is appropriate.

C. Cleft Lip and Palate (CLP)

1. Can be isolated or part of a syndrome.
2. **Risk factors**: Maternal smoking, heavy alcohol use, systemic corticosteroid use, folic acid and cobalamin deficiency.[18]
3. Submucosal clefts may be indicated by a bifid uvula.
4. **Evaluation**: Children can have difficulties with feeding, speech, and hearing (chronic otitis or hearing loss as part of a syndrome). If not an isolated anomaly, may need further work-up with ophthalmology and echocardiogram.

TABLE 13.8

DIAGNOSTIC GENETIC TESTING AND CLINICAL CONSIDERATIONS

Genetic Testing Technology	Description of Technology	Turnaround Time	Able to Detect	Specific Indications
Karyotype	Systematically arranged photomicrograph of chromosomes	1–2 weeks	Aneuploidy, larger deletions/duplications (≥5kb), translocation or balanced rearrangements	Indicated for suspected aneuploidy, recurrent miscarriage, looking for a balanced translocation
Fluorescence in situ hybridization (FISH)	Mapping a segment of DNA by molecular hybridization of a fluorescent probe	<1 week	Presence or absence of a specific site or chromosome	Not indicated, except in family studies and for rapid diagnosis of a suspected trisomy[32]
Microarray (a.k.a. Array CGH, SNP or oligo chromosomal microarray)	Comparative genome hybridization using a high-density SNP profile or oligos (short segments of DNA) across the genome	2–4 weeks	Genomic gains or losses (copy number variation [CNV]), regions of homozygosity (consanguinity). Incidental findings unrelated to phenotype.	First-line cytogenetic test for all patients with unexplained global developmental delay, intellectual disability, autism, and/or congenital anomalies
Single gene testing	Nucleotide-by-nucleotide Sanger sequencing of a single gene	~1 month	Mutations in specific gene of interest	Indicated when there is a strong clinical suspicion of a specific single gene disorder
Targeted mutation analysis	Detection of previously identified familial mutation or common population mutation	<1 month	Whether the patient has (or does not have) only the specific mutation tested	Confirmation of clinical diagnosis, presymptomatic genetic diagnosis, identification of carrier status, preimplantation genetic diagnosis, prenatal testing
Repeat expansion testing	Southern blot or triplet-repeat primed PCR	<1 month	The quantity of repeats in the specific gene tested	Indicated when there is a strong clinical suspicion of a triplet repeat disorder
Methylation analysis	Methylation multiplex ligation-dependent probe amplification	<1 month	Whether the region tested has normal or abnormal methylation	Indicated when there is a strong clinical suspicion of a specific methylation defect (e.g., Prader-Willi)

Genetic Testing Technology	Description of Technology	Turnaround Time	Able to Detect	Specific Indications
Next-generation sequencing (multiple gene panels)	Massively parallel sequencing of specific genes	1–2 months	Simultaneously identifies if there are any variants in multiple genes of interest	Used for syndromes with heterogeneity (mutations in different genes can cause the same phenotype, or the phenotypes are hard to distinguish clinically)
Whole exome sequencing (WES)	Massively parallel sequencing of almost all exons	2–6 months	Simultaneously identifies if there are any variants in the coding portions of genes that match the patient's phenotype. Incidental findings unrelated to phenotype.	More comprehensive genomic test indicated in an otherwise negative workup, or when cost-benefit ratio of more targeted testing is in favor of WES
Whole genome sequencing (WGS)	Massively parallel sequencing of entire genome	Variable	More uniform coverage of exonic, intronic, and splice site mutations. Incidental findings unrelated to phenotype.	Not widely clinically available; used mostly in research studies

CGH, Comparative genomic hybridization; *DNA*, deoxyribonucleic acid; *PCR*, polymerase chain reaction; *Kb*, kilobases; *SNP*, single nucleotide polymorphism.

TABLE 13.9

GENETIC SYNDROMES ASSOCIATED WITH CARDIAC DEFECTS[11]

Genetic Syndrome	Cardiac Defect	Other Features	Diagnostic Evaluation
Noonan Syndrome[a]	Pulmonary valve stenosis, hypertrophic cardiomyopathy	Short stature, broad neck, lymphatic dysplasia, low ears and hypertelorism, coagulation defects	"Rasopathy" gene panel including *PTPN11*
Williams Syndrome (7q11.23 deletion)[a]	Supravalvular aortic stenosis	Periorbital fullness, broad nasal tip, large ears, thick lips, small teeth, hypercalcemia, renal artery stenosis, connective tissue abnormalities, overfriendliness	Microarray
Holt-Oram Syndrome	ASD	Upper limb malformation, cardiac conduction disease	*TBX5* sequencing
Down Syndrome[a]	VSD, AV canal defect	(See Section V)	Karyotype
Turner Syndrome[a]	Coarctation of aorta	(See Section V)	Karyotype
22q11.2 Deletion Syndrome[a]	Tetralogy of Fallot, interrupted aortic arch, VSD	(See Section V)	Microarray

[a]Published clinical management guidelines available.[20]

ASD, Atrial septal defect; *AV*, atrioventricular; *VSD*, ventricular septal defect.

5. **Examples**: Autosomal dominant inheritance seen in Van der Woude syndrome (associated with lip pits) and Stickler syndrome (can have retinal detachment, hearing loss).

D. Connective Tissue Disorders

1. Consider when a patient has velvety skin, hyperextensible joints, abnormal scarring, poor healing, striae, pectus deformities, tall stature, myopia, lens dislocations, arachnodactyly.
2. **Evaluation**: Some connective tissue disorders are associated with dilated aorta (echocardiogram), dysplastic vessels, or fragility of lens/retina (ophthalmology evaluation).
3. **Examples**: Dilated aorta with characteristic physical features in Marfan syndrome; vascular fragility in vascular Ehlers-Danlos (type IV); isolated hyperextensibility of joints in hypermobile Ehlers-Danlos (type III).

E. Developmental Delay, Intellectual Disability

1. All children should be offered genetic evaluation.
2. See Chapter 9 for information on evaluation.
3. **Examples:** Microarray is first tier test because it can detect microdeletion and microduplication syndromes, such as 1p36 deletion syndrome. *FMR1* repeat testing can detect fragile X syndrome and heterozygous females, who can also have developmental delays. Further testing may be indicated to detect monogenic causes, such as Kleefstra syndrome.

F. Deafness, Hard of Hearing

1. Approximately 60% of hearing loss is genetic. It can be syndromic or nonsyndromic.
2. Consider perinatal infectious causes (e.g., cytomegalovirus).
3. **Evaluation**: Consider connexin 26 and 30 gene testing as first step if nonsyndromic and/or broad gene panel testing. Individualize inner ear/brain imaging. Ophthalmology assessment, ECG, and renal US should be done for those with negative connexin testing.
4. **Examples**: Approximately half of nonsyndromic hearing loss is from *GJB2* (encodes connexin 26) gene mutations. Syndromic causes include Usher syndrome, which can also have gradual blindness.

G. Hypotonia

1. **Central**: Abnormalities of brain function, normal strength or axial weakness, preserved/persistent newborn reflexes, normal CK, normal muscle bulk.
   a. **Evaluation**: CK to differentiate. Evaluate for causes such as hypothyroidism (TSH); evaluate brain structure and function with MRI and EEG.
   b. **Examples**: Beckwith-Wiedemann syndrome, Prader-Willi syndrome, peroxisomal disorders.
2. **Peripheral**: Alert, profound weakness that is often appendicular, absent reflexes, feeding difficulties, normal or increased CK.
   a. **Evaluation**: Evaluate for causes such as hypothyroidism (TSH) or mitochondrial disease (lactate/pyruvate). Electromyography (EMG) to determine if muscle or nerve affected. Consider that cardiac muscle could be affected (echocardiogram).
   b. **Examples:** Spinal muscular atrophy, myotonic dystrophy, muscular dystrophies.

H. Limb and Stature Disorders

1. Can be defects in collagen formation, bone formation, or remodeling.
2. **Evaluation**: Radiographic skeletal survey of all bones to localize dysplasia. Some disorders, including achondroplasia, can have narrowing at the foramen magnum or cervical instability (flexion/extension C-spine films). There can be a risk of central or peripheral sleep apneas (sleep study). Karyotype for females with short stature to evaluate for Turner syndrome. Unless a specific disorder suspected, broad genetic testing is appropriate.
3. **Examples**: Rhizomelic limb shortening and narrow foramen magnum seen in achondroplasia. Cervical instability seen in *COL2A1* gene mutations (spondyloepiphyseal dysplasia congenita, Stickler syndrome). The presence of multiple congenital joint contractures is called arthrogryposis, which is seen in many disorders. Fractures can be seen in osteogenesis imperfecta and hypophosphatasia.

I. Liver Disease

1. Liver failure and/or direct and indirect hyperbilirubinemia can be a manifestation of a metabolic disorder or the result of a genetic syndrome.

2. **Evaluation**: Metabolic work-up including PAA, UOA, urine succinylacetone, very-long-chain fatty acids, urine reducing substances. Some syndromes have ocular features (ophthalmology evaluation). Unless a specific disorder suspected, broad genetic testing is appropriate.
3. **Examples**: Cholestasis found in progressive familial intrahepatic cholestasis (type 1, 2, and 3). Liver dysfunction can be seen in tyrosinemia. Indirect/unconjugated hyperbilirubinemia can be seen in Gilbert and Crigler-Najjar syndromes.

J. Oncologic Disorders[19]

1. Approximately 9% of pediatric oncology patients have a heritable cancer predisposition syndrome or germline mutation. This puts them and affected family members at risk for certain cancers and may affect their individualized treatments.
2. Obtain a thorough family history with specific cancer diagnoses and age of diagnosis.
3. **Evaluation:** Many cancers warrant referral. Genetic testing is tailored to each specific diagnosis. Examples include myelodysplastic syndrome, medulloblastoma, atypical teratoid rhabdoid tumor, sarcomas, pituitary blastoma, and many more.
4. **Examples:** Early onset of cancers in Li-Fraumeni syndrome (especially sarcoma) and von Hippel-Lindau syndrome (especially hemangioblastoma).

K. Overgrowth

1. Generalized overgrowth can result in macrosomia at birth or height and/or head circumference greater than the 98th percentile.
2. Hemihypertrophy of a limb may be the result of mosaicism from somatic changes.
3. Be aware that certain overgrowth syndromes have associated cancer risks and may require routine monitoring (e.g., abdominal US screening in Beckwith-Wiedemann syndrome).
4. **Evaluation**: Disorder-specific genetic testing based on exam findings; may require skin biopsy. In some disorders, internal organs can be affected (echocardiogram, ECG, renal US).
5. **Examples**: Generalized overgrowth with developmental delays can be the result of Sotos syndrome, Beckwith-Wiedemann syndrome, or others. Segmental overgrowth/hemihypertrophy can result from somatic *PIK3CA* mutations affecting the brain (MCAP syndrome) or a limb (Klippel-Trénaunay syndrome).

L. Seizure Disorders

1. Consider genetics especially with positive family history, intractable epilepsy, infantile onset, developmental regression, intellectual disability, dysmorphic features, autism, or brain malformations.
2. Can be the result of metabolic conditions or syndromic disorders.
3. Increased recurrence risk in families even if no genetic cause identified.
4. **Evaluation**: Consideration of microarray, epilepsy panels, or whole exome sequencing (particularly if dysmorphic features present);

consider biochemical testing for inborn errors of metabolism; physical exam with Wood's lamp for cutaneous manifestations (e.g., hypopigmented macules).

5. **Examples**: Sodium channel defects (*SCN1A* mutations) can lead to a broad spectrum of seizures. Accompanying dermatologic findings can be characteristic for neurocutaneous disorders, including neurofibromatosis type 1 and tuberous sclerosis.

M. Skin Pigmentation Alterations

1. Can be the result of post-zygotic mosaicism. As a result, genetic variants may only be detectable in affected skin and not in blood.
2. Skin and the central nervous system are derived from the same neural crest lineage; many skin pigmentation anomalies have associated central nervous system abnormalities, including malformations or seizures. Often referred to as neurocutaneous disorders.
3. **Evaluation**: Examination with a Wood's lamp, ophthalmology evaluation
4. **Examples**: Multiple café-au-lait macules seen in neurofibromatosis type 1 and Legius syndrome. Genetic mosaicism in skin can lead to a pigmentation pattern called hypomelanosis of Ito.

N. Vascular Anomalies

1. Can involve arterial, vascular, and lymphatic systems. Can be caused by germline mutations or postzygotic somatic changes (mosaicism). Some are associated with segmental overgrowth.
2. Vascular syndromes can cause clinically significant arteriovenous malformations and arteriovenous fistulas in the skin, internal organs, and brain/spine.
3. **Evaluation**: Examine mucosal membranes. Some disorders require evaluation for intraorganal arteriovenous malformations with abdominal US and/or MRI/magnetic resonance angiography (MRA) of brain and spine. Several disorders are autosomal dominant—obtain family history for vascular lesions.
4. **Examples**: Autosomal dominant history of multiple capillary malformations could be from *RASA1* mutations. Port-wine stains seen in Sturge-Weber syndrome. Telangiectasias on lips, nose, and hands seen in hereditary hemorrhagic telangiectasia.

V. ETIOLOGIES OF DYSMORPHIC FEATURES (FIG. 13.5)[11,14,29]

A. Aneuploidy

Abnormal number of chromosomes.

1. Aneuploidy syndromes are most commonly due to maternal nondisjunction and more rarely due to chromosomal translocation or mosaicism. Risk increases with maternal age.
2. The evaluation for aneuploidy often begins prenatally with a first trimester screen (nuchal translucency, nasal bone, free β-human chorionic gonadotropin [β-hCG], PAPP-A) or circulating cell-free fetal DNA analysis showing increased risk.

3. Prenatal diagnostic testing options include chorionic villus sampling in the first trimester or amniocentesis during or after the second trimester.
4. Fluorescence in situ hybridization (FISH) may be performed in the first 24 to 48 hours of life to indicate number of chromosomes but will not determine the morphology of the chromosomes (e.g., if a translocation is present). Therefore karyotype analysis is still indicated in aneuploidy syndromes, both to provide a diagnosis and to provide accurate genetic counseling.
5. **Specific aneuploidy syndromes:**
   a. **Down syndrome (Trisomy 21):**
      (1) **Features**: Hypotonia and characteristic facial features (brachycephaly, epicanthal folds, flat nasal bridge, upward-slanting palpebral fissures, Brushfield spots, small mouth and ears), excess skin at the nape of the neck, single transverse palmar crease, short fifth finger with clinodactyly, wide gap between the first and second toes. Intellectual disability present in all, but severity is variable.
      (2) Full health supervision guidelines from the American Academy of Pediatrics (AAP) are available (see Section VII).
      (3) In brief: In addition to karyotype, neonates should have echocardiogram to assess for congenital heart disease, ophthalmologic evaluation to assess for cataracts, hearing screen, complete blood count (CBC) to assess for transient myeloproliferative disease, thyroid studies to assess for hypothyroidism, and referral to early intervention services. Annual thyroid studies, CBC (add ferritin and CRP for any child at risk of iron deficiency), hearing and vision assessments. Cervical spine x-ray at age 3 years if asymptomatic (sooner imaging with immediate neurosurgical referral if symptomatic). Monitor for signs of obstructive sleep apnea and neurologic dysfunction.
   b. **Edwards syndrome (Trisomy 18):**
      (1) **Features**: Intrauterine growth restriction and polyhydramnios, small for gestational age at birth, clenched hands with overlapping fingers, hypoplastic nails, short sternum, prominent occiput, low-set and structurally abnormal ears, micrognathia, rocker-bottom feet, congenital heart disease, cystic and horseshoe kidneys, seizures, hypertonia, significant developmental and cognitive impairments.
      (2) Ninety percent die before 1 year of life.
   c. **Patau syndrome (Trisomy 13):**
      (1) **Features**: Defects of forebrain development (holoprosencephaly), severe developmental disability, low-set malformed ears, cleft lip and palate (CLP), microphthalmia, aplasia cutis congenita, polydactyly (most frequently of the postaxial type), narrow hyperconvex nails, apneic spells, cryptorchidism, congenital heart defects.
      (2) Ninety-five percent die before 6 months of life.

d. **Turner syndrome (45, X):**
   (1) **Features**: Short stature, gonadal dysgenesis with amenorrhea and lack of a pubertal growth spurt, broad chest with hypoplastic or inverted nipples, webbed neck. The diagnosis should be considered prenatally in a female fetus with hydrops, increased nuchal translucency, cystic hygroma, or lymphedema. Intelligence is usually normal, but patients are at risk for cognitive, behavioral, and social disabilities.
   (2) Full health supervision guidelines from the AAP are available (see Section VII).
   (3) In brief: Obtain baseline echocardiogram, renal US, ophthalmology and audiology evaluations. Routine thyroid testing, biochemical liver tests, HgbA1C, vitamin D, TTG and immunoglobulin A (IgA), audiology, skin examinations, bone mineral density, and skeletal assessments.

e. **Klinefelter syndrome (47, XXY; 48, XXYY; 48, XXXY; and 49, XXXXY):**
   (1) **Features**: Primary hypogonadism, which may present in infancy with hypospadias or cryptorchidism or in adolescence/adulthood with infertility, gynecomastia, and small testes. Children may have expressive language delay.
   (2) There is an increased risk of breast carcinoma in 47, XXY.
   (3) Testosterone therapy is indicated at puberty for hypergonadotropic hypogonadism.

B. Copy Number Variation (Deletions and Duplications)

Partial loss or additional copies of genetic material on part of a chromosome.

1. **22q11 Deletion syndrome (Velocardiofacial syndrome, DiGeorge syndrome)**
   a. **Features**: Congenital heart disease (tetralogy of Fallot, interrupted aortic arch, ventricular septal defect [VSD], and truncus arteriosus most common), palatal abnormalities (velopharyngeal incompetence, cleft palate), characteristic facial features in approximately two-thirds, developmental delays, learning disabilities, immunodeficiency, hypocalcemia, feeding problems, renal anomalies, hearing loss, laryngotracheoesophageal anomalies, growth hormone deficiency, autoimmune disorders, seizures (with or without hypocalcemia), and psychiatric disorders.
   b. **Diagnostic evaluation**: Microarray; FISH is no longer recommended. Assessments should include serum calcium, absolute lymphocyte count, B- and T-cell subsets, renal US, chest x-ray, cardiac examination, and echocardiogram.
   c. **Health supervision**: Health supervision recommendations have been published. Hold live vaccines until immune function is assessed.
2. **5p– Syndrome (Cri-du-chat syndrome)**
   a. **Features**: High pitched cry, delayed development, intellectual disability, microcephaly, low birth weight, hypotonia, hypertelorism, low

set ears, small jaw, round face, congenital heart disease (VSD, atrial septal defect [ASD], PDA).
   b. **Diagnostic evaluation**: Can be detected on karyotype or microarray.
3. **1p36 Deletion syndrome**
   a. **Features**: Developmental delay, intellectual disability, delayed growth, hypotonia, seizures, speech delay, hearing and vision impairment, microcephaly, low ears with thick helices, congenital heart disease (structural defects or cardiomyopathy).
   b. **Diagnostic evaluation**: Microarray.

C. Disorders of Methylation/Epigenetics

Heritable changes that affect gene activity and expression.

1. **Prader-Willi syndrome**
   a. **Features**: Severe hypotonia and feeding difficulties in infancy, followed by an insatiable appetite in later infancy or early childhood. Developmental delays in motor and language abilities. All affected individuals have some degree of intellectual disability. Short stature is common; males and females have hypogonadism, and in most, infertility.
   b. **Diagnostic evaluation**: Results from missing *paternally* contributed region. Methylation testing can detect almost all individuals—whether due to abnormal paternal-specific imprinting, a paternal deletion, or maternal uniparental disomy within the Prader-Willi/Angelman critical region of 15q. Follow-up with further molecular testing.
   c. **Health supervision**: Full health supervision guidelines from the AAP are available (see Section VII). Monitor for feeding difficulties in infancy and close supervision beginning in childhood to prevent obesity. Evaluate for and treat hypothyroidism, sleep apnea (central and obstructive), central adrenal insufficiency,[21] and cryptorchidism.
   d. **Treatment**: Growth hormone can be beneficial, and hormone replacement therapy can aid in sexual development.
2. **Angelman syndrome**
   a. **Features**: Happy demeanor, hand-flapping, and fascination with water. Severe developmental delay, intellectual disability, severe speech impairment, gait ataxia, tremulous limbs, hypotonia, microcephaly, and seizures.
   b. **Diagnostic evaluation**: Results from missing *maternally* contributed region. Methylation testing can detect almost all individuals—whether due to abnormal maternal-specific imprinting, a maternal deletion, or paternal uniparental disomy within the Prader-Willi/Angelman critical region of 15q. Some individuals can be detected through *UBE3A* sequence analysis.
   c. **Health supervision**: Monitor for seizures, behavior problems, feeding issues, sleep disturbance, scoliosis, strabismus, constipation, and gastroesophageal reflux disease.

d. **Treatment**: Antiepileptic drugs for seizures; be careful not to overtreat, because Angelman syndrome also associated with movement abnormalities (*avoid* carbamazepine, vigabatrin, and tiagabine).[22] Speech therapy with a focus on nonverbal communication. Sedatives for nighttime wakefulness.

3. **Classic Rett syndrome**: X-linked disease present only in females because pathogenic *MECP2* variants are most often lethal in males who have only one X chromosome. Males who do survive with *MECP2* mutations have presentation different from Rett syndrome that often incudes neonatal encephalopathy.
   a. **Features**: Neurodevelopmental syndrome that presents after 6 to 18 months of typical development with acquired microcephaly, then developmental stagnation, followed by rapid regression. Gait ataxia or inability to ambulate, repetitive, stereotypical handwringing, fits of screaming or inconsolable crying, episodic breathing abnormalities (sighing, apnea, or hyperpnea), tremors, and generalized tonic-clonic seizures.
   b. **Diagnostic evaluation**: Molecular testing of *MECP2*.
   c. **Health Supervision**: Regular ECG to evaluate QT interval,[23] monitor for scoliosis.

D. Repeat Expansion

Pathogenic expansion of trinucleotide repeats during DNA replication.

1. **Fragile X syndrome**
   a. Most common cause of inherited intellectual disability.
   b. **Features**: Males have relative macrocephaly and prominent ears. Postpubertal macroorchidism and tall stature that slows in adolescence. Females have a range of intellectual disability due to the degree of X inactivation of the affected chromosome. Female premutation carriers (55 to 200 repeats) can develop primary ovarian insufficiency; males with 55 to 200 repeats can have a tremor/ataxia phenotype.
   c. **Diagnostic evaluation**: Repeat expansion testing of *FMR1* gene to assess number of CGG trinucleotide repeats (typically >200 in fragile X syndrome).
   d. **Health supervision**: Full health supervision guidelines from the AAP are available (see Section VII). Symptom and supportive psychopharmacologic medications.
2. Other examples include Huntington disease (CAG repeats), myotonic dystrophy (CTG repeats), and Friedrich ataxia (GAA repeats).

E. Mendelian/Single Gene Disorders

Mutation in a single gene causing a disorder.

1. **Marfan syndrome**
   a. **Features**: Myopia, ectopia lentis, aortic dilatation with predisposition to rupture, mitral valve prolapse, pneumothorax, bone overgrowth and joint laxity, pectus carinatum or excavatum, scoliosis, pes planus.

   b. **Diagnostic evaluation**: Clinical diagnosis based on the revised Ghent criteria (a "systemic score" system based on clinical features that can support a diagnosis if score is greater than or equal to 7). Molecular genetic testing of *FBN1* gene.
   c. **Health supervision**: Annual ophthalmologic examination; annual echocardiography; intermittent surveillance of the entire aorta with computed tomography (CT) or MRA scans beginning in young adulthood. Avoid contact sports, competitive sports, isometric exercise. Full health supervision guidelines from the AAP are available (see Section VII).
   d. **Treatment**: β-blocker (atenolol) and/or an angiotensin-II type 1 receptor blocker (losartan) is current standard of care. Valve-sparing surgery to replace aortic root when diameter exceeds ~4.5 cm in adults (or if rates of aortic dilation exceed ~0.5 cm/year) and significant aortic regurgitation is present.[24]
2. **Ehlers-Danlos syndrome (EDS)**
   a. **Features**: Smooth, velvety, hyperextensible skin, widened scars, poor healing, easy bruising, joint hypermobility with recurrent dislocations, chronic joint or limb pain, and a positive family history. The vascular-type EDS is distinct and involves translucent skin, characteristic facies (pinched nose), as well as risk for arterial, intestinal, and uterine fragility or rupture.
   b. **Diagnostic evaluation**: Clinical evaluation and family history. For classical and vascular types, echocardiogram and DNA testing. Vascular type additionally needs MRI/MRA imaging of aorta and iliac arteries. Joint hypermobility can be scored with Beighton criteria. No known genetic cause of hypermobile type.
   c. **Treatment**: Physical therapy to improve joint stability, low-resistance exercise, and pain medications as needed; treat gastroesophageal reflux. Vascular EDS requires management in a clinic specializing in connective tissue disorders.
3. **Achondroplasia**
   a. **Features**: Short arms and legs (especially rhizomelia); bowing of the lower legs; large head with characteristic facial features including frontal bossing and midface retrusion. Infantile hypotonia is typical, followed by delayed motor development. Gibbus deformity of the thoracolumbar spine leads to exaggerated lumbar lordosis. Rarely, children have hydrocephalus and restrictive pulmonary disease. Stenosis at the foramen magnum in infancy increases the risk of death; lumbar spinal stenosis may present in childhood but is more common in adulthood. Intelligence and lifespan are usually normal. Average adult height for males and females is approximately 4 feet.
   b. **Diagnostic evaluation**: Clinical diagnosis based on characteristic physical exam. *FGFR3* mutation testing available if diagnostic uncertainty.
   c. **Health supervision**: Full health supervision guidelines from the AAP are available (see Section VII). In brief: Use standard growth charts for achondroplasia. Baseline head CT including cervicomedullary junction in infancy, and precautions against uncontrolled head

movement or neck manipulation. Monitor for signs of obstructive sleep apnea, middle ear complications (e.g., otitis media), or spinal stenosis (more common in adults).

F. Teratogen Exposure (Table 13.10)

G. *In utero* Forces[25]

1. Uterine compression:
   a. Can be intrinsic (oligohydramnios, multiple fetuses, uterine deformities) or extrinsic (small pelvis).
   b. Results in deformations, including craniofacial (plagiocephaly, flattened facies, crumpled ear, craniosynostosis), extremities (dislocated hips, equinovarus or calcaneovalgus feet, tibial bowing, contractures), torticollis, lung hypoplasia, scoliosis.

TABLE 13.10

SELECTED TERATOGENS[11,30-31]

Exposure	Features
Intrauterine infections	See Chapter 17
Intrauterine substance exposure	Alcohol: Fetal alcohol spectrum disorder: microcephaly, small palpebral fissures with epicanthal folds, low nasal bridge with upturned nose, smooth philtrum and thin vermilion border, small chin, developmental delay, intellectual disability Cocaine: IUGR, developmental delay, learning disabilities, attention and behavioral challenges, occasional congenital anomalies
Intrauterine medication exposure *See Formulary for drug-specific information on risk in pregnancy*	Phenytoin: Fetal hydantoin syndrome: growth deficiency, hypertelorism, flat nasal bridge, cleft lip and palate, long philtrum and thin bowed upper lip, digitalized thumbs, hypoplasia of distal phalanges Warfarin: Nasal hypoplasia, epiphyseal stippling, hypoplastic distal phalanges, Peters anomaly, brain malformations Valproate: High forehead, broad nasal bridge, small mouth and chin, cardiac defects, long/thin phalanges, developmental delay Retinoic acid: Microtia, depressed nasal bridge, hypertelorism, cardiac defects, brain malformations, intellectual disability ACE inhibitors: Oligohydramnios, renal tubular dysgenesis, poor ossification of calvaria, cardiac defects, brain malformations Methotrexate: Microcephaly, growth restriction, hypoplasia of skull bones, micrognathia, low set ears, mesomelia, syndactyly
Maternal medical conditions	Diabetes mellitus: Polyhydramnios, macrosomia; variety of congenital anomalies including spina bifida, heart defects, skeletal anomalies, urinary/reproductive system anomalies Uncontrolled maternal PKU: Microcephaly, IUGR, hypertonia, cardiac defects, intellectual disability
Environmental exposures	High lead levels: Miscarriage, intrauterine growth restriction, learning and behavior problems High levels of radiation: Miscarriage, microcephaly, developmental delay; exposure of less than 5 rads (125 pelvic x-rays) not associated with increased risk of birth defects

This is not a comprehensive listing. Patient oriented resource for exposures during pregnancy and breastfeeding: mothertobaby.org.[31]

ACE, Angiotensin-converting enzyme; *IUGR*, intrauterine growth restriction; *PKU*, phenylketonuria.

2. Abnormal fetal muscular tone or posture can result in hyperextended knees, dislocated hips, contractures.
3. Placental compromise
4. Amniotic bands

VI. CONSENT AND DISCLOSURE OF GENETIC TESTING

A. Ethics of Genetic Testing in Pediatrics

Genetic testing in pediatric patients poses unique challenges given that children require proxies (most often parents) to give consent for testing. Several publications and statements have been made with regard to genetic testing in children, including the "Ethical Issues with Genetic Testing in Pediatrics" statement made by the AAP.[26] Important considerations include:

1. Testing and screening of a pediatric patient should be in his/her best interest and provide clear benefits.
2. If testing is performed for the interests of parents or other family members, it should not be to the detriment of the child.
3. Treatment and/or follow-up must be available after testing is sent.
4. Carrier testing or screening in children and adolescents is not broadly supported.
5. Predictive testing for late-onset disorders is discouraged until a patient is able to make an autonomous decision; in these cases, extensive pretest counseling is recommended.

B. Informed Consent

Pretest counseling and informed consent are important prior to sending any genome-wide testing and documentation of informed consent is recommended. Possible results from genetic testing include:

1. Positive—a causative/related variant is found.
2. Negative—either no causative/related variant is present, *or* the available technology or scope of the test methodology was unable to detect the causative/related variant. A negative result does not guarantee the condition does not have a genetic etiology.
3. Variant(s) of uncertain significance—variants for which the meaning is uncertain (could be variants without clinical significance or related to the patient's presentation but not previously reported).
4. Incidental finding(s)—variants anticipated to affect the patient's health that are unrelated to the indication for sending the test (and may be an adult-onset condition).
5. Discovery that parents are blood relatives and/or nonmaternity/nonpaternity.

C. Professional Disclosure of Familial Genetic Information

Pretest counseling should include the discussion that genetic testing may have implications for family members. With regard to disclosure of genetic testing results to at-risk family members when a patient or family member chooses not to disclose, the provider must weigh the duty to respect privacy and autonomy of the patient with the duty to prevent harm in another identifiable person. The ethical and legal duties of the physician are not well

defined. The American Society of Human Genetics released a statement on professional disclosure of familial genetic information which outlines "exceptional circumstances," which if all are present, disclosure may be permissible: (1) attempts to encourage disclosure by the patient have failed, (2) harm is "highly likely" to occur, (3) the harm is "serious and foreseeable," (4) either the disease is preventable/treatable, or early monitoring will reduce risks, (5) the at-risk relative(s) are identifiable, and (6) the harm of failure to disclose outweighs the harm that may result from disclosure.[27]

D. Disclosure of Incidental Findings

Patients are sometimes given the option to be informed of any incidental or secondary findings when they pursue genetic testing, but in general, it is recommended that incidental findings should be reported when there is strong evidence of benefit to the patient. The minimal list of reportable incidental findings may be found in the American College of Medical Genetics (ACMG) March 2013 statement and related updates.[28]

VII. WEB RESOURCES

A. Specific Genetic Disorders

1. Genetics Home Reference: http://ghr.nlm.nih.gov/. (Patient-friendly information)
2. GeneReviews: www.genereviews.org. (Expert-authored clinical descriptions including diagnosis and management recommendations)
3. National Organization for Rare Disorders: www.rarediseases.org
4. Online Mendelian Inheritance in Man (OMIM): http://omim.org (Curated primary literature, can be used to search for clinical features to build a differential)

B. Guidelines for Genetic Conditions

1. Patient Management Guidelines endorsed by AAP: https://www.aappublications.org/search/policy/policy [20]
2. Newborn screening ACT Sheets and Confirmatory Algorithms: https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx

C. Molecular Testing Resources

1. Concert Genetics: www.concertgenetics.com
2. Genetics Testing Registry: https://www.ncbi.nlm.nih.gov/gtr

D. Teratogen Evaluation

1. LactMed: Drugs and lactation database available through the U.S. National Library of Medicine. www.toxnet.nlm.nih.gov.
2. Patient oriented information on exposures during pregnancy: www.mothertobaby.org [31]

REFERENCES

A complete list of references can be found online at www.expertconsult.com.

VIII. ONLINE CONTENT

A. Patterns of Inheritance

1. **Autosomal dominant:**
   a. Disease manifestation with a variant in one allele of a gene; the other allele is normal.
   b. It can appear in multiple generations.
   c. An affected individual has a 50% risk of passing on the variant with *each* pregnancy.
2. **Autosomal recessive:**
   a. Disease manifestation requiring variants in both alleles of the gene.
   b. There can be multiple affected individuals in the same generation.
   c. An affected couple (each being a carrier) has a 25% chance of having an affected child, a 25% chance of having an *un*affected child, and a 50% chance of producing a carrier of the condition with *each* pregnancy.
3. **X-linked:**
   a. Because females have two X chromosomes and males have only one X chromosome, males are more commonly and more severely affected by X-linked conditions. Females can be unaffected or have a spectrum of manifestations. In carrier females, lyonization is the process of silencing one X chromosome in each cell and "unfavorable lionization" can result in a large proportion of cells that inactivated the normal X chromosome, and as a result clinical features are present.
   b. Females have a 50% chance of passing on an affected X to each male or female child. Males will pass on the affected X to all female children and will have *un*affected sons.
4. **Mitochondrial:**
   a. Classically a matrilineal inheritance pattern, caused by mitochondrial DNA inherited from one's mother that contributes to mitochondrial function. Sons will be affected but cannot pass the condition on to their offspring.
   b. There may be significant phenotypic variability due to "heteroplasmy," in which the relative proportion of affected and unaffected mitochondria may change as cells divide.
   c. Mitochondrial disease is currently known to be caused by either variants in mitochondrial DNA or by recessive variants in nuclear genes that code for proteins that function in the mitochondria.
5. **Genomic imprinting and uniparental disomy:**
   a. The two alleles of a gene may be functionally equivalent but may be expressed or silenced depending on the parent of origin of the chromosome. This is due to the presence of epigenetic machinery influencing the expression of genes and resulting in different methylation patterns.
   b. Uniparental disomy is a rare occurance in which offspring have inherited both copies of a chromosome from one parent. There are two types: (1) Uniparental isodisomy is an error in meiosis II, in

which the offspring receives two identical copies of a chromosome from one parent. This can result in autosomal recessive disorders because any variant on one parental allele could be present on both alleles of their offspring. (2) Uniparental heterodisomy is an error in meiosis I, in which the offspring receives both copies of a single parent's chromosome. This can result in disorders of imprinting because only one parent contributed to the epigenetic pattern of that chromosome.

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Chapter 14

Hematology

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See additional content on Expert Consult

I. ANEMIA

A. Screening for Anemia

1. The American Academy of Pediatrics (AAP) recommends screening between 9 and 12 months with a repeat level in 6 months.
2. Screen yearly in high-risk children: history of prematurity or low birth weight, exposure to lead, exclusive breastfeeding without supplemental iron beyond 4 months, diet without iron-fortified cereals or foods naturally rich in iron, feeding problems, poor growth, inadequate nutrition.[1]

B. Definition of Anemia

1. Anemia is defined as a reduction in hemoglobin (Hb) two standard deviations below the mean, based on age-specific norms.
2. See Table 14.1 at the end of the chapter for age-specific blood cell indices.

C. Causes of Anemia

1. See Fig. 14.1 for approach to anemia based on red blood cell (RBC) production, as measured by reticulocyte count and cell size. Note that normal ranges for Hb and mean corpuscular volume (MCV) are age-dependent.
2. See Tables 14.2 and 14.3 for more details regarding specific causes of nonhemolytic and hemolytic anemia.

D. Evaluation of Anemia

1. Useful equations in the evaluation of anemia:
   a. Mentzer index[2] = MCV/RBC
      (1) Index >13 suggests iron deficiency anemia (IDA).
      (2) Index <13 suggests thalassemia trait.
      (3) Sensitivity: 62% for IDA, 86% for beta thalassemia trait. Specificity: 86% for IDA, 62% for thalassemia.
   b. Reticulocyte index = % reticulocytes × patient hematocrit/normal hematocrit[3]
      (1) >2 is indicative of increased RBC production in appropriate response to anemia.
      (2) <2 is evidence of hypoproliferative anemia.
2. Other useful indices and tests
   a. RBC distribution width (RDW):
      (1) Normal in thalassemia.
      (2) Increased in IDA and sideroblastic anemia.
   b. Mean cell hemoglobin concentration (MCHC): Hb/hematocrit (Hct):
      (1) Allows for classification of anemia as hypochromic, normochromic, or hyperchromic.

TABLE 14.2

NONHEMOLYTIC ANEMIA

NUTRITIONAL DEFICIENCY	
Iron deficiency anemia (IDA)	Causes: Poor intake, malnutrition, GI bleed, menstrual cycle, malabsorption (with celiac disease, *Helicobacter pylori*, IBD). Ferritin falls first. Low MCHC, elevated transferrin receptor, low reticulocyte Hb content. Usually normocytic; microcytic if severe or prolonged.
UNDERLYING DISEASE	
Anemia of chronic disease	Typically secondary to prolonged/frequent infections, autoimmune conditions (SLE, JIA, IBD), vasculitis.[3] Low iron, TIBC, transferrin. High ferritin, CRP, and ESR.
Renal disease	Impaired erythropoietin production.
Endocrine disease	Hypothyroidism, hyperthyroidism, panhypopituitarism, hyperparathyroidism (primary or secondary).
TOXINS	
Lead poisoning	Lead interferes with iron absorption and inhibits heme synthesis enzymes.
BONE MARROW	
Acquired Failure	
Primary red cell aplasia	Autoimmune disorder with autoantibody-mediated disruption of erythroid cell differentiation. Bone marrow shows absent erythroblasts, but is otherwise normal.
Secondary red cell aplasia	Causes: Infection (parvovirus B19, EBV, CMV, HHV-6, HIV, hepatitis), radiation, medications, collagen vascular disease. Variable RBC size, variable platelet and WBC counts. Aspirate bone marrow for evidence of dysfunction, neoplasm, infection.
Aplastic anemia	Causes: Infection (parvovirus B19, EBV, CMV), radiation, chemical exposure (benzene), medications (chloramphenicol, gold, NSAIDs), autoimmune conditions, idiopathic or immune-mediated. Hypocellular bone marrow and peripheral cytopenia. Severe: ANC $<500 \times 10^6$/L, platelet <20,000/μL, reticulocyte count $<60{,}000 \times 10^6$/L.
Vitamin B12 or folate deficiency	Typically secondary to malabsorption or inadequate intake.
Myelophthisic anemia	Bone marrow fibrosis and infiltration by abnormal tissue. Primary myelofibrosis: Clonal myeloproliferative disease with extramedullary hematopoiesis, ineffective erythropoiesis, bone marrow fibrosis, hepatosplenomegaly. Secondary causes: Lymphoma, multiple myeloma, infiltrating metastatic cancer, autoimmune disease, granulomatous disease (sarcoidosis), vitamin D deficiency, hypo-/hyperparathyroidism. Presentation: Pancytopenia
Inherited Causes with Pure Anemia	
Diamond-Blackfan Anemia	Autosomal dominant mutations in multiple ribosomal protein genes identified. Presentation: Infant (average 3 months) with RBC aplasia (sometimes with neutropenia and/or thrombocytosis) and congenital anomalies (30%–47% of patients): short stature, craniofacial abnormalities (cleft lip), skeletal (triphalangeal thumb, short stature), genitourinary, cardiac abnormalities.

Continued

TABLE 14.2

NONHEMOLYTIC ANEMIA—Cont'd.

Inherited Causes with Pancytopenia	
Fanconi anemia	Autosomal recessive or X-linked disorder. Presentation: Child with pancytopenia, radial and thumb abnormalities, renal anomalies, microcephaly, short stature, skin findings (hyperpigmentation, café au lait spots).
Shwachman-Diamond syndrome	Autosomal recessive mutation in *SBDS* gene. Presentation: Young child with neutropenia +/– thrombocytopenia and macrocytic anemia, exocrine pancreatic dysfunction, bony abnormalities.
Dyskeratosis congenita	Mutation in gene encoding telomerase complex components. Presentation: Anemia, thrombocytopenia, abnormal skin reticular hyperpigmentation, nail dystrophy, oral leukoplakia.

ANC, Absolute neutrophil count; *CMV*, cytomegalovirus; *CRP*, C-reactive protein; *EBV*, Epstein Barr virus; *ESR*, erythrocyte sedimentation rate; *GI*, gastroenterology; *Hb*, hemoglobin; *HHV-6*, human herpesvirus 6; *HIV*, human immunodeficiency virus; *IBD*, inflammatory bowel disease; *JIA*, juvenile idiopathic arthritis; *MCHC*, mean corpuscular hemoglobin concentration; *NSAID*, nonsteroidal anti-inflammatory drug; *RBC*, red blood cell; *SBDS*, Shwachman-Bodian-Diamond syndrome gene; *SLE*, systemic lupus erythematosus; *TIBC*, total iron binding capacity; *WBC*, white blood cell.

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TABLE 14.3

HEMOLYTIC ANEMIA

EXTRINSIC HEMOLYTIC ANEMIA	
DAT –	
Microangiopathic hemolytic anemia (MAHA): HUS, TTP, DIC	Anemia due to RBC shearing with passage through microthrombi in microvasculature. Diagnosis: Intravascular hemolysis, thrombocytopenia, schistocytes on peripheral smear.
Hemoglobin disorders: Sickle cell disease, unstable hemoglobin	Denaturation of hemoglobin causes precipitation in RBC and reduces deformability. Diagnosis: Smear with Heinz bodies, bite or blister cells.
DAT +	
Warm autoimmune hemolytic anemia	Diagnosis: Jaundice +/– splenomegaly, +anti-IgG and/or +anti-C3 autoantibodies. Treatment: Corticosteroids (first line; prednisone), splenectomy, rituximab. Transfuse for severe anemia with cardiovascular compromise (i.e., Hb <5 g/dL) or reticulocytopenia.
Cold autoimmune hemolytic anemia	Diagnosis: Acrocyanosis, hemoglobinuria, +anti-IgM autoantibodies. Treatment: Cold avoidance.

TABLE 14.3

HEMOLYTIC ANEMIA—Cont'd.	
Secondary autoimmune hemolytic anemia	Causes: Infections,[a] drug-associated,[b] malignancy (Hodgkin lymphoma), systemic lupus erythematosus, autoimmune lymphoproliferative syndrome, common variable immunodeficiency, posttransplant (stem cell or solid organ).
Transfusion reactions (ABO or Rh incompatibility)	See Table 14.18 for presentation of transfusion reactions.
INTRINSIC HEMOLYTIC ANEMIA	
Membrane Disorders	
Neonatal hemolytic disease	Maternal antibodies to incompatible fetal RBC antigens (Rh, A, B) causes hemolytic disease in utero and in neonatal period. Diagnosis: Mild anemia to hydrops fetalis, early jaundice. Treatment: Intensive phototherapy, exchange transfusion.
Hereditary spherocytosis	Inheritance: 75% AD. 25% spontaneous mutation or AR. Protein defect → membrane instability → RBC destruction via extravascular hemolysis. Diagnosis: Family history with clinical suspicion and spherocytes on smear, osmotic fragility test, EMA flow cytometry if unclear clinical picture. Treatment: Folate supplementation if moderate-severe hemolysis, anticipatory guidance, splenectomy (for severe disease), cholecystectomy if needed for symptomatic cholelithiasis.
Hereditary elliptocytosis	Inheritance: Typically AD. Diagnosis: Elliptocytes on smear. Treatment: Same as for hereditary spherocytosis.
Enzyme Deficiencies	
G6PD deficiency	Inheritance: X-linked disorder. Enzyme deficiency predisposes to intravascular hemolysis with oxidative stress (e.g., with infections/illness, fava beans, medications). Diagnosis: G6PD assay when well (may be falsely elevated immediately after hemolytic episode). Treatment: Avoid oxidative triggers (see drug/chemical list), transfuse for severe anemia.
Pyruvate kinase (PK) deficiency	Inheritance: AR disorder of *PKLR* or *PKM* genes causes chronic hemolysis. Diagnosis: Measure PK activity in RBC. Treatment: Transfuse if symptomatic. Consider splenectomy if severe transfusion-dependent anemia.

[a]Infections include EBV, CMV, mycoplasma, pneumococcus, parvovirus.

[b]Causative drugs include penicillin, cephalosporins, quinine/quinidine, amphotericin B, NSAIDs, procainamide, IVIG.

ABO, Blood type; *AD*, autosomal dominant; *AR*, autosomal recessive; *CMV*, cytomegalovirus; *DAT*, direct antiglobulin test; *DIC*, disseminated intravascular coagulation; *EBV*, Epstein-Barr virus; *EMA*, eosin-5-maleimide; *G6PD*, Glucose-6-phosphate dehydrogenase; *Hb*, hemoglobin; *HUS*, hemolytic uremic syndrome; *Ig*, immunoglobulin; *IVIG*, intravenous immunoglobulin; *NSAID*, nonsteroidal anti-inflammatory drug; *RBC*, red blood cell; *Rh*, rhesus factor; *TTP*, thrombotic thrombocytopenic purpura.

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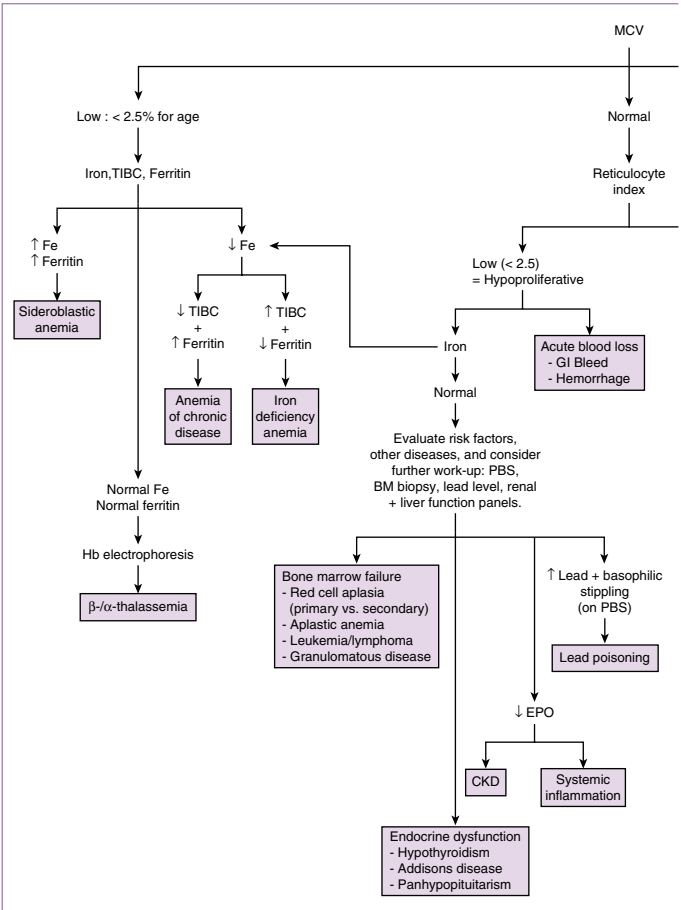

FIGURE 14.1

Approach to anemia. *AEDs*, Antiepileptic drugs; *BM*, bone marrow; *CKD*, chronic kidney disease; *DAT*, direct antiglobulin test; *EPO*, erythropoietin; Fe, iron; *G6PD*, Glucose-6-phosphate dehydrogenase; *GI*, gastrointestinal; *HUS*, hemolytic uremic syndrome; *LDH*, lactate dehydrogenase; *MAHA*, microangiopathic hemolytic anemia; *MCV*, mean corpuscular volume; *MMA*, methylmalonic acid; *PBS*, peripheral blood smear; *PK*, pyruvate kinase; *SC*, sickle cell; *SD*, standard deviation; *TIBC*, total iron binding capacity; *TTP*, thrombotic thrombocytopenic purpura. (Data from Wang, M. Iron deficiency and other types of anemia in infants and children. *Am Fam Physician*. 2016:93[4]:270–278; Orkin SH, Nathan DG, Ginsburg D, et al. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia: Saunders; 2015.)

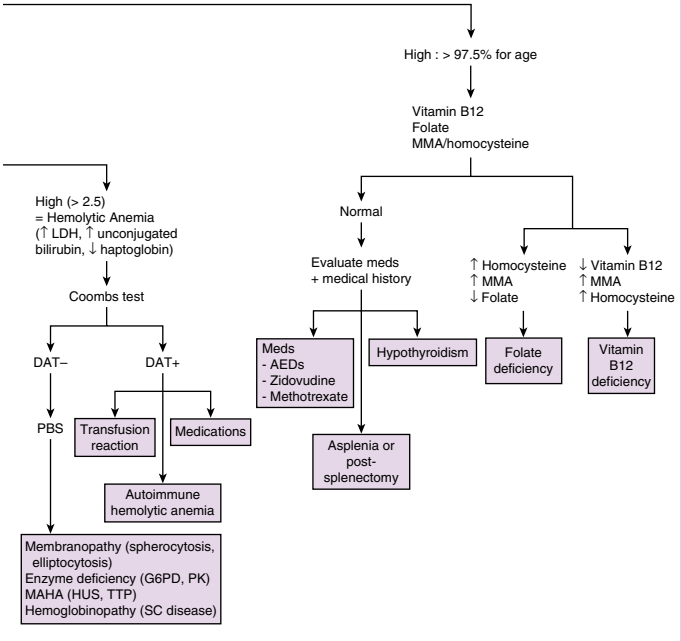

FIGURE 14.1–cont'd

(2) Low MCHC in iron deficiency and thalassemia.
(3) Elevated MCHC and spherocytes in hereditary spherocytosis and hemolytic disease of the newborn.

c. **Serum ferritin:**
(1) Reflects total body iron stores after 6 months of age.
(2) It is the first value to fall in early iron deficiency and is elevated with inflammation or infection.

d. **Coombs test:**[4]
(1) Direct (direct antiglobulin testing [DAT]): Detects antibody/complement bound to patient's RBCs by mixing prepared nonspecific antihuman globulin with patient's blood. RBC agglutination = positive test.
(2) Indirect (indirect antiglobulin testing): Detects antibodies to RBC antigens in patient's plasma by mixing reagent RBCs with patient's serum. RBC agglutination = positive test.

e. **Hemoglobin electrophoresis:**
(1) Involves separation of Hb variants based on molecular charge and size. All positive sickle preparations and solubility tests for sickle Hb (e.g., Sickledex) should be confirmed with electrophoresis or isoelectric focusing (component of mandatory newborn screening in many states).
(2) See Table 14.4 for neonatal Hb electrophoresis patterns.
(3) See Fig. 14.2 for changes in Hb polypeptide over time in a normal fetus/infant.

f. **Blood smear interpretation**[3]
(1) Howell-Jolly bodies = impaired splenic function, post-splenectomy
(2) Target cells = hemoglobinopathies, liver disease, post-splenectomy, thalassemia, HbSS, HbSC, HbC
(3) Bite cells, Heinz bodies = G6PD deficiency (during hemolysis)
(4) Toxic granulation of neutrophils, bandemia, atypical lymphocytes = infection
(5) Pencil poikilocytes = IDA, thalassemia
(6) Basophilic stippling = lead poisoning, sideroblastic anemia
(7) Pappenheimer bodies = sideroblastic anemia
(8) Hypersegmented neutrophils = Vitamin B12, folate deficiencies
(9) Blasts = leukemia, lymphoma
(10) Schistocytes (RBC fragments) = MAHA, burns, valve hemolysis
(11) Spherocytes = autoimmune hemolytic anemia, hereditary spherocytosis, ABO incompatibility/hemolytic disease of the newborn
(12) Elliptocytes = hereditary elliptocytosis, severe IDA
(13) Teardrop cells = myelofibrosis (and other BM infiltrating processes), thalassemia
(14) Echinocytes (Burr cells) = uremic patients
(15) Acanthocytes (Spur cells) = liver disease
(16) See Figs. EC 14.A to EC 14.L for examples of peripheral smears.

TABLE 14.4

NEONATAL HEMOGLOBIN ELECTROPHORESIS PATTERNS

FA	Fetal Hb and adult normal Hb; the normal newborn pattern.
FAV	Indicates presence of both HbF and HbA, but an anomalous band (V) is present that does not appear to be any of the common Hb variants.
FAS	Indicates fetal Hb, adult normal HbA, and HbS, consistent with benign sickle cell trait.
FS	Fetal and sickle HbS without detectable adult normal HbA. Consistent with clinically significant homozygous sickle Hb genotype (S/S) or sickle β^0-thalassemia, with manifestations of sickle cell disease during childhood.
FC[a]	Designates presence of HbC without adult normal HbA. Consistent with clinically significant homozygous HbC genotype (C/C), resulting in a mild hematologic disorder presenting during childhood.
FSC	HbS and HbC present. This heterozygous condition could lead to manifestations of sickle cell disease during childhood.
FAC	HbC and adult normal HbA present, consistent with benign HbC trait.
FSA	Heterozygous HbS/β^+-thalassemia, a clinically significant sickling disorder.
F[a]	Fetal HbF is present without adult normal HbA. May indicate delayed appearance of HbA, but is also consistent with homozygous β-thalassemia major or homozygous hereditary persistence of fetal HbF.
FV[a]	Fetal HbF and an anomalous Hb variant (V) are present.
AF	May indicate prior blood transfusion. Submit another filter paper blood specimen when infant is 4 months of age, at which time the transfused blood cells should have been cleared.

[a]Repeat blood specimen should be submitted to confirm original interpretation.

NOTE: HbA: $\alpha_2\beta_2$; HbF: $\alpha_2\gamma_2$; HbA_2: $\alpha_2\delta_2$.

Hemoglobin variants are reported in order of decreasing abundance; for example, FA indicates more fetal than adult hemoglobin.

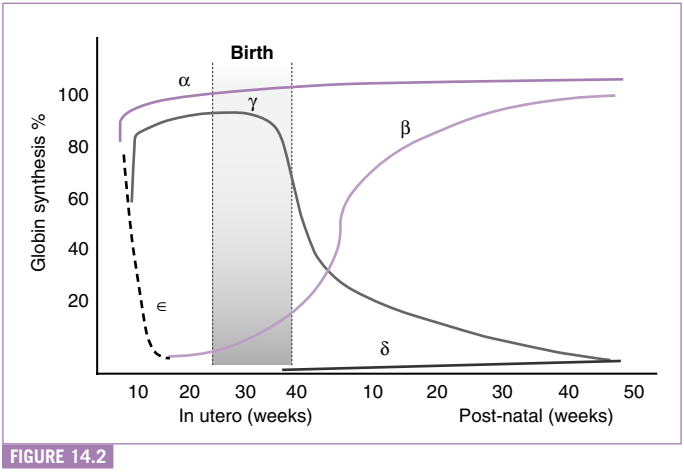

FIGURE 14.2

Neonatal hemoglobin electrophoresis patterns. (From Chandrakasan S, Kamat D. An overview of hemoglobinopathies and the interpretation of newborn screening results. *Pediatric Annals.* 2013:42[12]:502–508.)

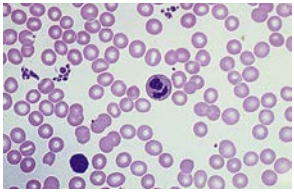

FIGURE EC 14.A
Normal smear. Round red blood cells with central pallor about one-third of the cell's diameter, scattered platelets, occasional white blood cells.

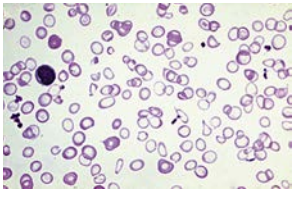

FIGURE EC 14.B
Iron deficiency. Hypochromic/microcytic red blood cells, poikilocytosis, plentiful platelets, occasional ovalocytes, and target cells.

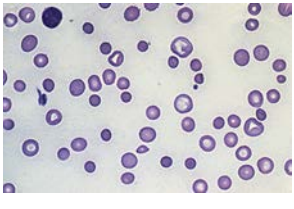

FIGURE EC 14.C
Spherocytosis. Microspherocytes (densely stained red blood cells with no central pallor) are a hallmark.

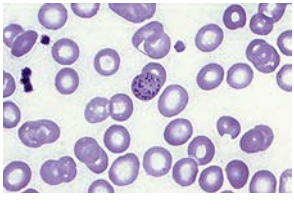

FIGURE EC 14.D
Basophilic stippling as a result of precipitated RNA throughout the cell; seen with heavy metal intoxication, thalassemia, iron deficiency, and other states of ineffective erythropoiesis.

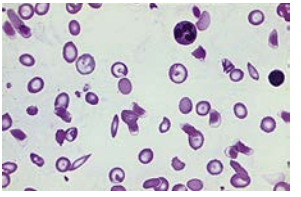

FIGURE EC 14.E
Sickle cell disease (hemoglobin SS) disease. Sickled cells, target cells, hypochromia, poikilocytosis, Howell–Jolly bodies; nucleated red blood cells common (not shown).

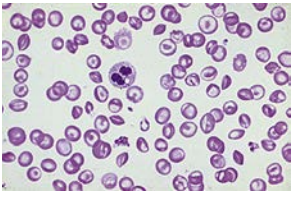

FIGURE EC 14.F
Sickle-hemoglobin C disease (hemoglobin SC) disease. Target cells, oat cells, poikilocytosis; sickle forms rarely seen.

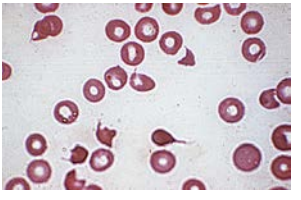

FIGURE EC 14.G
Microangiopathic hemolytic anemia. Red blood cell fragments, anisocytosis, polychromasia, decreased platelets.

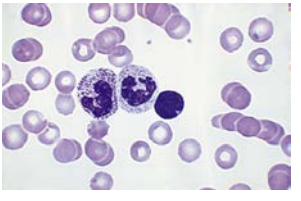

FIGURE EC 14.H
Toxic granulations. Prominent dark blue primary granules; commonly seen with infection and other toxic states (e.g., Kawasaki disease).

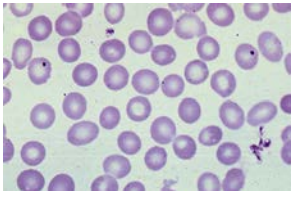

FIGURE EC 14.I
Howell–Jolly body. Small, dense nuclear remnant in a red blood cell; suggests splenic dysfunction or asplenia.

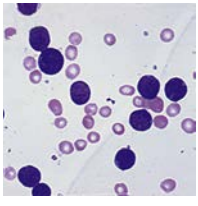

FIGURE EC 14.J
Leukemic blasts showing large nucleus-to-cytoplasm ratio.

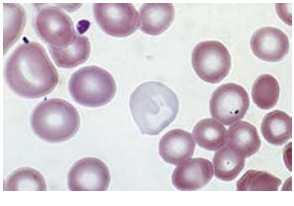

FIGURE EC 14.K
Polychromatophilia. Diffusely basophilic because of RNA staining; seen with early release of reticulocytes from the marrow.

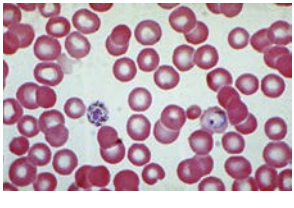

FIGURE EC 14.L
Malaria. Intraerythrocytic parasites.

E. Management of Anemia

1. **Iron deficiency anemia**
   a. Oral iron (ferrous sulfate)
      (1) Empirically treat children with microcytic anemia and history of poor dietary iron.[5]
      (2) In anemia of chronic disease, only use iron supplementation if evidence of absolute iron deficiency and ferritin <100 ng/mL.[5]
      (3) After initiation of iron supplementation, expect reticulocyte count to increase within the first week with a 1 g/dL increase in Hb in 4 weeks (if severe anemia with Hb <9 g/dL, a response should be seen in 2 weeks).[1]
   b. Iron transfusion (low molecular weight iron dextran[6] or iron sucrose[7]) is appropriate for children with iron malabsorption (PPI use, short bowel syndrome, primary malabsorption), poor response to oral iron therapy, inability to tolerate oral iron therapy, and hemodialysis-dependent patients receiving erythropoietin.
2. **Sickle cell anemia**
   a. **Etiology**: Caused by a genetic defect in β-globin that leads to polymerization and sickling with deoxygenation, leading to hemolysis, adherence to blood vessel endothelium, and vaso-occlusive ischemia.
   b. **Most common subtypes**: HbSS (sickle cell anemia) and HbSβ^0 (sickle-β^0-thalassemia) are most severe. HbSC (sickle-hemoglobin C disease) and HbSβ+ (sickle-β+-thalassemia) are often milder.
   c. **Diagnosis**: Often made on newborn screen with Hb electrophoresis. The sickle preparation and Sickledex are rapid tests that are positive in all sickle hemoglobinopathies. False-negative test results may be seen in neonates and other patients with a high percentage of fetal Hb.
   d. **Complications**: See Table 14.5. A hematologist should be consulted.
   e. **Acute management of anemia in sickle cell disease[8]:**
      (1) RBC exchange transfusions: Indicated for patients with symptomatic severe acute chest syndrome (ACS), stroke, intractable pain crisis, intrahepatic cholestasis, hepatic sequestration, refractory priapism, and multisystem organ failure. Also indicated for children with prior stroke or transcranial Doppler reading >200 cm/sec.[8] Replace with HbS-negative cells. Follow Hct carefully with goal Hct <30% to avoid hyperviscosity.[9]
      (2) Do not transfuse for asymptomatic anemia, acute kidney injury, or recurrent splenic sequestration.
   f. **Chronic management and health maintenance[8]:** See Table 14.6. Ongoing consultation and clinical involvement with a pediatric hematologist and/or sickle cell program are essential.
3. **Thalassemia**
   a. **Etiology**: Defects in α- or β-globin production leads to precipitation of excess chains, causing ineffective erythropoiesis and shortened survival of mature RBCs.

TABLE 14.5

SICKLE CELL DISEASE COMPLICATIONS

Complication	Presentation	Additional Testing	Disposition/Treatment
Fever	>101°F or 38.3°C	Blood cultures CXR Blood and urine cultures Throat and CSF cultures, if indicated	Admit if ill-appearing, temperature ≥40°C, infiltrate on CXR or abnormal SpO_2, WBC >30,000/μL or <5,000/μL, platelets <100,000/μL, Hb <5 g/dL, history of sepsis. Antibiotics: Ceftriaxone IV. Vancomycin if meningitis suspected or if severe illness. Clindamycin or levofloxacin if cephalosporin allergy.[34] Consider additional disease-specific coverage. If outpatient, return in 24 hr for second ceftriaxone dose.
Vaso-occlusive crisis	Dactylitis in <2 years old; unifocal or multifocal pain in >2 years old	Type and screen	Admit if signs of complications or pain not managed in outpatient setting. Recommendations for home pain control: • Mild-moderate pain: NSAIDs. • Moderate-severe pain: oxycodone, morphine, hydrocodone. Recommendations for emergency department or inpatient pain control: • Use IV opioids (morphine, hydromorphone). Use fentanyl if renal or hepatic dysfunction. • Use PCA and provide as needed doses for breakthrough pain. Schedule pain medication if not using PCA.[35] • Ketamine may be appropriate if poor response to opioids.[36] IV fluids as needed for dehydration. Evidence-based guidelines regarding amount or type of fluids are lacking.[37] Use incentive spirometry to reduce risk of ACS. Avoid transfusion unless other indication.
Acute chest syndrome	Fever, cough, chest pain, respiratory distress, hypoxia + new pulmonary infiltrate	CXR Type and screen Blood cultures	Admit. IV antibiotics: IV cephalosporin + oral macrolide. O_2 as needed for goal SpO_2 >95%, incentive spirometry. Analgesia, IV fluids (see above). Simple transfusion or partial exchange for moderate illness.[34] High-dose dexamethasone use is controversial.[38]

Splenic sequestration	Acutely enlarged spleen, Hb ≥2 g/dL below baseline	Type and screen	Admit for serial abdominal exams, IV fluid resuscitation. Simple transfusion if severe anemia. [a]Be cautious with transfused volume and use 5–10 mL/kg aliquots if hemodynamically stable as autotransfusion from spleen can cause rebound increase in Hb and viscosity.
Aplastic crisis	Acute illness (often viral, commonly parvovirus B19) + Hb < baseline, low reticulocyte count	Type and screen Parvovirus serology and PCR	Admit to isolated bed. IV fluids. Simple transfusion with RBCs.
Stroke	Focal neurologic signs May be precipitated by ACS, parvovirus, acute anemic events	MRI, TCD to detect increased velocities with stenosis	Emergency exchange transfusion preferable to simple transfusion, if possible.[39] Chronic transfusion to maintain sickle Hb to <30% in patients with abnormal TCD US findings or history of stroke.
Acute renal failure	Hematuria, proteinuria, hypertension	Urine spot protein, 24 hr collection	Monitor renal function. Avoid nephrotoxic drugs/contrast. Consult nephrology and initiate replacement therapy (hemodialysis) if necessary.
Avascular necrosis	Pain at site that worsens with activity, reduced range of motion. Hip most commonly involved, then shoulder and other joints.	XR of affected joint, MRI if necessary	Analgesics, physical therapy. Consult orthopedic surgery for assessment for possible decompression.
Priapism	Sustained painful erection lasting >4 hr	Not necessary	Oral and/or IV analgesia (as per VOC recommendations). Hydration with oral or IV fluids. Consider supplemental oxygen. Consult urology for possible aspiration and irrigation of corpus cavernosum (if does not self-resolve).

ACS, Acute chest syndrome; *CSF*, cerebrospinal fluid; *CXR*, chest x-ray; *Hb*, hemoglobin; *IV*, intravenous; *MRI*, magnetic resonance imaging; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *PCA*, patient-controlled analgesia; *PRN*, as needed; *PCR*, polymerase chain reaction test; *RBCs*, red blood cells; *SpO2*, peripheral oxygen saturation; *TCD*, transcranial Doppler; *VOC*, vaso-occlusive crisis; *WBC*, white blood cell; *XR*, X-ray.

National Heart, Lung, and Blood Institute. *Evidence-Based Management of Sickle Cell Disease: Expert Panel Report*, 2014. National Heart, Lung, and Blood Institute; 2014.

TABLE 14.6

SICKLE CELL DISEASE HEALTH MAINTENANCE

Medications	Penicillin	Twice daily in children with HbSS and HbSβ0 under 5 years old.[a]
	Hydroxyurea[40]	Offer in children with HbSS or HbSβ0 >9 months.[b] Treatment goal: HbF >20%.[41] Maximum dose parameters: ANC ≥2000–4000/μL, Hb ≥8 g/dL without transfusion, platelet ≥80,000/μL, absolute reticulocyte count ≥80–100,000/μL. Continue in acute hospitalization or illness. Discontinue in pregnant and breast-feeding women.
	Hormonal contraception	Progestin-only contraception (pills, injection, implant), levonorgestrel IUDs, and barrier methods preferred over estrogen-containing methods due to increased risk of blood clots.
Immunizations[42]	Pneumococcal vaccine	13-valent conjugate vaccine per routine childhood schedule. 23-valent polysaccharide vaccine at 2 years old with second dose 5 years later.
	Meningococcal vaccine	Give MenACWY-CRM (Menveo) at 2, 4, 6, 12 months. If over 2 years old, administer 2-dose series of MenACWY-CRM or MenACWY-D. Give Meningococcal B vaccine in patients 10 years or older.
	Influenza vaccine	Yearly starting at 6 months. Give to all household members and close contacts.
Imaging and labs	Transcranial doppler	Screen annually from 2 to 16 years old in HbSS or HbSβ0. Not necessary to screen in HbSβ+ or HbSC.
	Spot urine test	Screen for proteinuria at age 10; repeat annually. Refer those with proteinuria (>300 mg in 24 hr) to nephrologist.
Other	Ophthalmology	Annual exam starting at age 10 to evaluate for retinopathy.

[a]Prophylaxis may be discontinued by age 5 years if patient has had no prior severe pneumococcal infections or splenectomy and has documented pneumococcal vaccinations, including second 23-valent vaccination. May be continued based on family preference. May be considered for children with HbSC/HbSβ+, especially after splenectomy.[8] Practice patterns vary.

[b]Increases levels of fetal Hb and decreases HbS polymerization in cells. Has been shown to significantly decrease episodes of vaso-occlusive crises, dactylitis, acute chest syndrome, number of transfusions, and hospitalizations. May decrease mortality in adults. Consider in HbSC/HbSβ+ if recurrent sickle cell-associated pain interfering with daily activities or quality of life.[40,43]

ANC, absolute neutrophil count; *HbF*, hemoglobin F level; *HbSβ+*, sickle cell beta thalassemia disease; *HbSS*, Homozygous sickle cell disease; *HbSC*, hemoglobin SC disease; *IUD*, intrauterine device.

National Heart, Lung, and Blood Institute. *Evidence-Based Management of Sickle Cell Disease: Expert Panel Report*, 2014. National Heart, Lung, and Blood Institute; 2014. Available at: http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/.

b. **α-Thalassemia**:
   (1) Silent carriers (α–/αα): Not anemic; Hb electrophoresis usually normal.
   (2) α-Thalassemia trait (α–/α–) or (αα/–): Causes mild microcytic anemia from birth; Hb electrophoresis usually normal. Hb Barts can be seen in infancy (e.g., on state newborn screens) in patients with α-thalassemia trait.
   (3) HbH disease (β_4) (α–/––): Causes moderately severe anemia from birth; HbH (β-tetramer) may be seen on newborn screen and subsequent electrophoresis.
   (4) Hb Bart/hydrops fetalis (––/––): Hb Barts (γ_4) cannot deliver oxygen; usually fatal *in utero* or in neonatal period.

c. **β-Thalassemia**: Ineffective erythropoiesis is more severe in β-thalassemia than α-thalassemia. Patients often develop more severe iron overload from increased enteral absorption and transfusions. Adult Hb electrophoresis with decreased Hb A, increased Hb A_2, and increased Hb F.
   (1) Thalassemia trait/thalassemia minor (β/β+) or (β/β0): Mildly decreased β-globin production. Usually asymptomatic with mild anemia.
   (2) Thalassemia intermedia (β+/β+): Markedly decreased β-globin production. Presents at about 2 years of age with moderate compensated anemia (Hb 7 to 10 g/dL). Wide variability in presentation that may include features noted as follows.
   (3) Thalassemia major/Cooley anemia (β0/β0, β+/β0, or β+/β+): Minimal to no β-globin production. Presence of anemia within first 6 months of life requiring regular transfusions. Overstimulation of bone marrow, ineffective erythropoiesis, and iron overload results in jaundice, growth failure, hypersplenism, gallstones, skeletal abnormalities, liver cirrhosis, and cardiac impairment.

d. **Management**[10]
   (1) Patients with thalassemia major are transfusion dependent. Patients with thalassemia intermedia may need occasional transfusions.
   (2) Transfuse every 3 to 5 weeks for goal pretransfusion Hb 9 to 10.5 mg/dL.
   (3) Goal posttransfusion Hb <14 to 15 g/dL due to risk of hyperviscosity and stroke.
   (4) Treat iron overload with chelation (deferoxamine), which should be initiated in thalassemia major after 10 to 20 transfusions or when ferritin >1000 μg/L.
   (5) Bone marrow transplant is curative.

II. NEUTROPENIA

A. Definition of Neutropenia

1. Neutropenia is defined as an absolute neutrophil count (ANC) <1500/μL. Severe neutropenia is defined as an ANC <500/μL.

2. See Table 14.7 at the end of the chapter for age-specific leukocyte differentials.
3. Repeat CBC 2 to 3 weeks later to determine if transient (e.g., secondary to a medication, infection) or persistent.[11]

B. Causes and Evaluation of Neutropenia[11]

1. CBC +/– blood smear should be obtained to evaluate neutrophil morphology and concurrent presence of anemia or thrombocytopenia.
2. If pancytopenic, obtain bone marrow aspiration and biopsy with cytogenetics.
3. If persistent neutropenia for more than 2 to 4 weeks, consider further workup based on potential etiologies (Table 14.8).

C. Management of Neutropenia

1. **Additional diagnostic testing:**[12]
   a. Repeat CBC 2×/week for 6 to 8 weeks for cyclic neutropenia.
   b. Reticulocyte Index to differentiate between destructive processes and marrow failure.
   c. Blood smear for morphologic abnormalities.
   d. Immunologic testing (Coombs test, anti-double-stranded DNA, anti-neutrophil antibody) for autoimmune or alloimmune processes.
   e. IgG, IgA, IgM, lymphocyte subtypes for immunodeficiency.
2. **Treatment:**
   a. Myeloid-specific cytokine granulocyte colony-stimulating factor (G-CSF; filgrastim).
      (1) Indications for continuous use: Severe congenital neutropenia, cyclic neutropenia, glycogen storage disease 1b, bone marrow failure (e.g., aplastic anemia, Schwachman Diamond-Oski syndrome).[12,13]
      (2) Indications for intermittent use: Life-threatening infection or history of recurrent or serious infections in patients with neutropenia.[12]
      (3) Side effects: Bone pain, headache, rashes.
   b. Stem cell transplant: Indicated for bone marrow failure (e.g., Fanconi anemia), poor response to G-CSF, severe congenital neutropenia with high risk of myelodysplasia or acute myeloid leukemia.[12]
3. **Complications**: See Chapter 22 for management of neutropenic fever and typhlitis.
4. **Anticipatory guidance:**[11]
   a. Maintain good oral hygiene and skin care to prevent local infections.
   b. Avoid rectal temperatures, rectal examinations, or rectal medications due to risk of mucosal trauma and bacteremia.
   c. No live or attenuated-live vaccines for patients with impaired T-/B-lymphocyte function. Otherwise follow usual vaccination schedule.
   d. If fever >38.4°C, seek emergent care for CBC, blood culture, and empiric antibiotics.
   e. Children with mild-moderate neutropenia can attend school/daycare, if they avoid obviously ill children.

TABLE 14.8

CAUSES OF NEUTROPENIA

	Cause	Mechanism	Presentation
ACQUIRED			
Infections	Viruses (EBV, CMV, parvovirus, HHV6, HIV, viral hepatitis). Bacteria (typhoid fever, Brucellosis). Protozoa (Leishmania, malaria), Rickettsial infections, etc.	Bone marrow suppression, viral-induced immune neutropenia, redistribution to marginated pools.	Occurs early in illness, persists 3–8 days and resolves spontaneously and/or with effective treatment of underlying illness.
Medications	Many: sulfasalazine, antipsychotics (clozapine, phenothiazines), thionamides, antimicrobials (TMP/SMX).	Direct marrow suppression (more common) or drug-induced immune-mediated destruction.	Hypersensitivity reaction: fever, lymphadenopathy, rash. May have +ANA.
Nutritional	Vitamin B12 deficiency Folic acid deficiency Copper deficiency	Ineffective hematopoiesis due to impaired DNA processing and nuclear maturation (with B12/folate deficiency).	Mostly seen in chronically ill children, especially with malabsorption. Hypersegmented neutrophils, megaloblastic anemia with B12/folate deficiency. High MMA and HcY in B12 deficiency vs. high HcY in folate deficiency.
Hypersplenism	Inflammation, neoplasm, storage disorder, hemolytic anemia.	Sequestration of WBCs in spleen.	Concurrent anemia, thrombocytopenia. Rarely associated with infections.

Continued

TABLE 14.8

CAUSES OF NEUTROPENIA—cont'd.

	Cause	Mechanism	Presentation
Autoimmune	Neonatal alloimmune neutropenia	Transfer of maternal IgG alloantibodies against fetus neutrophil antigens that were produced in response to fetal cells in maternal circulation.	Severe neutropenia with fever, infection. Transient, resolves after 6–8 weeks.
	Primary autoimmune neutropenia	Antineutrophil antibodies cross-react with antigen on neutrophil surface resulting in neutrophil destruction.	Typically 5–15 months old child without recurrent infections despite severe neutropenia. +ANA. Marrow with myeloid hyperplasia and normal to increased mature neutrophils.
	Secondary autoimmune neutropenia	Secondary to systemic disease: Systemic lupus erythematosus, Evans syndrome, rheumatoid arthritis/Felty syndrome, systemic sclerosis), infections (HIV, EBV).	Presents with signs/symptoms of systemic autoimmune disease.
	Pure white cell aplasia	Associated with thymoma, drug reactions, antiglomerular basement membrane antibody disease.	At risk of severe, recurrent infections. Disappearance of granulocytopoietic tissue from bone marrow. +Antibodies (e.g., GM- CFU inhibitory activity).
Acquired bone marrow disorders	Leukemia, lymphoma, solid tumor infiltration, myelofibrosis, granulomatous infections, aplastic anemia.	Impaired production of all cell lines due to bone marrow infiltration.	Typically associated with anemia +/or thrombocytopenia. Bone marrow biopsy diagnostic.

INHERITED[a]			
Severe congenital neutropenia	Severe congenital neutropenia	AD mutation in *ELANE* or *GFII* genes results in rapid apoptosis of myeloid precursors, arrest at promyelocyte development stage. Risk of myelodysplastic syndrome and acute myelogenous leukemia.	Recurrent infections: mouth ulcers, gingivitis, otitis media, respiratory infections, skin cellulitis, abscesses. Often with oncocytosis, eosinophilia, anemia, thrombocytosis. Bone marrow: myeloid maturation arrest, normal/increased promyelocytes.
	Kostmann syndrome	Severe form of SCN. AR mutation in *HAX1* gene results in absent myeloid progenitors.	Recurrent infections as above. Typically with monocytosis, eosinophilia.
Cyclic neutropenia		AD mutation in *ELANE* gene.	Periodic ~21-day cycles of neutropenia, typically associated with fever, oral ulcerations, +/– gingivitis, pharyngitis, skin infections.
Benign ethnic neutropenia		*DARC* gene polymorphism reducing Duffy antigen expression.	Mild neutropenia in patient of West Indian, Yemenite, African, Greek, or Arab descent without increased infection incidence or severity.
Bone marrow failure syndromes	Fanconi anemia	See section VII. Online content for description of bone marrow failure in anemia.	Pancytopenia.
	Diamond Blackfan anemia		

[a]This is not an exhaustive list of all inherited causes of neutropenia.

AD, autosomal dominant; *ANA*, antinuclear antibody; *AR*, autosomal recessive; *CMV*, cytomegalovirus; *DARC*, Duffy antigen/chemokine receptor; *EBV*, Epstein-Barr virus; *GM-CFU*, granulocyte-macrophage colony forming unit; *HcY*, homocysteine; *HHV6*, human herpes virus 6; *HIV*, human immunodeficiency virus; *MMA*, methylmalonic acid; *SCN*, severe congenital neutropenia; *TMP-SMX*, trimethoprim-sulfamethoxazole; *WBC*, white blood cell.

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Moerdler S, LaTuga MS. Neonatal neutropenia. *NeoReviews.* 2018:19(1):e22–e28.

Orkin SH, Nathan DG, Ginsburg D, et al. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood.* 8th ed. Philadelphia: Saunders; 2015.

III. THROMBOCYTOPENIA AND IMPAIRED PLATELET FUNCTION

A. Definition of Thrombocytopenia

1. Defined as platelet count <150,000/μL.
2. See Table 14.1 for age-specific values.

B. Bleeding Risk with Thrombocytopenia

1. Risk of clinically significant bleeding is related to both platelet function and number. Unlikely with platelet counts >30,000/μL in the absence of other complicating factors.[14]
2. Risk of severe bleeding (CNS hemorrhage, gross hematuria, melena/hematochezia, hematemesis) increases with platelet counts <10,000/μL.[14]

C. Evaluation of Thrombocytopenia[15,16]

1. Platelet size: Large = mean platelet volume (MPV) >11 fL, normal = MPV 7 to 11 fL, small = MPV <7 fL.
   a. Large platelets suggest increased marrow production in destructive processes (e.g., immune thrombocytopenia [ITP]) or some congenital disorders.
   b. Small platelets suggest production defects, typically seen in congenital disorders.
2. Peripheral blood smear: Confirm platelet count, evaluate size and morphology, and rule out artifact platelet aggregation (i.e., due to artificial clumping in EDTA tube).
3. Immature platelet fraction: Correlates with measure of reticulated platelets, which reflects thrombopoiesis. Increases with peripheral destruction; is normal/low with bone marrow failure.
4. Bone marrow aspiration: Obtain if systemic symptoms concerning for underlying malignancy, involvement other cell lines, and/or blasts on smear. Differentiates decreased production versus increased destruction.

D. Causes of Thrombocytopenia and Impaired Platelet Function

1. See Table 14.9 for an approach to the differential of thrombocytopenia.
2. See Table 14.10 for differential of abnormal platelet function.

E. Management of Thrombocytopenia

1. **ITP**[17]
   a. Pathophysiology: Immune-mediated destruction of circulating platelets.
   b. Presentation: Otherwise healthy 2- to 10-year-old child with sudden bruising or bleeding after recent mild illness or vaccination, isolated thrombocytopenia (platelets <100,000/μL), and peripheral smear with thrombocytopenia and reticulated large platelets.
   c. Diagnostic testing: No additional testing needed if presentation consistent with ITP. If persists >3 to 6 months, pursue further workup: Infection testing (human immunodeficiency virus, hepatitis C, *Helicobacter pylori* infection), antinuclear antibody, anticardiolipin

TABLE 14.9

APPROACH TO THROMBOCYTOPENIA

ACQUIRED		
Destructive • Smear: large platelets • Increased IPF • Bone marrow: normal-increased megakaryocytes	Immune-mediated	Immune thrombocytopenia (ITP) Evans Syndrome: ITP + autoimmune hemolytic anemia Autoimmune disorders (antiphospholipid antibody syndrome, systemic lupus erythematosus) Drug-induced thrombocytopenia (heparin-induced thrombocytopenia) Neonatal alloimmune thrombocytopenia[a] Neonatal autoimmune thrombocytopenia[a]
	Platelet consumption	Thrombotic microangiopathies (TMAs; e.g., HUS, TTP) Disseminated intravascular coagulation (DIC) Kasabach-Merritt syndrome (giant cavernous hemangioma, other vascular malformation) Major surgery/trauma/burn
	Mechanical destruction	Extracorporeal membrane oxygenation (ECMO) Hemodialysis
	Sequestration	Hypersplenism (sickle-cell disease, malaria)
Impaired platelet production • Smear: normal sized platelets • Low/normal IPF • Infiltration of bone marrow or reduced megakaryocytes	Infection	EBV, CMV, parvovirus, varicella, rickettsia, HIV, sepsis (DIC), congenital infection
	Nutritional deficiency	Folate, vitamin B12, iron deficiency
	Acquired bone marrow failure	Aplastic anemia, myelodysplastic syndromes, medications (chemotherapy), radiation
	Inherited bone marrow failure	Fanconi Anemia, Schwachman-Diamond syndrome
	Infiltrative bone marrow disease	Leukemia, lymphoma, infectious granulomas, storage diseases
CONGENITAL		
Impaired platelet production	Small platelets	Wiskott-Aldrich syndrome[b] X-linked Thrombocytopenia
	Large/giant platelets	Bernard-Soulier syndrome[b] Gray platelet syndrome[b] *MYH9*-related disorders[b] Type 2B von Willebrand disease[b] Paris-Trousseau-Jacobsen syndrome DiGeorge syndrome
	Normal platelets	Congenital amegakaryocytic thrombocytopenia (CAMT) Thrombocytopenia with absent radius (TAR) syndrome[b] Amegakaryocytic thrombocytopenia with radioulnar synostosis Autosomal dominant thrombocytopenia

[a]Neonatal alloimmune thrombocytopenia occurs when maternal IgG antiplatelet antibodies cross placenta and destroy fetal platelets expressing a "foreign" antigen inherited from father. Neonatal autoimmune thrombocytopenia occurs in children of mothers with antiplatelet antibodies, often related to autoimmune disorders (e.g., immune thrombocytopenic purpura or systemic lupus erythematosus).

[b]These disorders typically also have disordered platelet function.

CMV, Cytomegalovirus; *EBV*, Epstein-Barr virus; *HIV*, human immunodeficiency virus, *HUS*, hemolytic uremic syndrome; *TTP*, thrombotic thrombocytopenic purpura.

Buchanan GR. Thrombocytopenia during childhood: what the pediatrician needs to know. *Pediatr Rev.* 2005:26(11):401–409.

Israels SJ, Kahr WH, Blanchette VS, et al. Platelet disorders in children: a diagnostic approach. *Pediatr Blood Cancer.* 2011:56(6):975–983.

TABLE 14.10

CAUSES OF PLATELET DYSFUNCTION

Medications	NSAIDs, Beta-lactam antibiotics, SSRIs
Underlying disease	Uremia, myeloproliferative disorders, myelodysplastic disorders
Inherited disorders	Glanzmann thrombasthenia
	Von Willebrand disease
	Bernard-Soulier syndrome
	Storage pool diseases: Wiskott-Aldrich syndrome, Thrombocytopenia with Absent Radii syndrome, Chediak-Higashi syndrome, Hermansky-Pudlak syndrome.

NSAIDs, Nonsteroidal anti-inflammatory drugs; *SSRIs*, selective serotonin reuptake inhibitors.

Israels SJ, Kahr WH, Blanchette VS, et al. Platelet disorders in children: a diagnostic approach. *Pediatr Blood Cancer.* 2011:56(6):975–983.

antibody and lupus anticoagulant (for antiphospholipid syndrome), serum immunoglobulins (IgG, IgA, IgM).[18]

d. Management: Observation if no or mild bleeding (e.g., skin manifestations). Treat if significant skin/mucosal bleeding with intravenous immunoglobulin (IVIG), steroids, *or* Anti-Rh (D) immune globulin in consultation with a hematologist.[18] Only transfuse platelets if life-threatening bleed, often with IVIG and high-dose steroids. May require emergent splenectomy.

2. **Thrombotic thrombocytopenic purpura (TTP)**[19]
   a. Pathophysiology: Decreased ADAMTS13 activity results in impaired processing of von Willebrand factor (vWF) multimers, which causes microthrombi.
   b. Presentation: Microangiopathic hemolytic anemia (MAHA), thrombocytopenia, acute kidney injury, fever, and neurologic symptoms (headache, hemiparesis, coma).
   c. Management: Early plasma exchange with fresh frozen plasma (FFP) and glucocorticoids. If high clinical suspicion, treat emergently before ADAMTS13 testing results.
3. **Hemolytic-uremic syndrome (HUS)**
   a. Pathophysiology: Due to Shiga toxin-producing *Escherichia coli* O157:H7 or *Shigella* diarrhea (sometimes *Streptococcus pneumoniae*, HIV).[20]
   b. Presentation: Early abdominal pain and bloody diarrhea, late thrombocytopenia and renal failure.
   c. Management: Supportive care with early/aggressive hydration, RBC/platelet transfusions as needed, antihypertensives, and neurologic monitoring.[21]
4. **Complement-mediated ("Atypical HUS")**
   a. Pathophysiology: Uncontrolled activation of complement on cell membranes.[21]
   b. Diagnostic testing: Complement panel, anti-CFH antibodies, consider genetic screening.
   c. Management: Eculizumab.

5. **Drug-induced thrombocytopenia**[22]
   a. Presentation: Lightheadedness, chills, fever, nausea/vomiting, purpura, petechiae ~7 days after starting medication (onset variable).
   b. Diagnostic testing for heparin-induced thrombocytopenia: +anti-PF4/heparin antibodies, +serotonin release assay.
   c. Management: Discontinue medication permanently, transfuse if severe thrombocytopenia to prevent intracranial or intrapulmonary hemorrhage.
6. **Neonatal alloimmune thrombocytopenia**[23]
   a. Pathophysiology: Maternal IgG antibodies (usually against paternally inherited PLA-1/HPA-1a) cross placenta and cause neonatal platelet destruction.
   b. Presentation: Severe thrombocytopenia, intracranial hemorrhage (ICH).
   c. Diagnostic testing: Identify antipaternal antibodies in infant circulation or maternal and infant platelet antigen typing.
   d. Management: Head ultrasound (US) to screen for ICH, transfuse platelets if <30,000/μL or signs of bleeding, consider IVIG if poor response to platelet transfusion.

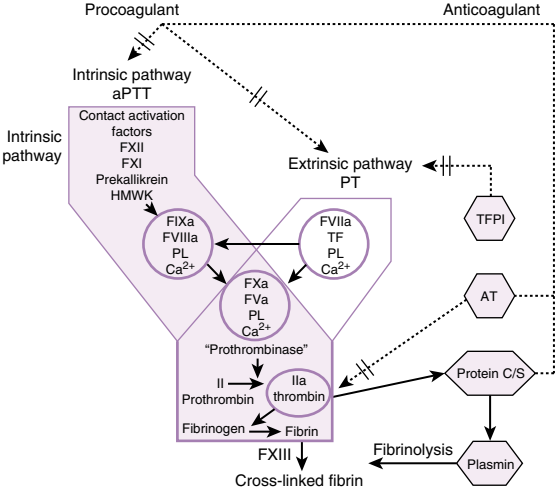
IV. COAGULATION

A. Evaluation of Coagulation and Platelet Function

1. Coagulation
   a. See Fig. 14.3 for coagulation cascade.
   b. **Activated partial thromboplastin time (aPTT)**: Measures intrinsic system and common pathway—Factors V, VIII, IX, X, XI, XII, fibrinogen, and prothrombin.
   c. **Prothrombin time (PT):** Measures extrinsic pathway and common pathway—Factors V, VII, X, fibrinogen, and prothrombin.
   d. **Thrombin time (TT):** Measures conversion of fibrinogen to fibrin. Prolonged with low or dysfunctional fibrinogen and anticoagulants (heparin, low molecular weight heparin, direct thrombin inhibitors), but not with common pathway abnormalities.
   e. **Reptilase time (RT):** Normal with heparin or direct thrombin inhibitors, but prolonged with fibrinogen abnormalities.
   f. **Mixing study:** Used in patients with abnormal clotting (i.e., prolonged PT, aPTT, or TT) to determine presence of factor deficiency (corrects with addition of normal plasma) or factor inhibitor (no correction would occur).
   g. **Dilute Russell viper venom time (dRVVT):** Russell viper activates factor X directly and is sensitive to inhibition by antiphospholipid antibodies. Prolonged dRVVT that corrects with addition of phospholipid to assay suggests presence of antiphospholipid antibodies (Lupus anticoagulants).[24]

Normal PT and PTT
- **von Willebrand disease (type 2B)**
- **Platelet dysfunction**
- **Thrombocytopenia**
- **Vascular abnormalities**
- **Factor XIII deficiency**
- **Fibrinolytic disorders**

Prolonged aPTT and normal PT
- **Factor VIII, IX, XI, XII deficiency or inhibitor**
- **Lupus anticoagulant**
- **von Willebrand disease**
- **Heparin**



Prolonged PT and aPTT
- **Normal TT:**
  - **Liver disease**
  - **Vitamin K deficiency (late)**
  - **Factor II/V/X deficiency or inhibitor**
  - **Combined factor deficiencies**
  - **Lupus anticoagulant**
- **Prolonged TT**
  - **DIC**
  - **Low fibrinogen**
  - **Dysfibrinogenemia**

Prolonged PT and normal aPTT
- **Factor VII deficiency or inhibitor**
- **Mild liver disease**
- **Vitamin K deficiency (early)**
- **Warfarin**

FIGURE 14.3

Coagulation cascade and differential diagnosis (DDX) of bleeding disorders. *aPTT*, Activated partial thromboplastin time; *DIC*, disseminated intravascular coagulation; *PT*, prothrombin time; *TT*, thrombin time. (Adapted from Rodriguez V. and Warad D, Pediatric coagulation disorders. *Pediatr Rev.* 2016:37[7]:279–290. Adaptation courtesy James Casella and Clifford Takemoto.)

h. **Fibrinogen:** Low levels (<50 to 100 mg/dL) causes impaired clot formation and prolongs PT and aPTT. Decreased in disseminated intravascular coagulation (DIC), liver disease, traumatic hemorrhage.
i. **D-dimer:** Fibrin degradation product increased with recent/ongoing fibrinolysis (e.g., deep vein thrombosis, pulmonary embolism, DIC, and many other clinical scenarios).
j. **Thromboelastography (TEG):** Whole blood test that rapidly measures time parameters of clot formation and overall clot strength, detects increased fibrinolysis. Useful for identification of coagulopathy and to guide transfusion in cardiac surgery and trauma.[25]

2. Platelet function[12]
   a. Always assess platelet number and use of platelet inhibitors (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]) before platelet function testing.
   b. **Light transmission aggregometry (LTA):** Measures platelet aggregation *in vitro*.[16]
   c. **Platelet function analyzer-100 (PFA-100):** Measures primary hemostasis (platelet adhesion, activation, and aggregation) *in vitro*.[16]
   d. **Bleeding time (BT):** Evaluates clot formation, including platelet number/function and vWF, *in vivo*. Technically challenging to perform and has been largely replaced by above tests.

B. Definition of Abnormal Coagulation

1. An incorrect anticoagulant-to-blood ratio will give inaccurate results.
2. See Table 14.11 at end of chapter which lists normal hematologic values for coagulation testing.

C. Causes and Management of Coagulopathy

1. **Medications**
   a. Heparin affects aPTT, thrombin time, dRVVT, and mixing studies.
   b. Warfarin affects PT, may mildly affect aPTT, and interferes with dRVVT by reducing the activity of vitamin K–dependent factors (II, VII, IX, X, protein C and S).
2. **Disseminated intravascular coagulation**
   a. Tissue damage (e.g., due to sepsis, trauma, malignancy) results in tissue factor release and systemic activation of coagulation system, consumption of coagulation factors and platelets, increased fibrin formation and fibrinolysis, MAHA, bleeding, and microthromboses.[26]
   b. Diagnosis: Prolonged P T and aPTT, decreased fibrinogen, thrombocytopenia, increased D-Dimer, increased fibrin degradation products, and presence of schistocytes on peripheral smear.
   c. Treatment: Address underlying condition and supportive care. May require FFP, cryoprecipitate, and/or platelet transfusions if active bleeding or high bleeding risk.
3. **Liver disease**
   a. The liver is the major site of synthesis of factors V, VII, IX, X, XI, XII, XIII.
   b. It is also involved in the synthesis of prothrombin, plasminogen, fibrinogen, proteins C and S, and ATIII.

4. **Vitamin K deficiency**
   a. Often secondary to liver disease, pancreatic insufficiency, malabsorption, exclusive breastfeeding, prolonged antibiotic use, malignancy.
   b. Necessary for synthesis of factors II, VII, IX, X, protein C, and protein S.[12]
   c. Treatment: Parenteral vitamin K corrects PT in 2 to 6 hours. Oral form corrects in 6-8 hours.[27] Give FFP if evidence of severe bleeding. Prothrombin complex concentrate can be given in cases of life-threatening hemorrhage or ICH.
5. **Hemophilia A (Factor VIII deficiency) and Hemophilia B (Factor IX deficiency)[28]**
   a. Etiology: X-linked recessive disorders. Females can be symptomatic carriers.
   b. Diagnosis: Prolonged aPTT that corrects with mixing study, normal PT, low factor assays. Mild forms can have normal aPTT.
   c. Classification of disease severity:[28]
      (1) Severe: <1% activity; spontaneous bleed (hemarthrosis, hematoma) without trauma.
      (2) Moderate: 1% to 5% activity; bleeding after minor trauma.
      (3) Mild: 5% to 40% activity; bleeding with surgery or significant trauma.
   d. Bleeding prophylaxis:
      (1) Home prophylaxis: Intravenous (IV) factor replacement (per individualized protocols) to maintain factor level >1 IU/dL to prevent spontaneous bleeds and preserve joint function. Initiate before onset of frequent bleeding, typically in 1- to 3-year-olds.[29] Emicizumab-kxwh is a bispecific antibody that is delivered subcutaneously (SQ) and can be used for prophylaxis.
      (2) Surgical prophylaxis: Factor replacement for goal factor level 80 to 100 IU/dL (major procedure) or 50 to 80 IU/dL (minor procedure) preoperatively and through postoperative period of bleeding risk.[28] Consult hematologist before any diagnostic or therapeutic procedure, including dental, endoscopy with biopsy, arterial blood gas, etc.
   e. Treatment of acute bleeds:
      (1) Always remember: **"Factor first!"** Do not delay first dose for evaluation.
      (2) Bolus dose FVIII or FVIX concentrate. May require additional doses.
      (3) Consult hematologist for all major bleeding.
      (4) See Table 14.12 for desired factor replacement level and dosing.
      (5) Half-life of Factor VIII: 8 to 12 hours. Half-life Factor IX: 18 to 24 hours.[28]
      (6) If suspected intracranial bleed, replete 100% factor level immediately on presentation and **before** additional diagnostic testing (e.g., CT scan).
      (7) Alternative treatments for mild Hemophilia A: Desmopressin (DDAVP) and antifibrinolytic agents (tranexamic acid, aminocaproic acid).

TABLE 14.12

DESIRED FACTOR REPLACEMENT IN HEMOPHILIA

Bleeding Site	Desired Level (%)
Minor soft tissue bleeding	20–30
Joint	40–70
Simple dental extraction	50
Major soft tissue bleeding	80–100
Serious oral bleeding	80–100
Head injury	100+
Major surgery (dental, orthopedic, other)	100+

NOTE: A hematologist should be consulted for all major bleeding and before surgery.
Round to the nearest vial; do not exceed 200%.

Dose calculation:

1. Units of factor VIII needed = weight (kg) × desired % replacement × 0.5.

2. Units of factor IX needed = weight (kg) × desired % replacement × 1.0 or 1.2.

Dosing adapted from Nathan D, Oski FA. *Hematology of Infancy and Childhood.* Philadelphia: WB Saunders; 1998.

(8) Can use cryoprecipitate (for Hemophilia A, not for Hemophilia B) or FFP if no factor available.

f. Factor inhibitors: IgG antibodies that develop with repeat factor exposure and complicate treatment. Patients with severe hemophilia A are at the highest risk.
   (1) Screen for inhibitors with inhibitor assay if poor clinical response to factor. Consider screen during initiation of factor treatment and preoperatively.
   (2) In the presence of inhibitors, patients may require higher doses of factor, recombinant FVIIa, or activated prothrombin complex concentrates.

g. Healthcare maintenance
   (1) Vaccinations: Given per routine schedule. Give prophylactic factor for intramuscular vaccines or give vaccine SQ with smallest gauge needle without factor prophylaxis.[28]
   (2) Physical activity: Avoid high contact (e.g., soccer, hockey) and high velocity (e.g., skiing) activities.[28]
   (3) Medications to avoid: Aspirin, NSAIDs, anticoagulants.
   (4) Many younger children will need a central venous catheter for factor delivery and must therefore follow strict fever guidelines.

6. **Von Willebrand (vW) disease**

a. Pathophysiology: Most common inherited bleeding disorder. Abnormal platelet adhesion and aggregation, low factor VIII.[30]

b. Diagnosis: Low circulating vWF antigen (VWF:Ag) and/or low vWF function on ristocetin-based platelet aggregation study (VWF:RCo), low or normal factor VIII activity, prolonged PFA-100. May require additional evaluation.

c. Classification:[30]
   (1) Type 1 (75% to 80% cases): Partial quantitative deficiency.
   (2) Type 2 (20% to 25%): Qualitative dysfunction.

(3) Type 3 (rare): Absence or near absence of vWF + markedly low factor VIII activity (can resemble Hemophilia A patient on labs and presentation).

d. Treatment:[30]

(1) Desmopressin (DDAVP): Stimulates vWF release. Given IV or intranasal. May be used as prophylaxis for minor surgeries or treatment for mild bleeding. Ineffective in Type 3, variable effect in Type 2. Patients should be tested for DDAVP response before using as prophylaxis.

(2) VWF-containing concentrates (Humate-P, Alphanate, or Wilate): Replaces vWF and factor VIII and derived from blood donors. Recombinant vWF available (VONVENDI). Used for severe bleeding events and surgery.

(3) Cryoprecipitate only appropriate for life-threatening situations if vWF concentrate unavailable.

(4) Alternative therapies: IV or oral antifibrinolytic therapy (tranexamic acid and aminocaproic acid) can be used to prevent or treat mild mucocutaneous bleeding alone or in conjunction with other therapies.

D. Causes of Hypercoagulability

1. Most thrombotic events are due to an acquired condition; however, an inherited thrombophilia is more likely if there is a family history, an unusual thrombus location, absence of an inciting factor, and/or recurrent thromboses.
2. See Table 14.13 for etiologies and evaluation of hypercoagulable states.
3. Acquired conditions associated with venous thromboembolism include endothelial damage (vascular catheters, sepsis, smoking, diabetes, hypertension, surgery, hyperlipidemia), disturbed blood flow (central venous lines, congenital heart disease), hyperviscosity (macroglobulinemia, polycythemia, sickle cell disease), platelet activation (essential thrombocytosis, oral contraceptives, heparin-induced thrombocytopenia), malignancy, inflammatory bowel disease, parenteral nutrition, nephrotic syndrome, paroxysmal nocturnal hemoglobinuria.

E. Thrombus Management

1. See Table 14.14 for anticoagulant use.
2. See Formulary for dosing and adjustment based on monitoring protocols.
3. Note: Children receiving anticoagulation therapy should be protected from trauma. Subcutaneous injections should be used when possible, and caution should be used with intramuscular injections. The use of antiplatelet agents and arterial punctures should be avoided.
4. See Table 14.15 for warfarin reversal guidelines.

V. BLOOD COMPONENT REPLACEMENT

A. Calculating Estimated Blood Volume (Table 14.16)

TABLE 14.13

HYPERCOAGULABLE STATES

Hypercoagulable Condition	Cause	Risk of VTE (Compared to General Population; Odds Radio)	Associated Test
Factor V Leiden (activated protein C resistance)	AD Factor V Leiden mutation.	3.77 (heterozygote)	1. Activated protein C resistance assay (screening test) 2. Factor V Leiden (DNA-based PCR assay)
Factor VIII, IX, XI abnormalities[a]	Inherited or acquired elevated factor levels.	6.7 (Factor VIII)	Factor VIII, IX, XI
Protein C and S deficiency[a]	AD. Homozygous more severe than heterozygous.	7.72 (protein C); 5.77 (protein S)	Protein C and S activity
Antithrombin III deficiency[a]	AD. Type I: low level and activity (homozygous not compatible with life). Type II: low activity or dysfunction.	9.44	Antithrombin III activity
Hyperhomocystinemia[a]	AR alteration in *MTFHR* gene.	1.27	1. Homocysteine level (fasting) 2. *MTHFR* genetic testing if homocysteine elevated
Prothrombin mutation	AD mutation in G20210A.	2.64 (heterozygote)	DNR-based PCR assay
Antiphospholipid antibodies[a]	Rarely inherited. Typically sporadic: spontaneous (primary) or secondary to autoimmune disorder (e.g., SLE) or infections.	High	Phospholipid-based clotting assays (aPTT, DRVVT) that correct with phospholipid addition ELISA assays: cardiolipin and β2-glycoprotein antibodies
High lipoprotein(a)	Levels determined by genetics and environment.	4.49	Lipoprotein(a) level
Plasminogen deficiency	Inherited hypoplasminogenemia (Type I) or dysplasminogenemia (Type II).		Plasminogen activity[b]

[a]These conditions may be inherited or acquired.

[b]Also consider testing tissue plasminogen activator (tPA) antigen and plasminogen activator inhibitor-1 (PAI-1) activity. Low tPA decreases fibrinolysis. Increased PAI-1 causes excess inhibition of tPA.

A hematologist should be consulted if initiating this workup.

AD, Autosomal dominant; *aPTT*, activated partial thromboplastin time; *AR*, autosomal recessive; *DRVVT*, dilute Russell's viper venom time; *ELISA*, enzyme-linked immunosorbent assay, *PCR*, polymerase chain reaction, *SLE*, systemic lupus erythematosus, *VTE*, venous thromboembolism.

Rodriguez V, Warad D. Pediatric coagulation disorders. *Pediatr Rev.* 2016;37(7):279–290.

Young G, Albisetti M, Bonduel M, et al. Impact of inherited thrombophilia on venous thromboembolism in children: a systematic review and meta-analysis of observational studies. *Circulation.* 2008;118(13):1373–1382.

TABLE 14.14

ANTICOAGULANTS

Medication	Indication	Contraindications and Adverse Effects	Monitoring	Reversal
Heparin/UFH (IV)	Acute treatment VTE, acute ischemic stroke (AIS), cerebral venous sinus thrombosis (CVST) without ICH. Prevention of thrombosis with cardiac catheterization, cardiopulmonary bypass surgery, extracorporeal circuits.	Heparin hypersensitivity, major active or high risk bleeding, platelets <50,000, known/suspected HIT, concurrent epidural therapy. Cautious use in patients with high bleeding risk or platelets <50,000/mm^3. Avoid IM injections and concurrent use drugs affecting platelet function (NSAIDs, aspirin, clopidogrel).	Anti-Xa level (goal 0.3–0.7 U/mL) or aPTT (1.5–2.5 times the control aPTT. The aPTT range in seconds (~50–80 sec) should be calibrated to anti-Xa of 0.3–0.7 U/mL.	Protamine sulfate
LMWH/enoxaparin (SQ)	Initial or ongoing therapy for VTE, CVST, AIS with cardioembolic source, recurrent AIS. Patients with history or risks for HIT.	HIT (lower risk than UFH) Chronic use (>6 months) use may decrease bone density.	Anti-Xa activity (goal 0.5–1 U/mL thrombosis, 0.1–0.3 U/mL for prophylaxis).	Protamine sulfate (partial neutralization)
Warfarin (PO)	Long-term anticoagulation after bridge from UFH or LMWH for VTE, CVST, AIS. Recurrent idiopathic VTE.	Interactions with diet and medications (see Table EC 14.A). Adjust dose in liver dysfunction, avoid in severe liver failure. Limited safety and efficacy data in newborns <3 months. Warfarin-induced skin necrosis has been reported in patients initiated without bridging anticoagulation. Teratogenic.	INR (2–3 with target 2.5, except with prosthetic cardiac valves) measured every 1–4 weeks.	Vitamin K (see Table 14.17)

DIRECT THROMBIN INHIBITORS				
Argatroban (IV)	Alternative to heparin in patients with HIT.	Avoid or alter dose in patients with hepatic impairment.	aPTT 1.5–2.5× baseline.	None
Bivalirudin (IV)	Inpatient treatment of VTE and prevention of thrombus during cardiac catheterization in patients with HIT.	Adjust dose with renal impairment.	aPTT 1.5–2.5× baseline.	None
Dabigatran (PO)[a]	Approved in adults to treat DVT/PE, reduce embolic risk in non-valvular AF.	*Studies ongoing for safety and efficacy in pediatric patients.*	None required.	Idarucizumab
FACTOR XA INHIBITORS				
Fondaparinux (SQ)[a]	Approved in adults to treat and prevent DVT/PE. Can be used in patients with HIT.	Adjust dose with renal impairment.	Anti-Xa level 0.5–1 mg/L.	None
Apixaban (PO)[a]	Approved in adults to treat and prevent DVT/ PE, reduction embolic risk in AF.	*Studies ongoing for safety and efficacy in pediatric patients.*	Can measure anti-Xa level.	Andexanet alfa
Rivaroxaban (PO)[a]	Approved in adults to treat and prevent recurrent DVT/PE, prevent non-valvular AF embolic complications.	*Studies ongoing for safety and efficacy in pediatric patients.*		

[a]These medications are undergoing Phase II/III trials for use in children and should not be used as first-line therapy.[44,45]

AF, Atrial fibrillation; *aPTT*, activated partial thromboplastin time; *DVT*, deep venous thrombosis; *HIT*, heparin-induced thrombocytopenia; *INR*, international normalized ratio; *IV*, intravenous; *LMWH*, low-molecular-weight heparin; *NSAID*, non-steroidal anti-inflammatory drug; *PE*, pulmonary embolism; *PO*, oral; *SQ*, subcutaneous; *UFH*, unfractionated heparin; *VTE*, venous thromboembolism.

Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *CHEST*. 2012;141(2):e737S–e801s.

Young G. Anticoagulation therapies in children. *Pediatr Clin North Am*. 2017;64(6):1257–1269.

TABLE 14.15

MANAGEMENT OF EXCESSIVE WARFARIN ANTICOAGULATION

INR and Bleeding	Intervention
INR 4–4.5 without serious bleeding	Hold or lower next warfarin dose. Recheck INR daily. For patients with high bleeding risk, consider standard dose of oral vitamin K.[a] When INR approaches therapeutic range, resume warfarin therapy.
INR ≥4.5 but <10 without serious bleeding	Hold warfarin. Recheck INR every 24 hr until <4. If high risk for bleeding, give standard dose of oral vitamin K[a]. When INR approaches therapeutic range, resume warfarin at a lower dose.
INR ≥10 without serious bleeding	Hold warfarin. Recheck INR every 12 hr. Give high dose oral vitamin K every 12–24 hr as necessary[b]. When INR approaches therapeutic range, resume warfarin at a lower dose.
Minor bleeding at any INR elevation	Hold warfarin. Monitor INR every 12–24 hr depending on bleeding severity. Give standard dose oral vitamin K and repeat as necessary if bleeding continues and INR not corrected at 24 hr[a]. Restart warfarin when INR approaches therapeutic range and when clinically appropriate at a lower dose.
Significant or life-threatening bleeding at any INR	Hold warfarin. Monitor INR every 4–6 hr. Administer high dose vitamin K IV, repeat as needed[b]. Transfusion of FFP (10–15 mL/kg IV), consider prothrombin complex concentrate; consult blood bank and/or hematology for dosing. Restart warfarin when INR approaches therapeutic range and when clinically appropriate at a lower dose.

[a]Standard dose Vitamin K: 0.03 mg/kg PO for patients <40 kg in weight; 1–2.5 mg PO for patients ≥40 kg. For rapid reversal, 0.5–2.5 mg IV slow infusion over 30 minutes. Expect INR reduction at 24–48 hr.

[b†]High dose Vitamin K: 0.06 mg/kg PO for patients <40 kg in weight; 5–10 mg for patients ≥40 kg. For emergent situations, 5–10 mg IV slow infusion over 30 minutes. Expect INR reduction at 12–14 hr.

NOTE: Always evaluate for bleeding risks and potential drug interactions. Do not give intramuscular Vitamin K to children on anticoagulants.

FFP, Fresh frozen plasma; *INR*, international normalized ratio; *IV*, intravenous; *PO*, by mouth.

The Johns Hopkins Hospital Children's Center pediatric policies, procedures, and protocols general care (Policy Number MDU043): Baltimore; 2019.

Adapted from: Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulation therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *CHEST*. 2012;141(2):e152S–e184S; Bolton-Maggs P, Brook L. The use of vitamin K for reversal of over-warfarinization in children. *Br J Haematol*. 2002;118:924–925.

TABLE 14.16

ESTIMATED BLOOD VOLUME

Age	Total Blood Volume (mL/kg)
Preterm infants	90–105
Term newborns	78–86
1–12 months	73–78
1–3 years	74–82
4–6 years	80–86
7–18 years	83–90
Adults	68–88

Data from Nathan D, Oski FA. *Hematology of Infancy and Childhood*. Philadelphia: WB Saunders; 1998.

B. Indications for and Expected Response Following Blood Transfusions

1. See Table 14.17 at the end of the chapter.
2. See Section VII. Online Content for information on directed donor transfusions.

C. Diagnosis and Management of Transfusion Reactions (Table 14.18)

D. Infectious Risks of Blood Transfusion

1. Transmission of infectious disease[31,32]
   a. Risk of HIV: 1 in 1,467,000.
   b. Human T-Lymphotropic virus (HTLV): 1 in 4,364,000.
   c. Hepatitis B: 1 in 765,000 to 1,006,000.
   d. Hepatitis C: 1 in 1,149,000.
   e. Parvovirus 1 in 10,000.
   f. Cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis A, parasites, tick-borne infections, and prior diseases may also be transmitted by blood products.
2. Sepsis related to bacterial contamination
   a. Risk of transmission of bacteria in RBCs is 1 in 5 million units.
   b. Risk of transmission in platelets is 1 in 100,000 units.
   c. Risk is higher in platelets because they are stored at room temperature.

VI. ADDITIONAL RESOURCES

A. Medications to avoid with G6PD Deficiency: http://g6pddeficiency.org/wp/living-with-g6pd-deficiency/drugs-to-avoid-list

B. Medications associated with thrombocytopenia: https://www.ouhsc.edu/platelets/ditp.html

C. Anemia Algorithm App: Created for adult patients, but provides useful framework for anemia differential.

REFERENCES

A complete list of references can be found online at www.expertconsult.com.

TABLE 14.18

TRANSFUSION REACTIONS

Reaction	Timeline	Pathophysiology	Signs/Symptoms	Labs	Treatment
Acute hemolytic transfusion reaction	Immediate	Blood group incompatibility results in intravascular hemolysis, acute renal failure, DIC	Fevers, chills, flank pain, tachycardia, hypotension, shock, hematuria, bleeding	ABO, CBC Hemolysis labs: DAT, haptoglobin, LDH, bilirubin +/– DIC labs: PT/aPTT, fibrinogen, D-dimer Urinalysis (evaluate for hemoglobinuria)	Stop transfusion Notify blood bank Supportive measures: IV normal saline to achieve UOP >1 mL/kg/hr, vasopressors as needed, nephrology consult if necessary for acute renal failure
Febrile nonhemolytic reaction	1–6 hr	Either cytokines from donor WBCs in product or recipient anti-neutrophil or anti-HLA antibodies against WBCs in donor product.	Fever, chills, diaphoresis	Exclude alternative reactions (AHTR, sepsis)	Decreased incidence with leukoreduced products Stop transfusion Notify blood bank Antipyretics Consider future pre-medication with antipyretics (little evidence supporting practice)
Urticarial reaction	Immediate	Reaction to donor plasma proteins	Urticarial rash, respiratory distress	Possible formation IgE anti-IgA antibody	Stop transfusion Notify blood bank Epinephrine/steroids for respiratory compromise Antihistamines Resolved mild (cutaneous only) allergic reaction is the only time that a transfusion may be resumed with remainder of product

TABLE 14.18

TRANSFUSION REACTIONS—Cont'd.

Reaction	Timeline	Pathophysiology	Signs/Symptoms	Labs	Treatment
Delayed transfusion reaction	>24 hr post-transfusion (up to 30 days)	Minor blood group antigen incompatibility results in extravascular hemolysis	Fatigue, jaundice, dark urine	Anemia +DAT Evidence of hemolysis New RBC Abs	Monitor Hb level closely Supportive care

ABO, Blood type; *AHTR*, acute hemolytic transfusion reaction; *aPTT*, activated partial thromboplastin time; *CBC*, complete blood count; *DAT*, direct antiglobulin test; *DIC*, disseminated intravascular coagulation; *Hb*, hemoglobin; *HLA*, human leukocyte antigen; *IV*, intravenous; *LDH*, lactate dehydrogenase; *PRBCs*, packed red blood cells; *PT*, prothrombin time; *RBC*, red blood cell; *UOP*, urine output; *WBCs*, white blood cells.

Delaney M, Wendel S, Bercovitz RS, et al. Transfusion reactions: prevention, diagnosis, and treatment. *Lancet*. 2016;388(10061):2825–2836.

Bachowski G, Borge D, Brunker PAR, et al. *A Compendium of Transfusion Practice Guidelines*. 3rd ed. American Red Cross; 2017.

TABLE 14.1

AGE-SPECIFIC BLOOD CELL INDICES

Age	Hb (g/dL)[a]	HCT (%)[a]	MCV (fL)[a]	MCHC (g/dL RBC)[a]	Reticulocytes	WBCs (×10³/mL)[b]	Platelets (10³/mL)[b]
26–30 weeks gestation[c]	13.4 (11)	41.5 (34.9)	118.2 (106.7)	37.9 (30.6)	—	4.4 (2.7)	254 (180–327)
28 weeks	14.5	45	120	31.0	(5–10)	—	275
32 weeks	15.0	47	118	32.0	(3–10)	—	290
Term[d] (cord)	16.5 (13.5)	51 (42)	108 (98)	33.0 (30.0)	(3–7)	18.1 (9–30)[e]	290
1–3 days	18.5 (14.5)	56 (45)	108 (95)	33.0 (29.0)	(1.8–4.6)	18.9 (9.4–34)	192
2 weeks	16.6 (13.4)	53 (41)	105 (88)	31.4 (28.1)	—	11.4 (5–20)	252
1 month	13.9 (10.7)	44 (33)	101 (91)	31.8 (28.1)	(0.1–1.7)	10.8 (4–19.5)	—
2 months	11.2 (9.4)	35 (28)	95 (84)	31.8 (28.3)	—	—	—
6 months	12.6 (11.1)	36 (31)	76 (68)	35.0 (32.7)	(0.7–2.3)	11.9 (6–17.5)	—
6 months–2 years	12.0 (10.5)	36 (33)	78 (70)	33.0 (30.0)	—	10.6 (6–17)	(150–350)
2–6 years	12.5 (11.5)	37 (34)	81 (75)	34.0 (31.0)	(0.5–1.0)	8.5 (5–15.5)	(150–350)
6–12 years	13.5 (11.5)	40 (35)	86 (77)	34.0 (31.0)	(0.5–1.0)	8.1 (4.5–13.5)	(150–350)
12–18 YEARS							
Male	14.5 (13)	43 (36)	88 (78)	34.0 (31.0)	(0.5–1.0)	7.8 (4.5–13.5)	(150–350)
Female	14.0 (12)	41 (37)	90 (78)	34.0 (31.0)	(0.5–1.0)	7.8 (4.5–13.5)	(150–350)
ADULT							
Male	15.5 (13.5)	47 (41)	90 (80)	34.0 (31.0)	(0.8–2.5)	7.4 (4.5–11)	(150–350)
Female	14.0 (12)	41 (36)	90 (80)	34.0 (31.0)	(0.8–4.1)	7.4 (4.5–11)	(150–350)

[a]Data are mean (–2 SD).

[b]Data are mean (±2 SD).

[c]Values are from fetal samplings.

[d]1 month, capillary hemoglobin exceeds venous: 1 hour: 3.6-g difference; 5 day: 2.2-g difference; 3 weeks: 1.1-g difference.

[e]Mean (95% confidence limits).

Hb, Hemoglobin; *HCT*, hematocrit; *MCHC*, mean cell hemoglobin concentration; *MCV*, mean corpuscular volume; *RBC*, red blood cell; *WBC*, white blood cell.

Data from Forestier F, Dattos F, Galacteros F, et al. Hematologic values of 163 normal fetuses between 18 and 30 weeks of gestation. *Pediatr Res*. 1986;20:342; Oski FA, Naiman JL. *Hematological Problems in the Newborn Infant*. Philadelphia: WB Saunders; 1982; Nathan D, Oski FA. *Hematology of Infancy and Childhood*. Philadelphia: WB Saunders; 1998; Matoth Y, Zaizor K, Varsano I, et al. Postnatal changes in some red cell parameters. *Acta Paediatr Scand*. 1971;60:317; and Wintrobe MM. *Clinical Hematology*. Baltimore: Williams & Wilkins; 1999.

TABLE 14.7

AGE-SPECIFIC LEUKOCYTE DIFFERENTIAL

Age	Total Leukocytes[a]	Neutrophils[b]		Lymphocytes		Monocytes		Eosinophils	
	Mean (Range)	Mean (Range)	%	Mean (Range)	%	Mean	%	Mean	%
Birth	18.1 (9–30)	11 (6–26)	61	5.5 (2–11)	31	1.1	6	0.4	2
12 hr	22.8 (13–38)	15.5 (6–28)	68	5.5 (2–11)	24	1.2	5	0.5	2
24 hr	18.9 (9.4–34)	11.5 (5–21)	61	5.8 (2–11.5)	31	1.1	6	0.5	2
1 week	12.2 (5–21)	5.5 (1.5–10)	45	5.0 (2–17)	41	1.1	9	0.5	4
2 weeks	11.4 (5–20)	4.5 (1–9.5)	40	5.5 (2–17)	48	1.0	9	0.4	3
1 month	10.8 (5–19.5)	3.8 (1–8.5)	35	6.0 (2.5–16.5)	56	0.7	7	0.3	3
6 months	11.9 (6–17.5)	3.8 (1–8.5)	32	7.3 (4–13.5)	61	0.6	5	0.3	3
1 year	11.4 (6–17.5)	3.5 (1.5–8.5)	31	7.0 (4–10.5)	61	0.6	5	0.3	3
2 years	10.6 (6–17)	3.5 (1.5–8.5)	33	6.3 (3–9.5)	59	0.5	5	0.3	3
4 years	9.1 (5.5–15.5)	3.8 (1.5–8.5)	42	4.5 (2–8)	50	0.5	5	0.3	3
6 years	8.5 (5–14.5)	4.3 (1.5–8)	51	3.5 (1.5–7)	42	0.4	5	0.2	3
8 years	8.3 (4.5–13.5)	4.4 (1.5–8)	53	3.3 (1.5–6.8)	39	0.4	4	0.2	2
10 years	8.1 (4.5–13.5)	4.4 (1.5–8.5)	54	3.1 (1.5–6.5)	38	0.4	4	0.2	2
16 years	7.8 (4.5–13.0)	4.4 (1.8–8)	57	2.8 (1.2–5.2)	35	0.4	5	0.2	3
21 years	7.4 (4.5–11.0)	4.4 (1.8–7.7)	59	2.5 (1–4.8)	34	0.3	4	0.2	3

[a]Numbers of leukocytes are $\times 10^3/\mu L$; ranges are estimates of 95% confidence limits; percentages refer to differential counts.

[b]Neutrophils include band cells at all ages and a small number of metamyelocytes and myelocytes in the first few days of life.

Adapted from Cairo MS, Brauho F. Blood and blood-forming tissues. In: Randolph AM, ed. *Pediatrics*. 21st ed. New York: McGraw-Hill; 2003.

TABLE 14.11

AGE-SPECIFIC COAGULATION VALUES

Coagulation Test	Preterm Infant (30–36 Weeks), Day of Life 1[a]	Term Infant, Day of Life 1	Day of Life 3	1 Month–1 Year	1–5 Years	6–10 Years	11–16 Years	Adult
PT (s)	13.0 (10.6–16.2)	15.6 (14.4–16.4)	14.9 (13.5–16.4)	13.1 (11.5–15.3)	13.3 (12.1–14.5)	13.4 (11.7–15.1)	13.8 (12.7–16.1)	13.0 (11.5–14.5)
INR		1.26 (1.15–1.35)	1.20 (1.05–1.35)	1.00 (0.86–1.22)	1.03 (0.92–1.14)	1.04 (0.87–1.20)	1.08 (0.97–1.30)	1.00 (0.80–1.20)
aPTT (s)[b]	53.6 (27.5–79.4)	38.7 (34.3–44.8)	36.3 (29.5–42.2)	39.3 (35.1–46.3)	37.7 (33.6–43.8)	37.3 (31.8–43.7)	39.5 (33.9–46.1)	33.2 (28.6–38.2)
Fibrinogen (g/L)	2.43 (1.50–3.73)	2.80 (1.92–3.74)	3.30 (2.83–4.01)	2.42 (0.82–3.83)	2.82 (1.62–4.01)	3.04 (1.99–4.09)	3.15 (2.12–4.33)	3.1 (1.9–4.3)
Bleeding time (min)[a]					6 (2.5–10)	7 (2.5–13)	5 (3–8)	4 (1–7)
Thrombin time (s)	14 (11–17)	12 (10–16)[a]		17.1 (16.3–17.6)	17.5 (16.5–18.2)	17.1 (16.1–18.5)	16.9 (16.2–17.6)	16.6 (16.2–17.2)
Factor II (U/mL)	0.45 (0.20–0.77)	0.54 (0.41–0.69)	0.62 (0.50–0.73)	0.90 (0.62–1.03)	0.89 (0.70–1.09)	0.89 (0.67–1.10)	0.90 (0.61–1.07)	1.10 (0.78–1.38)
Factor V (U/mL)	0.88 (0.41–1.44)	0.81 (0.64–1.03)	1.22 (0.92–1.54)	1.13 (0.94–1.41)	0.97 (0.67–1.27)	0.99 (0.56–1.41)	0.89 (0.67–1.41)	1.18 (0.78–1.52)
Factor VII (U/mL)	0.67 (0.21–1.13)	0.70 (0.52–0.88)	0.86 (0.67–1.07)	1.28 (0.83–1.60)	1.11 (0.72–1.50)	1.13 (0.70–1.56)	1.18 (0.69–2.00)	1.29 (0.61–1.99)
Factor VIII (U/mL)	1.11 (0.50–2.13)	1.82 (1.05–3.29)	1.59 (0.83–2.74)	0.94 (0.54–1.45)	1.10 (0.36–1.85)	1.17 (0.52–1.82)	1.20 (0.59–2.00)	1.60 (0.52–2.90)
vWF (U/mL)[a]	1.36 (0.78–2.10)	1.53 (0.50–2.87)			0.82 (0.47–1.04)	0.95 (0.44–1.44)	1.00 (0.46–1.53)	0.92 (0.5–1.58)
Factor IX (U/mL)	0.35 (0.19–0.65)	0.48 (0.35–0.56)	0.72 (0.44–0.97)	0.71 (0.43–1.21)	0.85 (0.44–1.27)	0.96 (0.48–1.45)	1.11 (0.64–2.16)	1.30 (0.59–2.54)

TABLE 14.11

AGE-SPECIFIC COAGULATION VALUES—Cont'd.

Factor X (U/mL)	0.41 (0.11–0.71)	0.55 (0.46–0.67)	0.60 (0.46–0.75)	0.95 (0.77–1.22)	0.98 (0.72–1.25)	0.97 (0.68–1.25)	0.91 (0.53–1.22)	1.24 (0.96–1.71)
Factor XI (U/mL)	0.30 (0.08–0.52)	0.30 (0.07–0.41)	0.57 (0.24–0.79)	0.89 (0.62–1.25)	1.13 (0.65–1.62)	1.13 (0.65–1.62)	1.11 (0.65–1.39)	1.12 (0.67–1.96)
Factor XII (U/mL)	0.38 (0.10–0.66)	0.58 (0.43–0.80)	0.53 (0.14–0.80)	0.79 (0.20–1.35)	0.85 (0.36–1.35)	0.81 (0.26–1.37)	0.75 (0.14–1.17)	1.15 (0.35–2.07)
PK (U/mL)[a]	0.33 (0.09–0.57)	0.37 (0.18–0.69)			0.95 (0.65–1.30)	0.99 (0.66–1.31)	0.99 (0.53–1.45)	1.12 (0.62–1.62)
HMWK (U/mL)[a]	0.49 (0.09–0.89)	0.54 (0.06–1.02)			0.98 (0.64–1.32)	0.93 (0.60–1.30)	0.91 (0.63–1.19)	0.92 (0.50–1.36)
Factor XIIIa (U/mL)[a]	0.70 (0.32–1.08)	0.79 (0.27–1.31)			1.08 (0.72–1.43)	1.09 (0.65–1.51)	0.99 (0.57–1.40)	1.05 (0.55–1.55)
Factor XIIIs (U/mL)[a]	0.81 (0.35–1.27)	0.76 (0.30–1.22)			1.13 (0.69–1.56)	1.16 (0.77–1.54)	1.02 (0.60–1.43)	0.97 (0.57–1.37)
D-dimer		1.47 (0.41–2.47)	1.34 (0.58–2.74)	0.22 (0.11–0.42)	0.25 (0.09–0.53)	0.26 (0.10–0.56)	0.27 (0.16–0.39)	0.18 (0.05–0.42)
FDPs[a]								Borderline titer = 1:25–1:50 Positive titer <1:50

Continued

TABLE 14.11

AGE-SPECIFIC COAGULATION VALUES—cont'd.

Coagulation Test	Preterm Infant (30–36 Weeks), Day of Life 1[a]	Term Infant, Day of Life 1	Day of Life 3	1 Month–1 Year	1–5 Years	6–10 Years	11–16 Years	Adult
COAGULATION INHIBITORS								
ATIII (U/mL)[a]	0.38 (0.14–0.62)	0.63 (0.39–0.97)			1.11 (0.82–1.39)	1.11 (0.90–1.31)	1.05 (0.77–1.32)	1.0 (0.74–1.26)
α_2-M (U/mL)[a]	1.10 (0.56–1.82)	1.39 (0.95–1.83)			1.69 (1.14–2.23)	1.69 (1.28–2.09)	1.56 (0.98–2.12)	0.86 (0.52–1.20)
C1-Inh (U/mL)[a]	0.65 (0.31–0.99)	0.72 (0.36–1.08)			1.35 (0.85–1.83)	1.14 (0.88–1.54)	1.03 (0.68–1.50)	1.0 (0.71–1.31)
α_2-AT (U/mL)[a]	0.90 (0.36–1.44)	0.93 (0.49–1.37)			0.93 (0.39–1.47)	1.00 (0.69–1.30)	1.01 (0.65–1.37)	0.93 (0.55–1.30)
Protein C (U/mL)	0.28 (0.12–0.44)	0.32 (0.24–0.40)	0.33 (0.24–0.51)	0.77 (0.28–1.24)	0.94 (0.50–1.34)	0.94 (0.64–1.25)	0.88 (0.59–1.12)	1.03 (0.54–1.66)
Protein S (U/mL)	0.26 (0.14–0.38)	0.36 (0.28–0.47)	0.49 (0.33–0.67)	1.02 (0.29–1.62)	1.01 (0.67–1.36)	1.09 (0.64–1.54)	1.03 (0.65–1.40)	0.75 (0.54–1.03)
FIBRINOLYTIC SYSTEM[a]								
Plasminogen (U/mL)	1.70 (1.12–2.48)	1.95 (1.60–2.30)			0.98 (0.78–1.18)	0.92 (0.75–1.08)	0.86 (0.68–1.03)	0.99 (0.7–1.22)
TPA (ng/mL)					2.15 (1.0–4.5)	2.42 (1.0–5.0)	2.16 (1.0–4.0)	4.90 (1.40–8.40)
α_2-AP (U/mL)	0.78 (0.4–1.16)	0.85 (0.70–1.0)			1.05 (0.93–1.17)	0.99 (0.89–1.10)	0.98 (0.78–1.18)	1.02 (0.68–1.36)
PAI (U/mL)					5.42 (1.0–10.0)	6.79 (2.0–12.0)	6.07 (2.0–10.0)	3.60 (0–11.0)

[a]Data from Andrew M, Paes B, Milner R, et al. Development of the human anticoagulant system in the healthy premature infant. *Blood.* 1987;70:165–172; Andrew M, Paes B, Milner R, et al. Development of the human anticoagulant system in the healthy premature infant. *Blood.* 1988;72(5):1651–1657; and Andrew M, Vegh P, Johnston M, et al. Maturation of the hemostatic system during childhood. *Blood.* 1992;8:1998–2005.

[b]aPTT values may vary depending on reagent.

α_2-AP, α_2-Antiplasmin; *α_2-AT*, α_2-antitrypsin; *α_2-M*, α_2-macroglobulin; *aPTT*, activated partial thromboplastin time; *ATIII*, antithrombin III; *FDPs*, fibrin degradation products; *HMWK*, high-molecular-weight kininogen; *INR*, international normalized ratio; *PAI*, plasminogen activator inhibitor; *PK*, prekallikrein; *PT*, prothrombin time; *TPA*, tissue plasminogen activator; *VIII*, factor VIII procoagulant; *vWF*, von Willebrand factor.

Adapted from Monagle P, Barnes C, Ignjatovic, V, et al. Developmental haemostasis. Impact for clinical haemostasis laboratories. *Thromb Haemost.* 2006;95;362–372.

TABLE 14.17

BLOOD PRODUCTS

Product	Contains	Indications	Dose	Volume of 1 Unit (U)	Change in blood count
PRBCs	Concentrated RBCs w/ Hct 55%–70%.	Generally Hb <7 gm/dL,[a] but consider clinical picture. Use typed and cross-matched products when possible. O− can be provided emergently without crossmatch if transfusion cannot be delayed. See Section VII. Online content for specific types of PRBCs.	10–15 mL/kg (at max 2–4 mL/kg/hr). RBCs must be transfused within 4 hours of leaving blood bank.	300–350 mL after processing	To determine volume necessary for desired Hct: PRBC volume (mL) = (EBV [mL] × [desired Hct − actual Hct])/Hct of PRBCs.[b]
Platelets		Severe (<10,000/μL) thrombocytopenia, symptomatic thrombocytopenia, to achieve platelets >50,000/μL before minor or >100,000/μL before major surgery or intracranial operation. Transfusion indications for neonates: Platelets <20,000/μL; platelets <30,000/μL + weight <1 kg, age <1 week, clinically unstable, history major bleed (e.g., IVH), current bleed, coagulopathy/DIC, preprocedure; platelets >50,000/μL only if significant bleed.	Children ≤30 kg[c]: 5–10 mL/kg or 1 equivalent unit per 5–10 kg. Children >30 kg: 1 apheresis unit. Transfuse as rapidly as able.	300 mL for 1 apheresis unit, 50 mL for 1 equivalent unit.	10 mL/kg increases platelets by 50,000/μL.
FFP	Physiologic quantities all coagulation factors[d]	Treat severe clotting factor deficiencies with active bleeding (DIC, Vitamin K deficiency with active bleeding, TTP) or before invasive procedure. Combine with vitamin K for emergency reversal warfarin.	15 mL/kg; repeat PRN.	250–300 mL	1 unit activity of all factors except V and VIII.

TABLE 14.17

BLOOD PRODUCTS—cont'd.

Product	Contains	Indications	Dose	Volume of 1 Unit (U)	Change in blood count
Cryoprecipitate	Enriched factors VIII and XIII, vWF, fibrinogen, fibronectin	For hypofibrinogenemia, dysfibrinogenemia.	Children <5 kg: 1 single donor unit. Children 5–50 kg: 1 unit per 5–10kg. Children >50 kg: 1–2 pools (5–10 units).	10–15 mL for 1 unit, 50–100 mL for a pool.	1units contains approximately 80 units factor VIII, 150 mg fibrinogen.[e]

[a]Restrictive transfusion protocol with Hb threshold 7 g/dL associated with fewer transfusions without differences in clinical outcomes.

[b]Hct of PRBCs is typically 55% to 70% depending on storage anticoagulant.

[c]1 unit of apheresis platelets is derived from a single donor and contains >3 x 10^{11} platelets/mL. 1 equivalent unit is ~1/5th-1/6th an apheresis unit. Single donor platelet concentrates are derived from a single donor and contain >5.5 x 10^{10} platelets in approximately 50 mL. 4-6 equivalent units or platelet concentrates can be pooled to make equivalent of 1 apheresis unit.

[d]FFP does not include platelets or fibrinogen. Does include anticoagulant factors (antithrombin III, proteins C/S). Note: FFP unlikely to have significant effect when INR ≤1.6.[46]

[e]This is an estimation. 1 unit of cryoprecipitate is derived from 500mL of blood from 1 donor. A pool is 5 individual donor units pooled together.

DIC, Disseminated intravascular coagulation; *EBV*, estimated blood volume; *FFP*, fresh frozen plasma; *Hct*, Hb/hematocrit; *PRBCs*, packed red blood cells; *PRN*, as needed; *RBCs*, red blood cells; *TTP*, thrombotic thrombocytopenic purpura; *vWF*, von Willebrand Factor.

Bachowski G, Borge D, Brunker PAR, et al. *A Compendium of Transfusion Practice Guidelines*. 3rd ed. American Red Cross; 2017

Behrman RE, Kliegman RM, Jenson AH. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia: Saunders; 2004.

TABLE EC 14.A

MEDICATIONS THAT INFLUENCE WARFARIN THERAPY

Significant Increase in INR	Significant Decrease in INR
Amiodarone	Amobarbital
Anabolic steroids	Aprepitant
Bactrim (TMP/SMZ)	Butabarbital
Chloramphenicol	Carbamazepine
Disulfiram	Dicloxacillin
Fluconazole	Griseofulvin
Isoniazid	Methimazole
Metronidazole	Phenobarbital
Miconazole	Phenytoin
Phenylbutazone	Primidone
Quinidine	Propylthiouracil
Sulfinpyrazone	Rifabutin
Sulfisoxazole	Rifampin
Tamoxifen	Secobarbital
Moderate Increase in INR	**Moderate Decrease in INR**
Cimetidine	Atazanavir
Ciprofloxacin	Efavirenz
Clarithromycin	Nafcillin
Delavirdine	Ritonavir
Efavirenz	
Itraconazole	
Lovastatin	
Omeprazole	
Propafenone	

Numerous medications not listed in this table can affect warfarin administration.
INR, International normalized ratio; *TMP/SMZ*, trimethoprim/sulfamethoxazole.

VII. ONLINE CONTENT

A. Specific PRBC Types

1. Leukoreduced RBCs: 99.9% white blood cells (WBCs) removed to reduce risks of pathogen transmission (e.g., CMV), HLA alloimmunization and febrile nonhemolytic transfusion reaction.
2. Washed RBCs: Removal of plasma proteins in products for recipients with history of anaphylactic transfusions reactions or complete IgA deficiency.
3. CMV-safe RBCs: Leukoreduced units likely comparable to low transmission risk with CMV-seronegative units (from donors with negative CMV serology). Preferred for vulnerable populations: CMV-negative bone marrow transplant or solid organ recipients, immunodeficient patients, premature or low birth weight infants, intrauterine transfusions, pregnant women.
4. Irradiated blood products: Inactivated donor lymphocytes capable of causing transfusion-associated graft versus host disease (GVHD).[33] Used for susceptible patients: leukemia, lymphoma, BMT, solid organ transplant, intensive chemotherapy, known/suspected immune deficiency, intrauterine transfusions, neonate transfusions, patients receiving T-cell suppressive therapy. Also necessary in directed donation from a relative.

B. Directed Donor Transfusions

1. When to consider directed donor:
   a. Chronic transfusion programs (e.g., "blood buddy" programs), where donors provide antigen-matched red cells repetitively for the same patient requiring frequent transfusions (e.g., thalassemia, sickle cell disease).
   b. NAIT, where maternal platelets lack causative antigens and represent optimal therapy.
2. Reasons to not consider directed donor:
   a. Practice not often feasible. Specific screening, donation, product testing, and processing causes delays (2 to 3 days or more) when compatible blood is often readily available.
   b. Directed donor may not be compatible: must be at least ABO/RhD compatible, and may require other RBC antigen compatibility if recipient has antibodies.
   c. Directed donors less likely to be truthful in donor screening, causing potential increased infection risk.
   d. Products from a relative require irradiation for increased risk of transfusion-related graft-versus-host disease (GVHD).
   e. If RBC donor is also a potential bone marrow transplant donor for recipient, donation increases risk of development of donor-directed human leukocyte antigen (HLA) antibodies in recipient, which may cause graft failure.

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Chapter 15

Immunology and Allergy

Carlos A. Salgado, MD

I. ALLERGIC RHINITIS[1–6]

A. Epidemiology

1. Most common pediatric chronic medical condition: Prevalence in children up to 40%.
2. Increases risk for recurrent otitis media, asthma, and acute and chronic sinusitis.
3. Risk factors: Atopic family history, serum immunoglobulin (Ig) E >100 IU/mL before age 6 years, higher socioeconomic status, and infant exposure to maternal smoking in utero and during early childhood.

B. Diagnosis

1. **History:**
   a. Allergen-driven mucosal inflammation leading to cyclical exacerbations or persistent symptoms.
   b. Symptoms: Nasal (congestion, rhinorrhea, and pruritus), ocular (pruritus and tearing), and postnasal drip (sore throat and cough).
   c. Patterns: Seasonal (depending on local allergens) versus perennial (with seasonal peaks)
   d. Coexisting atopic diseases common (eczema, asthma, and food allergy).
2. **Physical examination:**
   a. Allergic facies with shiners, mouth breathing, transverse nasal crease ("allergic salute"), and accentuated lines below lower eyelids (Dennie-Morgan lines).
   b. May have swollen nasal turbinates.
   c. Injected sclera with or without clear discharge, conjunctival cobblestoning.
3. **Diagnostic studies:**
   a. Diagnosis can be made on clinical grounds, however allergy with skin tests or allergen-specific IgE testing can identify specific allergic sensitivities.
   b. Total IgE, peripheral blood eosinophil count and imaging studies are not recommended due to poor specificity.

C. Differential Diagnosis

Vasomotor/nonallergic rhinitis (hypersensitivity to scents, alcohol, or changes in climate), infectious rhinitis, adenoid hypertrophy, rhinitis medicamentosa (rebound rhinitis from prolonged use of nasal vasoconstrictors), sinusitis, nonallergic rhinitis with eosinophilia syndrome, and nasal polyps.

D. Treatment

1. **Allergen avoidance:**
   a. Relies on identification of triggers, most common of which are pollens, fungi, dust mites, insects, and animals.
   b. HEPA filter may be useful when animal allergens are a concern.
   c. Thorough housecleaning and allergy-proof bed coverings can be useful.
2. **Oral antihistamines:**
   a. First-line treatment for mild or episodic symptoms or young patients who cannot tolerate or refuse nasal sprays.
   b. Second- and third-generation preparations preferable (loratadine, desloratadine, fexofenadine, cetirizine, and levocetirizine) due to reduced central nervous system (CNS) side effects.
   c. Adverse effects: Sedation and anticholinergic side effects (more prominent with first-generation agents).
3. **Intranasal corticosteroids** (fluticasone, mometasone, budesonide, flunisolide, ciclesonide, and triamcinolone):
   a. First-line for persistent or moderate-to-severe symptoms, as it is the most effective single maintenance therapy for nasal congestion and reduction of ocular symptoms.
   b. Maximal therapeutic benefit when used over several days or weeks. No effect with as-needed use.
   c. Adverse effects: Nasal irritation, sneezing, bleeding, and potential risk of reduction in growth velocity and adrenal suppression at high doses, especially in patients on multiple steroid preparations. Growth monitoring recommended.
   d. Administration: Clear mucus crusting, keep head pointed slightly down and avoid pointing medication at nasal septum.
4. **Leukotriene inhibitors** (montelukast):
   a. More effective in combination with antihistamines.
   b. Consider in patients with concomitant asthma.
5. **Intranasal antihistamines** (azelastine and olopatadine):
   a. Effective for acute symptoms; faster onset of action than glucocorticoid nasal spray.
   b. Adverse effects: Bitter taste, systemic absorption with potential for sedation.
6. **Intranasal combination agents** (azelastine/fluticasone): Useful for patients with moderate-to-severe allergic rhinitis.
7. **Immunotherapy:**
   a. Success rate is high when patients are chosen carefully and when performed by an allergy specialist.
   b. Consider when symptoms are inadequately controlled with medications and allergen avoidance.
   c. In addition to traditional subcutaneous immunotherapy, sublingual products have now been approved for several allergens.
   d. Not recommended for patients with poor adherence to therapy or those with poorly controlled asthma.

e. Not well studied in children younger than 5 years.
f. May reduce risk for future development of asthma, and treatment of allergic rhinitis may improve asthma control.

8. **Nasal irrigation with hypertonic saline:** Use distilled, sterile, or boiled water (at least 3 minutes) for homemade solutions.
9. **Ophthalmic agents:** Can be used to treat allergic conjunctivitis. Up to 60% of patients with allergic rhinitis have concomitant conjunctivitis. Avoid the use of steroids unless under the direction of an ophthalmologist.
   a. Mast cell stabilizers: Cromolyn sodium, lodoxamide-tromethamine, nedocromil, and pemirolast.
   b. H_1-antagonists and mast cell stabilizers: Alcaftadine, azelastine HCl, bepotastine, emedastine, epinastine, ketotifen fumarate, and olopatadine.

II. FOOD ALLERGY[7–12]

A. Epidemiology

1. Prevalence is 6% to 8% in young children and 3% to 4% in adolescence.
2. Most common allergens in children: Milk, eggs, peanuts, tree nuts (e.g., cashew, walnut), soy, fish, shellfish, and wheat.

B. Manifestations of Food Allergy

1. Often a combination of several syndromes; symptoms can occur within minutes to hours of ingesting food.
2. Diagnosis requires both sensitization (demonstration of allergen-specific IgE) and clinical symptoms after exposure to allergens.
3. **Anaphylaxis:** See Chapter 1.
4. **Skin syndromes:**
   a. **Urticaria/angioedema:**
      (1) Chronic urticaria is rarely related to food allergy.
      (2) Acute urticaria due to food allergy may be a risk factor for future anaphylaxis.
   b. **Atopic dermatitis/eczema:**
      (1) Food allergy is more common in patients with atopic dermatitis.
      (2) Even if not apparent by history, at least one-third of children with moderate to severe atopic dermatitis have IgE-mediated food allergies.
5. **Gastrointestinal syndromes:**
   a. **Oral allergy syndrome:**
      (1) Pollen-associated food allergy caused by cross-reactivity of antibodies to pollens (e.g., apple and tree pollen).
      (2) Pruritus of oral mucosa after ingestion of certain fresh fruits and vegetables in patients with pollen allergies. Rarely results in edema of oral mucosa, or progresses beyond mouth/throat.
      (3) Inciting antigens are usually denatured by cooking.

b. **Allergic eosinophilic gastroenteritis, esophagitis: see Chapter 12**
c. **Food protein induced enterocolitis syndrome (FPIES):**
   (1) Presents in infancy.
   (2) Vomiting and diarrhea (may contain blood); when severe, may lead to lethargy, dehydration, hypotension, acidosis.
   (3) Most commonly associated with milk and soy, but may occur with a wide variety of foods (e.g., rice, oat, fruits, and vegetables).
d. **Infantile proctocolitis:**
   (1) Confined to distal colon and can present with diarrhea or blood-streaked and mucous-containing stools.
   (2) Symptoms usually resolve within 72 hours of stopping offending agent; rarely leads to anemia.

C. Diagnosis of Food Allergy (Fig. 15.1)

1. **History and physical examination:**
   a. Identify specific foods and whether fresh vs. cooked.
   b. Establish timing and nature of reactions.
2. **Skin testing:**
   a. Skin prick test has poor positive predictive value, but very good negative predictive value.
   b. Patient must not be taking antihistamines.
   c. Widespread skin conditions (e.g., dermatographism, urticaria, severe eczema) may limit ability to perform skin tests.
3. **Measurement of allergen-specific IgE:**
   a. Similar to skin tests, it has poor positive predictive value and excellent negative predictive value.
   b. Levels above a certain range (variable amongst different antigens) have increasing positive predictive value.
   c. Useful in patients with dermatologic conditions that preclude skin testing.
   d. Component testing (measuring IgE to specific food proteins rather than crude extracts) may improve diagnostic accuracy for peanut and possibly other foods.
4. **Oral food challenges:**
   a. Can verify clinical reactivity to a specific food allergen or document that a food allergy has been outgrown.
   b. Must be performed under close medical supervision with emergency medications readily available.
   c. Patient must not be taking antihistamines.
   d. Most accurate when double-blinded using graded doses of disguised food.
5. **Trial elimination diet:**
   a. Helpful if improvement with removal of food from diet.
   b. Essential, especially in infants and for non-IgE-mediated food allergy.

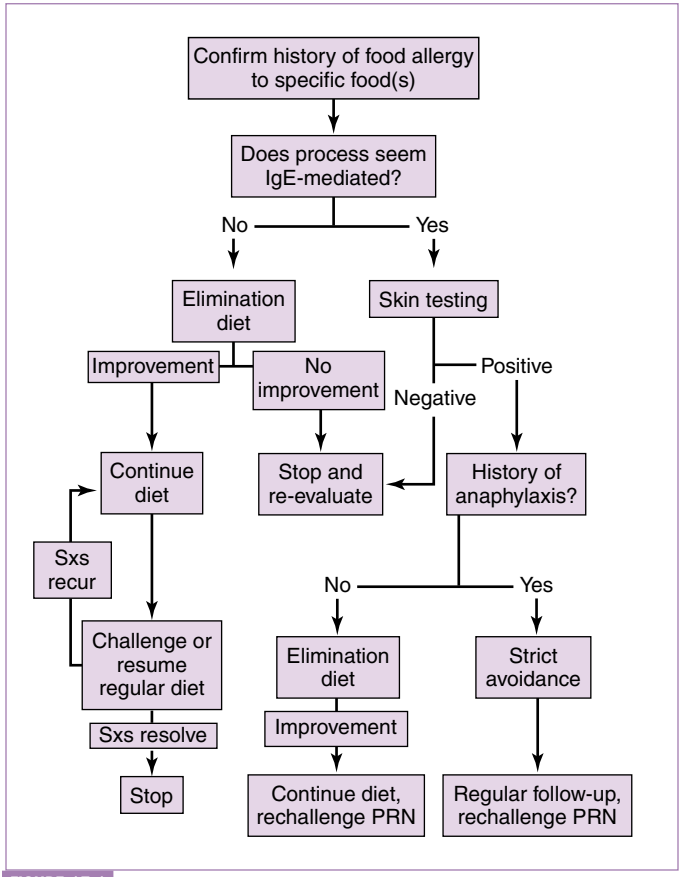

FIGURE 15.1

Evaluation and management of food allergy. *IgE*, Immunoglobulin E; *PRN*, as needed *Sxs*, symptoms. (Data from Wood RA. The natural history of food allergy. *Pediatrics*. 2003;111:1631–1637.)

D. Differential Diagnosis

1. **Food intolerance:** Nonimmunologic, based on toxins or other properties of foods leading to adverse effects.
2. **Malabsorption syndromes:**
   a. Cystic fibrosis, celiac disease (see Chapter 12), and lactase deficiency.
   b. Gastrointestinal malformations.

E. Treatment

1. **Allergen avoidance:**
   a. Most important intervention for all types of food allergy.
   b. Patients must pay close attention to food ingredients. Implement an *"If you can't read it, you can't eat it"* approach to avoid risky unlabeled foods.
   c. Nutritional counseling and regular growth monitoring are recommended.
2. **Nonanaphylactic angioedema/urticaria:**
   a. Antihistamines or corticosteroids, based on severity and duration of symptoms.
   b. Omalizumab used for chronic urticaria.
3. **Atopic dermatitis:** Symptomatic control (see Chapter 8).
4. **Anaphylaxis:**
   a. See Chapter 1 for management of anaphylaxis.
   b. Prescribe epinephrine auto-injector for all at-risk patients. Counsel to call 9-1-1 if using.
   c. Develop Anaphylaxis Action Plan indicating specific allergies, symptoms for which to observe, and medications to be administered.
   d. Counsel families to always have epinephrine auto-injector readily available.
   e. Make school aware of Anaphylaxis Action Plan and ensure they can administer lifesaving medications.
5. **Food-specific immunotherapy** is under investigation. It is used to induce clinical desensitization to specific allergens.

F. Natural History

1. About 50% of milk, egg, soy, and wheat allergies are outgrown by school age.
2. Peanut, tree nut, and shellfish allergies are outgrown only in 10% to 20%.
3. Skin tests and allergen-specific IgE may remain positive, even though symptoms resolve.

III. DRUG ALLERGY[13,14]

A. Definition

1. **Drug allergy:** Immunologically mediated response to an agent in a sensitized person.
2. **Drug intolerance:** Undesirable pharmacologic effect.
3. Although 10% of patients report penicillin allergy, after evaluation, about 90% of these individuals can tolerate penicillin.

B. Diagnosis

1. Cutaneous manifestations are the most common presentation for drug allergic reactions.
2. **Diagnostic studies:** Penicillin is the only drug for which standardized skin testing reagents and procedures have been validated. Skin testing or supervised graded dose challenge may be done with caution for other

medications, but the results must be carefully considered in the context of the clinical pictures, as both false positive and false negative results are common.

C. Management (Fig. 15.2)

1. **Avoidance**: When able, utilize alternative therapy.
2. **Desensitization:** Progressive administration of an allergenic substance to render immune system less reactive.

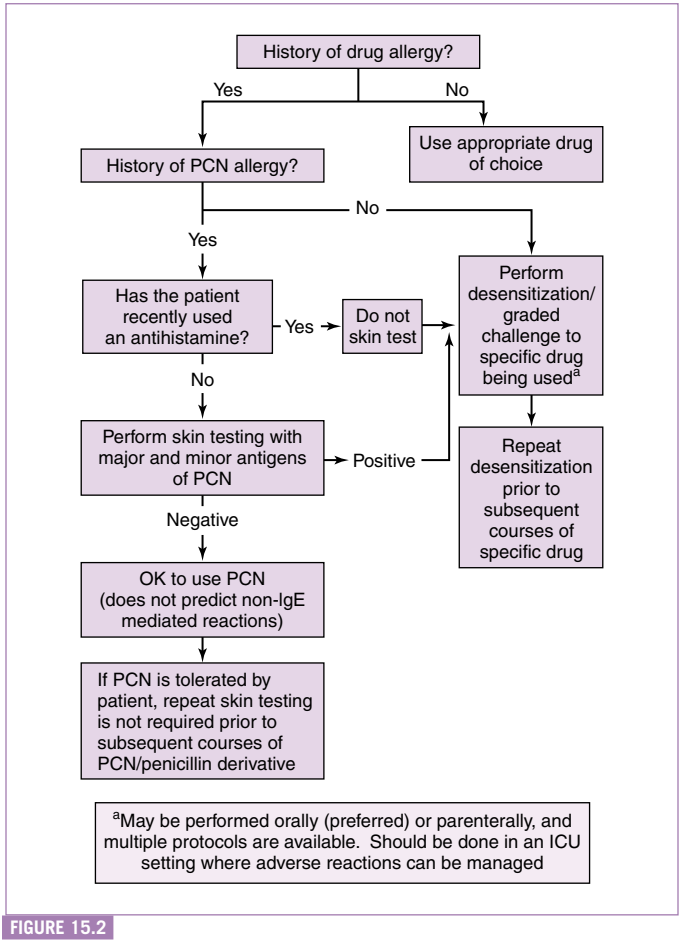

FIGURE 15.2

Evaluation and management of penicillin allergy. *ICU*, Intensive care unit; *IgE*, immunoglobulin E; *PCN*, penicillin. (Adapted from Mirakian R, Leech SC, Krishna MT, et al. Management of allergy to penicillins and other beta-lactams. *Clin Exp Allergy*. 2015;45:300.)

TABLE 15.1

WHEN TO SUSPECT IMMUNODEFICIENCY

Recurrent Infections	Opportunistic Infections	Severe Infections	Other Conditions
Six or more new infections in 1 year Recurrent tissue or organ abscesses Two or more serious sinus infections in 1 year Two or more pneumonias in 1 year	*Pneumocystis jiroveci* pneumonia *Pseudomonas* sepsis Invasive infection with *Neisseria* spp.	Two or more months of antibiotics with little effect Sepsis in the absence of a known risk (e.g., indwelling vascular catheter, neutropenia) Bacterial meningitis Pneumonia with empyema Resistant superficial or oral candidiasis	Failure to gain weight or grow normally Family history of immunodeficiency or unexplained early deaths Lymphopenia in infancy Complications from a live vaccine Part of a syndrome complex (e.g., Wiskott-Aldrich [with thrombocytopenia, eczema], DiGeorge syndrome [with facial dysmorphism, congenital cardiac disease, hypoparathyroidism])

Adapted from Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameters for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol.* 2015;136(5):1186–1205; and Ballow M. Approach to the patient with recurrent infections. *Clinic Rev Allerg Immunol.* 2008;34:129.

3. **Graded challenge:** Administration of progressively increasing doses of a drug until full dose is reached; does not modify a patient's response to the drug, but is used to optimize safety when the history and test results are not completely reassuring.

IV. EVALUATION OF SUSPECTED IMMUNODEFICIENCY

See Tables 15.1 and 15.2.[15–21]

V. IMMUNOGLOBULIN THERAPY[22–25]

A. Intravenous Immunoglobulin (IVIG)

1. **Indications:**
   a. Replacement therapy for antibody-deficient disorders:
      (1) Children with severe hypogammaglobulinemia (<100 mg/dL) may benefit from a higher total *loading* dose in two separate doses a few days apart, followed by standard dosing every 3 to 4 weeks.
      (2) Useful in human immunodeficiency virus (HIV), antibody deficiency (IgG concentration <400 mg/dL from failure to form antibodies to common antigens), recurrent serious bacterial infections, or prior to measles prophylaxis.

TABLE 15.2

EVALUATION OF SUSPECTED IMMUNODEFICIENCY

Suspected Functional Abnormality	Clinical Findings	Initial Tests	More Advanced Tests
Humoral (e.g., common variable immunodeficiency, X-linked agammaglobulinemia, IgA deficiency)	Sinopulmonary and systemic infections (pyogenic bacteria) Enteric infections (enterovirus, other viruses, *Giardia* spp.) Autoimmune diseases (immune thrombocytopenia, hemolytic anemia, inflammatory bowel disease)	Immunoglobulin levels (IgG, IgM, IgA) Antibody levels to T-cell-dependent protein antigens (e.g., tetanus or pneumococcal conjugate vaccines) Antibody levels to T-cell-independent polysaccharide antigens in a child ≥2 years (e.g., pneumococcal polysaccharide vaccine, such as Pneumovax)	B-cell enumeration Immunofixation electrophoresis
Cell-mediated immunity (e.g., severe combined immunodeficiency, DiGeorge syndrome)	Pneumonia (pyogenic bacteria, fungi, *Pneumocystis jiroveci*, viruses)	TRECs newborn screening[a] Total lymphocyte counts HIV ELISA/Western blot/PCR	T-cell enumeration (CD3, CD4, CD8) In vitro T-cell proliferation to mitogens, antigens, or allogeneic cells Chromosomal Microarray or FISH 22q11 for DiGeorge deletion
Phagocytosis (e.g., chronic granulomatous disease (CGD), leukocyte adhesion deficiency, Chédiak-Higashi syndrome)	Cutaneous infections, abscesses, lymphadenitis (staphylococci, enteric bacteria, fungi, mycobacteria) Poor wound healing	WBC/neutrophil count and morphology	CGD: Nitroblue tetrazolium (NBT) test or dihydro-rhodamine (DHR) reduction test Chemotactic assay Phagocytic assay
Spleen	Bacteremia/hematogenous infection (pneumococcus, other streptococci, *Neisseria* spp.)	Peripheral blood smear for Howell-Jolly bodies Hemoglobin electrophoresis (HbSS)	Technetium-99 spleen scan or sonogram
Complement	Bacterial sepsis and other bloodborne infections (encapsulated bacteria, especially *Neisseria* spp.) Lupus, glomerulonephritis Angioedema	CH50 (total hemolytic complement)	Alternative pathway assay (AH50) Mannose-binding lectin level Individual complement component assays

[a]Newborn screening using TRECs has now been implemented in multiple states. TRECs identify lymphopenia in children and prompt further testing for SCID or other immunodeficiencies associated with lymphopenia.
ELISA, Enzyme-linked immunosorbent assay; *FISH*, fluorescent in situ hybridization; *HIV*, human immunodeficiency virus; *PCR*, polymerase chain reaction; *TRECs*, T-cell receptor excision circles; *WBC*, white blood cell.
From Lederman HM. Clinical presentation of primary immunodeficiency diseases. In: McMillan J, ed. *Oski's Pediatrics*. Philadelphia: Lippincott Williams & Wilkins; 2006:2441–2444.

b. Immune thrombocytopenic purpura (see Chapter 14):
   (1) Initially given on a single day or in divided doses over 2 to 5 consecutive days.
   (2) Maintenance dose given every 3 to 6 weeks based on clinical response and platelet count.
c. Bone marrow transplantation:
   (1) Adjust dosing to maintain trough IgG level of at least 400 mg/dL.
   (2) May decrease incidence of infection and death but not acute graft-versus-host disease.
d. Other indications:
   (1) Kawasaki disease (see Chapter 7).
   (2) Guillain-Barré syndrome.
   (3) Refractory dermatomyositis and polymyositis.
   (4) Chronic inflammatory demyelinating polyneuropathy.

2. **Precautions and adverse reactions:**
   a. Severe systemic symptoms (hemodynamic changes, respiratory difficulty, and anaphylaxis).
   b. Less-severe systemic reactions (headache, myalgia, fever, chills, nausea, and vomiting).
      (1) Decrease infusion rate and/or premedicate with intravenous corticosteroids, and/or antipyretics.
      (2) Can progress to aseptic meningitis syndrome.
   c. Acute renal failure (increased risk with preexisting renal insufficiency and with sucrose-containing IVIG).
   d. Acute venous thrombosis (increased risk with sucrose-containing IVIG).
   e. Use with caution in patients with confirmed undetectable IgA levels (e.g., patients with partial B-cell immunodeficiencies or familial IgA deficiency), as antibodies against IgA may trigger anaphylactic reaction.

B. Intramuscular Immunoglobulin (IMIG)

1. **Prophylaxis Indications:** Hepatitis A, measles, rubella, rabies, and varicella-zoster (see Chapter 16).
2. **Precautions and adverse reactions:**
   a. Similar to IVIG (discussed previously).
   b. Local reaction at injection site increases with repeated use.
   c. Intravenous or intradermal use of IMIG is absolutely contraindicated due to high risk for anaphylactoid reactions.
3. **Administration:**
   a. No more than 5 mL should be given at one site in large child/adolescent, and 1 to 3 mL for smaller children/infants.
   b. Administration of greater than 15 mL at one time is essentially never warranted.
   c. Peak serum levels achieved by 48 hours; immune effect lasts 3 to 4 weeks.

C. Subcutaneous Immunoglobulin

1. **Indication:** Replacement therapy for antibody deficiency.
2. **Dose:**
   a. See the Formulary for dosages and administration instructions.
   b. Larger doses can be given simultaneously in multiple sites or more frequently than once weekly.
   c. Using the same areas for injections improves tolerability.
3. **Precautions and adverse reactions:**
   a. Systemic side effects are rare because of the small volumes given and the slow absorption rate.
   b. Local redness and swelling are expected and generally decrease with every infusion.
4. **Considerations:** Does not require venous access or special nursing (parents can administer), but may require multiple needlesticks in larger children, depending on the volume to be infused.

D. Specific Immunoglobulins

1. **Hyperimmune globulins:**
   a. Prepared from donors with high titers of specific antibodies.
   b. Includes hepatitis B immune globulin, varicella-zoster immune globulin, cytomegalovirus immune globulin, Rho(D) immune globulin, botulism immune globulin, and others.
2. **Monoclonal antibody preparations** (rituximab, palivizumab, and others).

E. Vaccination Timing

See Chapter 16 for discussion of timing of routine vaccination after immunoglobulin administration.

VI. IMMUNOLOGIC REFERENCE VALUES

A. Serum IgG, IgM, IgA, and IgE Levels (Table 15.3)

B. Serum IgG, IgM, IgA, and IgE Levels for Low Birth Weight Preterm Infants (Table 15.4)

C. Lymphocyte Enumeration (Table 15.5)

D. Serum Complement Levels (Table 15.6)

TABLE 15.3

SERUM IMMUNOGLOBULIN LEVELS[a]

Age	IgG (mg/dL)	IgM (mg/dL)	IgA (mg/dL)	IgE (IU/mL)
Cord blood (term)	1121 (636–1606)	13 (6.3–25)	2.3 (1.4–3.6)	0.22 (0.04–1.28)
1 month	503 (251–906)	45 (20–87)	13 (1.3–53)	
6 weeks				0.69 (0.08–6.12)
2 months	365 (206–601)	46 (17–105)	15 (2.8–47)	
3 months	334 (176–581)	49 (24–89)	17 (4.6–46)	0.82 (0.18–3.76)
4 months	343 (196–558)	55 (27–101)	23 (4.4–73)	
5 months	403 (172–814)	62 (33–108)	31 (8.1–84)	
6 months	407 (215–704)	62 (35–102)	25 (8.1–68)	2.68 (0.44–16.3)
7–9 months	475 (217–904)	80 (34–126)	36 (11–90)	2.36 (0.76–7.31)
10–12 months	594 (294–1069)	82 (41–149)	40 (16–84)	
1 year	679 (345–1213)	93 (43–173)	44 (14–106)	3.49 (0.80–15.2)
2 years	685 (424–1051)	95 (48–168)	47 (14–123)	3.03 (0.31–29.5)
3 years	728 (441–1135)	104 (47–200)	66 (22–159)	1.80 (0.19–16.9)
4–5 years	780 (463–1236)	99 (43–196)	68 (25–154)	8.58 (1.07–68.9)[b]
6–8 years	915 (633–1280)	107 (48–207)	90 (33–202)	12.89 (1.03–161.3)[c]
9–10 years	1007 (608–1572)	121 (52–242)	113 (45–236)	23.6 (0.98–570.6)[d]
14 years				20.07 (2.06–195.2)
Adult	994 (639–1349)	156 (56–352)	171 (70–312)	13.2 (1.53–114)

[a]Numbers in parentheses are the 95% confidence intervals (CIs).

[b]IgE data for 4 years.

[c]IgE data for 7 years.

[d]IgE data for 10 years.

Data from Kjellman NM, Johansson SG, Roth A. Serum IgE levels in healthy children quantified by a sandwich technique (PRIST). *Clin Allergy.* 1976;6:51–59; Jolliff CR, Cost KM, Stivrins PC, et al. Reference intervals for serum IgG, IgA, IgM, C3, and C4 as determined by rate nephelometry. *Clin Chem.* 1982;28:126–128; and Zetterström O, Johansson SG. IgE concentrations measured by PRIST in serum of healthy adults and in patients with respiratory allergy: a diagnostic approach. *Allergy.* 1981;36:537–547.

TABLE 15.4

SERUM IMMUNOGLOBULIN LEVELS FOR LOW BIRTH WEIGHT PRETERM INFANTS

Age (months)	Plasma Ig Concentrations in 25- to 28-Weeks Gestation Infants			Plasma Ig Concentrations in 29- to 32-Weeks Gestation Infants		
	IgG (mg/dL)[a]	IgM (mg/dL)[a]	IgA (mg/dL)[a]	IgG (mg/dL)[a]	IgM (mg/dL)[a]	IgA (mg/dL)[a]
0.25	251 (114–552)	7.6 (1.3–43.3)	1.2 (0.07–20.8)	368 (186–728)	9.1 (2.1–39.4)	0.6 (0.04–1.0)
0.5	202 (91–446)	14.1 (3.5–56.1)	3.1 (0.09–10.7)	275 (119–637)	13.9 (4.7–41)	0.9 (0.01–7.5)
1.0	158 (57–437)	12.7 (3.0–53.3)	4.5 (0.65–30.9)	209 (97–452)	14.4 (6.3–33)	1.9 (0.3–12.0)
1.5	134 (59–307)	16.2 (4.4–59.2)	4.3 (0.9–20.9)	156 (69–352)	15.4 (5.5–43.2)	2.2 (0.7–6.5)
2.0	89 (58–136)	16.0 (5.3–48.9)	4.1 (1.5–11.1)	123 (64–237)	15.2 (4.9–46.7)	3.0 (1.1–8.3)
3	60 (23–156)	13.8 (5.3–36.1)	3.0 (0.6–15.6)	104 (41–268)	16.3 (7.1–37.2)	3.6 (0.8–15.4)
4	82 (32–210)	22.2 (11.2–43.9)	6.8 (1.0–47.8)	128 (39–425)	26.5 (7.7–91.2)	9.8 (2.5–39.3)
6	159 (56–455)	41.3 (8.3–205)	9.7 (3.0–31.2)	179 (51–634)	29.3 (10.5–81.5)	12.3 (2.7–57.1)
8–10	273 (94–794)	41.8 (31.1–56.1)	9.5 (0.9–98.6)	280 (140–561)	34.7 (17–70.8)	20.9 (8.3–53)

[a]Geometric mean (Numbers in parentheses are ±2 SD).

From Ballow M, Cates KL, Rowe JC, et al. Development of the immune system in very low birth weight (less than 1500 g) premature infants: concentrations of plasma immunoglobulins and patterns of infections. *Pediatr Res.* 1986;9:899–904.

TABLE 15.5

T AND B LYMPHOCYTES IN PERIPHERAL BLOOD

Age	CD3 (Total T Cell) Count[a] (%)[b]	CD4 Count[a] (%)[b]	CD8 Count[a] (%)[b]	CD19 (B Cell) Count[a] (%)[b]
0–3 months	2.50–5.50 (53–84)	1.60–4.00 (35–64)	0.56–1.70 (12–28)	0.30–2.00 (6–32)
3–6 months	2.50–5.60 (51–77)	1.80–4.00 (35–56)	0.59–1.60 (12–23)	0.43–3.00 (11–41)
6–12 months	1.90–5.90 (49–76)	1.40–4.30 (31–56)	0.50–1.70 (12–24)	0.61–2.60 (14–37)
1–2 years	2.10–6.20 (53–75)	1.30–3.40 (32–51)	0.62–2.00 (14–30)	0.72–2.60 (16–35)
2–6 years	1.40–3.70 (56–75)	0.70–2.20 (28–47)	0.49–1.30 (16–30)	0.39–1.40 (14–33)
6–12 years	1.20–2.60 (60–76)	0.65–1.50 (31–47)	0.37–1.10 (18–35)	0.27–0.86 (13–27)
12–18 years	1.00–2.20 (56–84)	0.53–1.30 (31–52)	0.33–0.92 (18–35)	0.11–0.57 (6–23)
Adult[c]	0.70–2.10 (55–83)	0.30–1.40 (28–57)	0.20–0.90 (10–39)	

[a]Absolute counts (number of cells per microliter $\times 10^{-3}$).

[b]Normal values (10th to 90th percentile).

[c]From Comans-Bitter WM, de Groot R, van den Beemd R, et al. Immunotyping of blood lymphocytes in childhood. Reference values for lymphocyte subpopulations. *J Pediatr.* 1997;130:388–393.

From Shearer WT, Rosenblatt HM, Gelman RS, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: the Pediatric AIDS Clinical Trials Group P1009 study. *J Allergy Clin Immunol.* 2003;112:973–980.

TABLE 15.6

SERUM COMPLEMENT LEVELS[a]

Age	C3 (mg/dL)	C4 (mg/dL)
Cord blood (term)	83 (57–116)	13 (6.6–23)
1 month	83 (53–124)	14 (7.0–25)
2 months	96 (59–149)	15 (7.4–28)
3 months	94 (64–131)	16 (8.7–27)
4 months	107 (62–175)	19 (8.3–38)
5 months	107 (64–167)	18 (7.1–36)
6 months	115 (74–171)	21 (8.6–42)
7–9 months	113 (75–166)	20 (9.5–37)
10–12 months	126 (73–180)	22 (12–39)
1 year	129 (84–174)	23 (12–40)
2 years	120 (81–170)	19 (9.2–34)
3 years	117 (77–171)	20 (9.7–36)
4–5 years	121 (86–166)	21 (13–32)
6–8 years	118 (88–155)	20 (12–32)
9–10 years	134 (89–195)	22 (10–40)
Adult	125 (83–177)	28 (15–45)

[a]Numbers in parentheses are the 95% confidence intervals (CIs).

Modified from Jolliff CR, Cost KM, Stivrins PC, et al. Reference intervals for serum IgG, IgA, IgM, C3, and C4 as determined by rate nephelometry. *Clin Chem.* 1982;28:126–128.

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Chapter 16

Immunoprophylaxis

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See additional content on Expert Consult

I. IMMUNIZATION SCHEDULES

A. Immunizations for Children Ages 0 to 18

1. Table 16.1: Routine Vaccines for Children and Adolescents in the United States[1]
2. All schedules: https://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html
   a. Comprehensive schedule
   b. By vaccine and age-group
   c. By medical indications
   d. Catch-up immunization schedule
3. Schedules updated annually and put forth by the Advisory Committee on Immunization Practices (ACIP)[2] and approved by the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP), among others.

B. Nonroutine Vaccines Used in the United States[3]

1. For details on vaccines not routinely given in the United States, including bacille Calmette-Guérin (BCG; tuberculosis vaccine), Japanese encephalitis, rabies, typhoid, and yellow fever, see Table 16.2.
2. For information on other vaccines licensed but not routinely distributed, including anthrax and smallpox, see: http://emergency.cdc.gov/bioterrorism/.

II. IMMUNIZATION GUIDELINES

A. Vaccine Informed Consent

1. Vaccine Information Statements (VISs) can be found at: http://www.cdc.gov/vaccines/hcp/vis/current-vis.html.
2. The most recent VIS must be provided to the patient (nonminor) or parent/guardian, with documentation of version date and date of administration.
3. Multivaccine VISs for DTaP, *Haemophilus influenzae* type b (Hib), HepB, Polio, and PCV13 can be used when two or more of these vaccines are administered during the same visit.

B. Vaccine Administration

1. For information on vaccine storage, handling, and administration, see: http://www.cdc.gov/vaccines/hcp/admin/.
2. See Chapter 4 for details on intramuscular and subcutaneous administration procedures.

TABLE 16.1

ROUTINE VACCINES FOR CHILDREN AND ADOLESCENTS IN THE UNITED STATES

Disease	Vaccine Description	Dose and Administration	Side Effects[a]
Diphtheria, Tetanus, Pertussis	DTaP: Diphtheria and tetanus toxoids with acellular pertussis vaccine (preferred vaccine for children <7 years) DT: Diphtheria and tetanus toxoids without pertussis vaccine Td: Tetanus toxoid with reduced dose of diphtheria toxoid Tdap: Tetanus and diphtheria toxoids with acellular pertussis vaccine	0.5 mL IM × 5 doses (2, 4, 6, 15–18 months, and 4–6 years) • Dose #4 may be given as early as 12 months as long as it is 6 months after dose #3 • If dose #4 is inadvertently given ≥4 months but <6 months after dose #3 to a child ≥12 months, it does NOT need to be repeated Use DT for age <7 years if pertussis vaccine is contraindicated 0.5 mL IM × 1 dose at 11–12 years • May be administered regardless of interval since last tetanus and diphtheria toxoid-containing vaccine • 1 dose during each pregnancy (ideally 27–36 weeks gestation) Use Td for age ≥7 years if pertussis vaccine is contraindicated	Local reaction (common), fever ≥38.0°C (≤30%), drowsiness (≤50%), vomiting (4%–7%), crying ≥1 hr (1%–2%) Severe side effects of allergic reactions, persistent crying >3 hr, hypotonic-hyporesponsive episode, seizures, and body temperature >40.5°C that were more common with DTP vaccine are very rare with DTaP
Haemophilus influenzae type B (Hib)	Hib PRP-OMP: Capsular polysaccharide antigen conjugated to outer membrane protein of *Neisseria meningitidis* Hib PRP-T: Capsular polysaccharide antigen conjugated to tetanus toxoid	0.5 mL IM × 2–3 doses (2, 4, +/– 6 months), with booster at 12–15 months • 3 doses of PRP-T and 2 doses of PRP-OMP recommended • Should not be given prior to 6 weeks of age • No need to use same formulation for entire series • See Section IV.B.1 for children with high-risk conditions	Mild local pain, redness, swelling in 25% of recipients for <24 hr
Hepatitis A (HepA)	Inactivated virus purified from human fibroblast cultures	0.5 mL IM × 2 doses (12–23 months with 6–18-month interval between doses) Use 1 mL IM per dose if age ≥19 years International travel: • Age ≥12 months: 1 dose before departure • Age 6–11 months: give 1 dose before departure and revaccinate with 2 doses starting at 12 months	Mild injection site tenderness (≤37%) or redness (≤29%); irritability (42%), drowsiness (28%), fever (≤27%), headache (<9%)

Hepatitis B (HepB)	Produced by recombinant DNA technology; monovalent formulations may be used interchangeably	0.5 mL IM × 3 doses (Birth, 1–2 months, and 6–18 months) Use 1 mL IM per dose if age ≥ 20 years or giving 2-dose adolscent series (age 11-15 years). • 4 doses acceptable if combined vaccines used after birth dose • Monovalent HepB vaccine should be given to all term newborns within 24 hr of birth • See Section IV.C for details regarding preterm infants	Pain at injection site (3%–29%) or fever >37.7°C (1%–6%)
Human papilloma virus (HPV)	HPV9: Protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 HPV4: Protects against HPV types 6, 11, 16, and 18	0.5 mL IM × 2 doses (separated by 6–12 months) for age 11–12 years • Vaccination may be started at age 9; consider if history of sexual abuse or assault • If first dose at age ≥15 years or immunocompromised, give 3 doses at 0, 1–2, and 6 months	Pain, swelling, and erythema at injection site (≤90%, 48%, and 34%, respectively), headache (11%–15%), syncope Observation for syncope for 15 min after administration is recommended
Influenza NOTE: Influenza vaccine recommendations can change annually; see CDC for up-to-date recommendations[34]	LAIV4: Intranasal live, attenuated quadrivalent vaccine for healthy children age ≥2 years IIV4: Subvirion or purified surface-antigen quadrivalent vaccines for age ≥6 months ccIIV4: Cell culture-based quadrivalent vaccine for age ≥4 years RIV4: Recombinant quadrivalent vaccine for age ≥18 years	0.2 mL intranasally (0.1 mL per nare) 0.25–0.5 mL IM if age 6–35 months (see manufacturer recommendations) 0.5 mL IM if age ≥3 years • Give annually starting at age 6 months • Children ≤8 years who have not previously received ≥2 total doses (regardless of interval) should receive 2 doses separated by ≥ 4 weeks	Local reactions, fever within 24 hr after immunization in children <2 years (10%–35%) Possible association with GBS; however, the risk is rare (1–2 cases per million doses)
Measles, Mumps, Rubella (MMR)	Combination vaccine composed of live, attenuated viruses	0.5 mL SQ × 2 doses (12–15 months and 4–6 years) • Dose #2 may be given to age <4 years as long as there has been a 4-week interval International travel: • Age 6–11 months: Give 1 dose prior to departure, then revaccinate with 2 doses—dose #1 at 12–15 months, dose #2 ≥4 weeks later • Age ≥ 12 months (and unvaccinated): Give 2 doses at 4-week interval prior to departure	High fever (>39.4°C) in 5%–15%, usually 6–12 days after immunization, and may last ≤5 days; febrile seizures may occur 5–12 days after the first dose (rare) Other reactions include transient rash (5%), transient thrombocytopenia (1 in 22,000–40,000), encephalitis, and encephalopathy (<1 in 1 million)

Continued

TABLE 16.1—cont'd

ROUTINE VACCINES FOR CHILDREN AND ADOLESCENTS IN THE UNITED STATES

Disease	Vaccine Description	Dose and Administration	Side Effects[a]
N. meningitidis (Meningococcal)	MenACWY-D (Menactra): Quadrivalent (serogroups A, C, Y, W) polysaccharide diphtheria toxoid conjugate for age ≥9 months MenACWY-CRM (Menveo): Quadrivalent (serogroups A, C, Y, W) oligosaccharide diphtheria conjugate for age ≥2 months	0.5 mL IM at age 11–12 years with booster at age 16 years • See Section IV.B.2 for children with high-risk conditions	Mild localized tenderness (10%–41%) or erythema (11%–15%), irritability (18%–57%), sleepiness (14%–50%), headache (11%–30%)
	MenB-4C (Bexsero): Serogroup B vaccine for age 10–25 years MenB-FHbp (Trumenba): Serogroup B vaccine for age 10–25 years	0.5 mL IM x 2 doses • May be given at clinical discretion to adolescents 16–23 years (preferred age 16–18 years) who are not at increased risk • Dose interval for Bexsero is 1 month and for Trumenba is 6 months (vaccines are not interchangeable) • See Section IV.B.2 for children with high-risk conditions	Injection-site pain (85%), fatigue (35%–40%), headache (35%), and muscle pain (30%–48%)
Polio	IPV: Inactivated injectable vaccine containing 3 types of poliovirus Note: OPV, a live, attenuated oral vaccine, is no longer available in the United States; see Table 16.2	0.5 mL IM/SQ × 4 doses (2, 4, 6–18 months, and 4–6 years) • 4 or more doses of IPV can be administered before the 4th birthday when a combination vaccine containing IPV is used. However, a dose is still recommended after the 4th birthday and ≥ 6 months after the previous dose.	Local reactions (≤30%), irritability (≤65%), tiredness (≤61%), fever ≥39°C (≤4%)
Rotavirus	RotaTeq (RV5): Pentavalent live, attenuated oral vaccine containing five reassortant human and bovine rotavirus strains Rotarix (RV1): Monovalent live, attenuated oral vaccine	2 mL PO × 3 doses (2, 4, and 6 months) • If any dose RotaTeq or unknown, 3 doses should be given • First dose must be given before 15 weeks • Do NOT readminister if infant spits out or vomits dose 1 mL PO × 2 doses (2 and 4 months) • First dose must be given before 15 weeks • If the infant spits out or vomits a dose, 1 replacement dose can be given at same visit	Diarrhea (24%), vomiting (15%), otitis media (14.5%), nasopharyngitis (7%), and bronchospasm (1%); rates similar to placebo Small risk of intussusception (1 excess case per 30,000–100,000 vaccinated infants) usually within 1 week of vaccination

Streptococcus pneumoniae (Pneumococcal)	PCV13: Pneumococcal conjugate vaccine containing 13 purified capsular polysaccharides of *S. pneumoniae*, each coupled to a variant of diphtheria toxin: PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) + additional serotypes (1, 3, 5, 6A, 7F, and 19A) for age ≥ 6 weeks PPSV23: Purified capsular polysaccharide from 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) for age ≥2 years	0.5 mL IM × 4 doses (2, 4, 6, 12–15 months) • See Section IV.B.3 for children with high-risk conditions • PCV13 and PPSV23 should not be administered during the same visit. 0.5 mL IM/SQ • See Section IV.B.3 for children with high-risk conditions • When both PCV13 and PPSV23 are indicated, administer PCV13 first.	Pain or erythema at injection site (>50%), irritability (20%–70%), decreased appetite (20%–40%), decreased sleep (≤40%), increased sleep (≤40%), fever (≤20%)
Varicella	Cell-free live, attenuated varicella virus vaccine for age ≥ 12 months	0.5 mL SQ × 2 doses (12–15 months and 4–6 years) • Dose #2 may be given to age <4 years as long as there has been a 3-month interval • A second dose given ≥4 weeks after the first is valid	Injection site reactions (20%–25%) and fever (10%–15%) Mild varicelliform rash within 5–26 days of vaccine administration (3%–5%) may occur, though not all postimmunization rashes are attributable to vaccine; vaccine rash is often mild, but patient may be infectious

[a]Unless otherwise indicated, side effect profiles for vaccines are derived from vaccine-specific package inserts. Available online at: http://www.immunize.org/fda/.[35]

DT, Diphtheria and tetanus vaccine; *DTaP,* diphtheria, tetanus, acellular pertussis vaccine; *GBS*, Guillain-Barré syndrome; *Hib, Haemophilus influenzae* type b; *IIV,* inactivated influenza vaccine; *IM,* intramuscular; *IPV,* inactivated polio vaccine; *LAIV,* live, attenuated influenza vaccine; *OPV,* oral polio vaccine; *PCV13,* pneumococcal 13-valent conjugate vaccine; *PO,* per os; *PPSV23,* pneumococcal 23-valent polysaccharide vaccine; *SQ,* subcutaneous; *Td,* tetanus and diphtheria vaccine; *Tdap,* tetanus, diphtheria, acellular pertussis vaccine.

TABLE 16.2

NONROUTINE VACCINES FOR CHILDREN AND ADOLESCENTS

Disease	Indication	Type	Dose and Administration	Side Effects[a]
Japanese encephalitis (JE)	≥1-month travel in endemic areas (most rural areas of Asia) during the JE season May also be considered for shorter-term travel with higher exposure risk (i.e., during epidemic or time outdoors in rural areas)	JE-VC: Inactivated cell culture–derived JE vaccine for age ≥2 months	0.25 mL IM if age 2 months to 2 years 0.5 mL IM ≥3 years 2 doses at 4-week interval, followed by annual boosters for persons age ≥17 years (if still indicated)	Fever (>10%–20%), irritability (>15%), and diarrhea (>10%) in young children; pain (>15%–25%) and headache (>20%) in adolescents and adults
Polio Oral polio vaccine (OPV) See Table 16.1 for IPV	Not used in the United States, but used worldwide Trivalent vaccine: Protective against all 3 poliovirus types in >95% of recipients In 2016, most countries switched to the bivalent vaccine	Trivalent (tOPV): Live, attenuated vaccine against wild types 1, 2, and 3 Bivalent (bOPV): Live, attenuated vaccine against wild types 1 and 3, but not 2	3 doses at minimum 4 week intervals starting at 6 weeks • Give additional OPV at birth in countries with endemic polio or high risk of importation • Give ≥1 IPV dose, starting at 14 weeks (can be coadministered with OPV)	Rare vaccine-associated paralytic poliomyelitis (VAPP) occurs for ~1 in 2.4 million doses.
Rabies	High-risk groups: Veterinarians, animal handlers, laboratory workers, children living in high-risk environments, those traveling to high-risk areas, spelunkers Postexposure prophylaxis (see Table 16.5)	HDCV: Inactivated virus cultured in human diploid cells PCECV: Inactivated virus cultured in purified chicken embryo cells	Preexposure: 1 mL IM × 3 doses (Days 0, 7, and 21 or 28) Postexposure: 1 mL IM × 4 doses (Days 0, 3, 7, and 14) • Do not administer in same part of body or in same syringe as RIG • Serum Ab titers should be followed at 6-month intervals for those at continuous risk and at 2-year intervals for those at risk of frequent exposure • Give booster doses only if titers are nonprotective	Uncommon in children; in adults, local reactions (≤25%), mild systemic reactions (≤20%) Arthus-like reaction (urticaria, arthralgia, angioedema, vomiting, fever, malaise) 2–21 days after immunization with HDCV is rare in primary series, but 6% after booster dose

Disease	Indication	Type	Dose and Administration	Side Effects[a]
Respiratory Syncytial Virus (RSV)[36]	Preterm infants: • Born <29 WGA and <12 months at the start of RSV season • Chronic lung disease of prematurity in first year of life or requiring ongoing medical support in second year of life Children <12 months with: • Anatomic pulmonary abnormality or neuromuscular disorder impairing upper airway clearance • Moderate-to-severe pulmonary hypertension • Hemodynamically significant heart disease (discuss with cardiologist) Children <2 years with: • Cardiac transplant • Profound immunocompromise	Palivizumab: Humanized mouse IgG1 monoclonal antibody to RSV	15 mg/kg IM Give every 28-30 days during RSV season for up to 5 doses • First dose should be given prior to the beginning of RSV season • Children who develop an RSV infection should discontinue use of Palivizumab	Fever and rash (local skin reaction)
Tuberculosis (TB)	1 dose of BCG should only be considered in the United States if a child is frequently and unavoidably exposed to contagious pulmonary TB that is untreated, ineffectively treated, or resistant to treatment, and the child cannot be given long-term primary preventive therapy (if nonresistant) Children should be HIV-negative and those ≥2 months should have a negative purified protein derivative (PPD)	BCG: Live, attenuated vaccine prepared from *Mycobacterium bovis*. Variable composition and efficacy worldwide, but ≤80% effective	Reconstitute 1 vial of vaccine (50 mg) in 1 mL sterile water (2 mL if age <1 month) Give 0.2–0.3 mL of reconstituted vaccine percutaneously with a multiple puncture device in the deltoid region	In 1%–2%, axillary or cervical lymphadenopathy and pustule formation at injection site can occur Rare complications are disseminated BCG infection or BCG osteitis (more common if immunocompromised)

Continued

TABLE 16.2—cont'd

NONROUTINE VACCINES FOR CHILDREN AND ADOLESCENTS

Disease	Indication	Type	Dose and Administration	Side Effects[a]
Typhoid	Travel to areas with risk of exposure to *Salmonella* serotype Typhi, people with frequent close contact with a documented carrier, laboratory workers in contact with *Salmonella* serotype Typhi, and people living in areas with endemic infection	ViCPS: Vi capsular polysaccharide vaccine for age ≥2 years Ty21a: Oral live, attenuated vaccine for age ≥6 years	0.5 mL IM Give 1 dose ≥2 weeks prior to exposure; booster every 2 years 1 dose by mouth every other day for a total of 4 doses ≥1 week prior to exposure; booster every 5 years	Local discomfort or erythema (up to 14%), subjective fever (3%), decreased activity (2%) Mild reactions including abdominal pain, nausea, diarrhea, vomiting, fever, or headache
Yellow fever	Travel to endemic areas including parts of sub-Saharan Africa and South America Required by some countries as a condition of entry	YF-Vax: Live, attenuated (17D strain) vaccine approved for age ≥9 months	0.5 mL SQ Give 1 dose ≥10 days prior to travel No booster doses indicated unless immunocompromised or at increased risk due to location or duration of exposure (e.g., prolonged travel or lab workers)	Rare viscerotropic disease (multiple-organ system failure) and neurotropic disease (encephalitis) Increased risk of adverse events in persons with thymic dysfunction; increased risk of postvaccine encephalitis in ages <9 months

[a]Unless otherwise indicated, side effect profiles for vaccines are derived from vaccine-specific package inserts. Available online at: http://www.immunize.org/fda/.[35]

Ab, Antibody; *BCG*, bacille Calmette-Guérin; *HDCV*, human diploid cell vaccine; *IgG1*, immunoglobulin G 1; *IM*, intramuscular; *IPV*, inactivated polio vaccine; *PCECV*, purified chick embryo cell vaccine; *RIG*, rabies immune globulin; *SQ*, subcutaneous; *WGA*, weeks gestational age.

3. Combination vaccines can reduce number of injections.
   a. MMR-Varicella (ProQuad)[4] can be used for children 12 months through 12 years of age. There is an increased risk of febrile seizures if given as first dose for ages 12 to 47 months.
   b. HepB-containing[5] combination vaccines should not be administered to infants <6 weeks because of the other components.
4. Simultaneous administration
   a. Routine childhood vaccines are safe and effective when administered simultaneously at different sites. There is no maximum number of vaccines that can be coadministered.
   b. If live vaccines are not given at the same visit, they should be separated by an interval of 28 days.

C. Live, Attenuated Vaccines

1. Certain vaccines have live components that must replicate to produce immunity: Influenza (intranasal), MMR, oral polio vaccine (OPV), BCG, typhoid (oral), varicella, yellow fever.
2. Systemic adverse reactions following these vaccines are usually mild, and usually occur 3 to 21 days after the vaccine is given.
3. Special consideration must be taken when administering these vaccines to patients with certain underlying medical conditions (see Section IV).

D. Timing and Spacing of Vaccine Doses

1. For information on recommended timing and spacing of vaccines, see: http://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html.
2. Combination vaccines
   a. Minimum age for administration is the oldest age for any of the individual components.
   b. Minimum interval between doses is equal to the greatest interval of any of the individual components.

E. Contraindications and Precautions[6]

1. Contraindication: A condition that increases the likelihood of a serious adverse reaction to a vaccine for a patient with that condition.
2. Precaution: A condition that may increase the likelihood or severity of an adverse reaction in a vaccine recipient, or may compromise the ability of the vaccine to produce immunity.
3. Table 16.3: Contraindications and precautions to select vaccines.
4. Table 16.4: Conditions incorrectly perceived as contraindications or precautions to vaccination (vaccines may be given under these conditions).
5. For full details, see: www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html.

TABLE 16.3

CONTRAINDICATIONS AND PRECAUTIONS TO SELECT VACCINES[6,7,9]

Vaccine	Contraindication	Precaution
All vaccines	Severe (life-threatening) allergic reaction after 1 dose or to any vaccine component (see package inserts)	Moderate-severe acute illness (wait until after recovery if possible) Latex allergy: www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf
Live vaccines	Most forms of altered immunocompetence (see Section IV.A for exceptions) Solid organ transplant Pregnancy: Wait until after pregnancy; avoid becoming pregnant for ≥1 month after vaccine	Patients on corticosteroids: See Table 16.6 HSCT patients • Delay ≥3 months after immunosuppressive therapy has been discontinued • See Table EC 16.B Patients on biologic response modifier therapies: Contraindicated during therapy and for weeks to months after discontinuation Received other live vaccines in past 4 weeks
Diphtheria, Tetanus, Pertussis	Encephalopathy (including coma or status epilepticus) within 7 days of administration of prior dose of DTaP/Tdap not attributable to another identifiable cause	Evolving/progressive neurologic disorder, including uncontrolled seizures: Defer DTaP/Tdap temporarily; use DT or Td instead in children age ≥1 year, reconsider pertussis immunization at each visit (i.e., if condition stabilized) GBS within 6 weeks of previous dose History of Arthus-type hypersensitivity reaction (including severe pain or swelling) after tetanus or diphtheria toxoid-containing vaccine: Defer vaccination for 10 years after last administration DTaP/Tdap: Temp ≥40.5°C (104.8°F) within 48 hr of a previous dose
Hepatitis A	Anaphylaxis to aluminum hydroxyphosphate sulfate, aluminum hydroxide, or neomycin	
Hepatitis B	Anaphylaxis to yeast	Defer for infants <2,000 g if mother HBsAg negative; see Fig. 16.1 for details
HPV	Anaphylaxis to yeast	Pregnancy: Delay vaccination until after pregnancy.
Influenza (IIV)		History of GBS within 6 weeks after a previous dose Egg allergy other than hives (administer in a supervised medical setting)

Continued

TABLE 16.3—cont'd

Vaccine	Contraindication	Precaution
Influenza (LAIV)	Anaphylaxis to eggs or gelatin Contacts (including providers) of severely immunocompromised patients requiring care in protective environment Children <5 years with history of wheezing in past 12 months On aspirin or aspirin-containing products Use of influenza antiviral therapy in the past 48 hr (may interfere with immunogenicity)	History of GBS within 6 weeks after a previous dose Asthma or breathing problems in children ≥5 years Medical conditions that might be at higher risk of complications from influenza
Japanese Encephalitis	Anaphylaxis to protamine sulfate	
MMR	Anaphylaxis to neomycin or gelatin	History of thrombocytopenia or TTP Recent blood product administration (within 3–11 months, depending on product and dose). See Table EC 16.D Need for TB testing Other live vaccines in past 4 weeks Personal or family history of seizures (MMRV only)
Meningococcal (ACWY and B)	Anaphylaxis to tetanus or diphtheria toxoid	Pregnancy or breastfeeding: Not much information about potential risks; should be used only if clearly needed
Pneumococcal	PCV13: Anaphylaxis to any vaccine containing diphtheria toxoid	PPSV23 in Pregnancy: No evidence of harm, but avoid or give prior to pregnancy if possible
Polio	IPV: Anaphylaxis to neomycin, streptomycin, polymyxin B, 2-phenoxyethanol, and formaldehyde OPV: Immunocompromised patients and close/household contacts	Pregnancy: No evidence of harm, but avoid or give prior to pregnancy if possible
Rabies	Anaphylaxis to gelatin (present in some vaccines, check package insert) Severe allergic reaction to prior dose (switch to PCECV if there is a reaction to HDCV)	
Rotavirus	SCID History of intussusception Severe allergic reaction to latex (RV1 only)	Concern for immunocompromise, preexisting chronic gastrointestinal disease, spina bifida, or bladder exstrophy Preterm infants: Defer initiation of routine vaccination if still hospitalized to prevent nosocomial spread
Tuberculosis (BCG)	HIV infection Burns or skin infections	

TABLE 16.3—cont'd

Vaccine	Contraindication	Precaution
Typhoid (Ty21a only)		Active gastrointestinal tract illness Certain antibiotics or antimalarials that would be active against *Salmonella* serovar Typhi or interfere with immunogenicity
Varicella[37]	Anaphylaxis to neomycin or gelatin	On aspirin or aspirin-containing products; avoid using salicylates for 6 weeks after vaccination Recent blood product administration (within 3–11 months, depending on product and dose, see Table EC 16.D) Tuberculosis or positive PPD Other live vaccines in past 4 weeks Receipt of antiviral drugs (acyclovir, famciclovir, or valacyclovir) 24 hr before vaccination; avoid for 14 days after vaccination
Yellow fever[38]	Anaphylaxis to eggs or gelatin Symptomatic HIV infection or $CD4^+$ count <200/mm^3 (or <15% for age <6 years) Age <6 months Thymus disorder	Age 6–8 months: Risk of vaccine-associated encephalitis Pregnant or breastfeeding: Rare cases of in utero or breastfeeding transmission of the vaccine virus Asymptomatic HIV infection with $CD4^+$ count 200–499/mm^3 (or 15%–24% for age <6 year)

DT, Diphtheria and tetanus vaccine; *DTaP,* diphtheria, tetanus, acellular pertussis vaccine; *GBS,* Guillain-Barré syndrome; *HDCV,* human diploid cell vaccine; *HIV,* human immunodeficiency virus; *HPV,* human papilloma virus; *HSCT,* hematopoietic stem cell transplant; *IIV,* inactivated influenza vaccine; *LAIV,* live, attenuated influenza vaccine; *MMR,* measles, mumps, rubella; *MMRV,* measles, mumps, rubella, varicella; *PCECV,* purified chick embryo cell vaccine; *PPD,* purified protein derivative; *SCID,* severe combined immunodeficiency; *Td,* tetanus and diphtheria vaccine; *Tdap,* tetanus, diphtheria, acellular pertussis vaccine; *TTP,* thrombotic thrombocytopenic purpura.

Modified from Table 4.1, Centers for Disease Control and Prevention. "Contraindications and Precautions." Vaccine Recommendations and Guidelines of the ACIP. Last updated 14.09.2018. Available online at: http://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html.

TABLE 16.4

CONDITIONS INCORRECTLY PERCEIVED AS CONTRAINDICATIONS OR PRECAUTIONS TO VACCINATION[6,7,9]

Vaccine	NOT Contraindication/Precaution
All vaccines	Mild acute illness with or without fever Mild-moderate local reaction (i.e., swelling, redness, soreness); low-grade or moderate fever after previous dose Recent exposure to an infectious disease Current antimicrobial therapy (Exceptions: oral typhoid, varicella) Convalescent phase of illness Breastfeeding Preterm birth (Exception: hepatitis B vaccine in specific circumstances; see Fig. 16.1) History of penicillin allergy, other nonvaccine allergies, relatives with allergies, or receiving allergen extract immunotherapy History of GBS (Exception: within 6 weeks of influenza or tetanus toxoid–containing vaccine)

TABLE 16.4—Cont'd

Vaccine	NOT Contraindication/Precaution
DTaP	Personal or family history of seizures, including seizures after previous dose of DTaP: Consider antipyretic use for 24 hr after vaccination. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hr of a previous dose Persistent, inconsolable crying lasting ≥3 hr within 48 hr of a previous dose Stable neurologic conditions (e.g., cerebral palsy, well-controlled seizures, or developmental delay)
Hepatitis B	Autoimmune disease (e.g., SLE or RA)
HPV	Evidence of active or prior HPV infection, such as abnormal Pap smear, history of genital warts, or positive HPV DNA test
Influenza (IIV)	Nonsevere allergy to egg or latex Pregnancy: Give regardless of trimester
Influenza (LAIV)	Contacts of persons with chronic disease or altered immunocompetence not requiring care in a protected environment Breastfeeding
MMR	Positive tuberculin skin test (PPD) Simultaneous PPD or interferon-γ release assay (IGRA) testing: may be done on the day of immunization but otherwise should be postponed 4–6 weeks Nonanaphylactic reactions to gelatin or neomycin or anaphylactic reaction to egg (consider observation for 90 min; skin testing not predictive)
Polio (IPV)	Previous receipt of ≥1 dose of OPV
PPSV23	History of invasive pneumococcal disease or pneumonia
Rotavirus	Prematurity (give at hospital discharge)
Varicella	Immunodeficient household contact (Exception: If patient experiences a presumed vaccine-related rash 7–25 days after vaccination, the person should avoid direct contact with immunocompromised persons for the duration of the rash) Humoral immunodeficiency (e.g., agammaglobulinemia)

DNA, Deoxyribonucleic acid; *DTaP,* diphtheria, tetanus, acellular pertussis vaccine; *GBS,* Guillain-Barré syndrome; *HPV,* human papilloma virus; *IIV,* inactivated influenza vaccine; *IPV,* inactivated polio vaccine; *LAIV,* live, attenuated influenza vaccine; *OPV,* oral polio vaccine; *PPD,* purified protein derivative; *PPSV23,* pneumococcal 23-valent polysaccharide vaccine; *RA,* rheumatoid arthritis; *SLE,* systemic lupus erythematosus.

Modified from Table 4.2, Centers for Disease Control and Prevention. "Contraindications and Precautions." Vaccine Recommendations and Guidelines of the ACIP. Last updated 14.09.2018. Available online at: http://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html.

III. POSTEXPOSURE PROPHYLAXIS (TABLE 16.5)

IV. SPECIAL PATIENT POPULATIONS[7]

A. Altered Immunocompetence[8,9]

1. For full details, see: www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html.
2. **General principles**
   a. Primary immunodeficiency: Congenital and usually inherited conditions defined by an inherent absence or deficiency in cellular or humoral components that provide immunity.

TABLE EC 16.A

VACCINE INFORMATION FOR PATIENTS WITH IMMUNODEFICIENCIES[6-9]

Specific Immunodeficiency	Contraindicated Vaccines	Risk-Specific Recommended Vaccines	Effectiveness and Comments
B LYMPHOCYTE (HUMORAL)			
Severe antibody deficiencies (e.g., X-linked agammaglobulinemia, CVID)	OPV[a] Smallpox LAIV BCG Ty21a Yellow fever MMR MMRV	Pneumococcal Hib (ages 12–59 months)	The effectiveness of any vaccine is uncertain if it depends only on the humoral response
Less severe antibody deficiencies (e.g., IgA deficiency, IgG subclass deficiency)	OPV[a] BCG Yellow fever[5] Other live vaccines appear to be safe	Pneumococcal Hib (ages 12–59 months)	All vaccines likely effective; immune response might be attenuated
T LYMPHOCYTE (CELL MEDIATED AND HUMORAL)			
Complete defects (e.g., SCID, complete DiGeorge syndrome)	All live vaccines[b]	Pneumococcal Hib (ages 12–59 months)	Vaccines likely to be effective
Partial defects (e.g., most DiGeorge syndrome patients, Wiskott-Aldrich)	All live vaccines[b]	Pneumococcal Meningococcal Hib (ages 12–59 months)	Effectiveness of any vaccine depends on degree of immune suppression
IFN-γ/ IL-12 axis deficiencies	All live bacterial vaccines (All live vaccines[b] contraindicated in IFN-γ or IFN-α deficiencies)	None	

Continued

TABLE EC 16.A—cont'd

Specific Immunodeficiency	Contraindicated Vaccines	Risk-Specific Recommended Vaccines	Effectiveness and Comments
COMPLEMENT			
Persistent complement, properdin, or factor B deficiency	None	Pneumococcal Meningococcal Hib (ages 12–59 months)	All routine vaccines likely effective
Eculizumab (Soliris) therapy	None	Meningococcal	
PHAGOCYTIC FUNCTION			
Chronic granulomatous disease	All live bacterial vaccines[b]	None	Live viral vaccines likely safe and effective
Phagocytic deficiencies that are undefined or accompanied by defects in T- and NK cell dysfunction (e.g., Chediak-Higashi syndrome, leukocyte adhesion deficiency)	All live vaccines[b]	Pneumococcal	All inactivated vaccines safe and likely effective
SECONDARY IMMUNODEFICIENCY			
HIV/AIDS	OPV[a] Smallpox BCG LAIV MMRV Withhold MMR, varicella, and zoster in severely immunocompromised persons Yellow fever vaccine may have a contraindication or precaution depending on clinical parameters of immune function (see CDC for details)	Pneumococcal Hib HepB	MMR and varicella vaccine in those with mild immunosuppression, rotavirus, and all inactivated vaccines, including IIV as per routine vaccination schedule, may be effective

Specific Immunodeficiency	Contraindicated Vaccines	Risk-Specific Recommended Vaccines	Effectiveness and Comments
Generalized malignant neoplasm, transplantation, immunosuppressive or radiation therapy	Live viral and bacterial,[b] depending on immune status	Pneumococcal Hib	Effectiveness of any vaccine depends on degree of immune suppression
Asplenia	LAIV	Pneumococcal Meningococcal Hib	All routine vaccines likely effective
Chronic renal disease	LAIV	Pneumococcal HepB (indicated based on risk from dialysis-based bloodborne transmission)	All routine vaccines likely effective

[a]OPV is no longer available in the United States.

[b]Live bacterial vaccines: BCG, adenovirus, and oral Ty21a *Salmonella typhi* vaccine; Live viral vaccines: MMR, MMRV, OPV, LAIV, yellow fever, zoster, rotavirus, varicella, and vaccinia (smallpox). Nonemergency smallpox vaccination is not recommended for children <18 years old or the general public.

AIDS, Acquired immunodeficiency syndrome; *BCG*, bacille Calmette-Guérin; *CDC*, Centers for Disease Control and Prevention; *CVID*, common variable immunodeficiency; *HepB*, hepatitis B; *Hib*, *Haemophilus influenzae* type b; *HIV*, human immunodeficiency virus; *IFN*, interferon; *IgA*, immunoglobulin A; *IgG*, immunoglobulin G; *IL*, interleukin; *LAIV*, live, attenuated influenza vaccine; *MMR*, measles, mumps, rubella; *MMRV*, measles, mumps, rubella, varicella; *OPV*, oral polio vaccine; *SCID*, severe combined immunodeficiency.

Modified from Appendix A from Centers for Disease Control and Prevention. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. In: Hamborsky J, Kroger A, Wolfe S, eds. 13th ed. Washington, DC: Public Health Foundation; 2015. Available online at: www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/A/immuno-table.pdf.

b. Secondary immunodeficiency: Acquired loss or deficiency in cellular or humoral immune components as a consequence of a disease process or its therapy.
c. See Chapter 15 for specific information about immunodeficiencies.
d. See Table EC 16.A for specific vaccine recommendations and contraindications in patients with immunodeficiency.

3. **Primary immunodeficiency**
   a. Live vaccines generally contraindicated.
   b. Other vaccines should be given according to routine schedule. Immune response may vary.
   c. Increased incidence or severity of some vaccine-preventable diseases: recommendations for additional vaccination.
   d. Passive immunoprophylaxis with immunoglobulin therapy may be indicated.
      (1) See Chapter 15 for specific details.
      (2) See Table 16.5 for postexposure prophylaxis guidelines.
   e. Routine immunization of household contacts. Only exception is live, attenuated influenza vaccine (LAIV) if immunocompromise is severe (e.g., severe combined immunodeficiency [SCID]).
4. **Functional or anatomic asplenia (including sickle cell disease)**
   a. Penicillin prophylaxis: See Chapter 14 for details.
   b. See Section IV.B for Hib, meningococcal, and pneumococcal vaccination recommendations.
   c. Children ≥2 years undergoing elective splenectomy
      (1) Give pneumococcal and meningococcal vaccines ≥2 weeks before surgery for optimal immune response.
      (2) Consider another dose of Hib.
5. **Known or suspected human immunodeficiency virus (HIV) disease**
   a. See Section IV.B for Hib, meningococcal, and pneumococcal vaccination recommendations.
   b. Varicella: Administer when $CD4^+$ ≥15%.
   c. MMR: Give 2 doses to all HIV-infected children without evidence of severe immunosuppression (i.e., age ≤5 years with $CD4^+$ ≥15% for ≥6 months OR age >5 years with $CD4^+$ ≥15% and $CD4^+$ count ≥200 cells/mm for ≥6 months).
   d. Do not give MMR-Varicella combined vaccine.
   e. Do not administer LAIV.
   f. Do not administer OPV and BCG unless in areas where infection risk outweighs possibility of vaccine-associated disease.
   g. Consider passive immunoprophylaxis or chemoprophylaxis after exposures (see Table 16.5).
6. **Malignancy**
   a. Always consult with the patient's oncologist first. Recommendations vary based on the patient's specific treatment regimen.
   b. General strategies include the following
      (1) Presuming loss of immunity and revaccinating per CDC catch-up immunization schedule.

TABLE 16.5

POSTEXPOSURE PROPHYLAXIS (PEP)

Disease	Prophylaxis Type	Indication/Administration Details
Hepatitis A	Vaccine	Indicated for children ≥12 months if ≤2 weeks since exposure OR if >2 weeks since exposure and exposure ongoing
	IMIG	For children <12 months if ≤2 weeks since exposure Immunocompromised children with exposure Dosing: 0.1 mL/kg IM
Hepatitis B See Table 16.7 for details on percutaneous exposure to blood.	Vaccine	Give series to any previously unimmunized person with percutaneous blood exposure Give within 12 hr after birth to any infant with maternal HBsAg status positive/unknown
	HBIG: Prepared from plasma containing high-titer anti-HBsAg antibodies	Give within 12 hr after birth to infants with maternal HBsAg positive; see Fig. 16.1 for guidance when maternal HBsAg unknown Give to any previously unimmunized person or known nonresponder with percutaneous blood exposure to HBsAg positive blood Dosing: • 0.5 mL IM for infants <12 months • 0.06 mL/kg IM for children ≥12 months
Hib (invasive)	Vaccine	Invasive Hib ≤24 months: Initiate 1 month after acute illness and continue immunization series as if previously unimmunized Not required if invasive Hib disease develops in children >24 months Consider immunologic workup for any child with invasive Hib disease after completing immunization series
	Chemoprophylaxis	Exposure only: Rifampin prophylaxis recommended for household contacts in certain circumstances (see Table 3.11 of the 2018 Red Book for details[29])

Continued

TABLE 16.5—cont'd

Disease	Prophylaxis Type	Indication/Administration Details
Influenza NOTE: Recommendations vary by season; see CDC for up-to-date recommendations[34]	Chemoprophylaxis	Most commonly used: Neuraminidase inhibitors (e.g., oseltamivir) given the high resistance to adamantanes (e.g., amantadine) Indications: • Unimmunized high-risk children, including those for whom the vaccine is contraindicated or children immunized <2 weeks before exposure • Unimmunized individuals in close contact with high-risk individuals • Immunodeficient individuals unlikely to have protective response to vaccine • Control of outbreaks in a closed setting • Immunized high-risk individuals if vaccine strain different from circulating strain Delay for ≥2 weeks if LAIV has been given Not a substitute for immunization
Measles	Vaccine	Intervention of choice for measles outbreak; prevents or modifies disease if given within 72 hr of exposure
	IMIG	Indicated in children <1 year or nonimmune individuals who cannot receive the vaccine Prevents or modifies disease if given within 6 days of exposure
	IVIG	Recommended for nonimmune pregnant women and severely immunocompromised hosts (including HIV-infected children) regardless of immunization status Additional therapy not required if given within 3 weeks before exposure
Mumps	Vaccine	Persons ≥12 months who previously received ≤2 doses of MMR and are identified by public health authorities to be at increased risk during a mumps outbreak should receive 1 dose of MMR[39]
Meningococcal	Vaccine Chemoprophylaxis	Adjunct to chemoprophylaxis when an outbreak is caused by a vaccine-preventable serogroup Indications: • Direct exposure to an infected person's oral secretions (including unprotected healthcare workers) • Close contact in the 7 days prior to onset of disease (e.g., child care, preschool, and household contacts and passengers seated next to the index patient during airline flights ≥8 hr) Initiate within 24 hr of index patient diagnosis See Table 3.42 of the 2018 Red Book for details[29]

Disease	Prophylaxis Type	Indication/Administration Details
Pertussis	Vaccine Chemoprophylaxis	Immunize all unimmunized or partially immunized close contacts based on the recommended schedule Azithromycin, erythromycin, or clarithromycin recommended for household contacts and other close contacts. Alternatives include TMP-SMX (see Table 3.52 of the 2018 Red Book for details[29])
Rabies See Table 16.8 for details based on type of exposure Note: PEP indicated for bites, scratches, or contamination of open wound or mucous membrane with infectious material of potentially rabid animal or human	Vaccine RIG: Antirabies Ig prepared from plasma of donors hyperimmunized with rabies vaccine Other management	If unimmunized: give vaccine on days 0, 3, 7, and 14 with 1× RIG on day 0 If immunosuppressed, give a fifth dose on day 28 If RIG is unavailable, give vaccine alone If previously immunized: booster doses on days 0 and 3 If unimmunized: • Give 1× RIG on day 0 with vaccine • If no vaccine, give RIG alone • May be given within 7 days after initiating immunization Do not give RIG if previously immunized Dosing: 20 units/kg; infiltrate around the wound, give remainder IM Consider tetanus prophylaxis and antibiotics, if indicated General wound management: • Clean immediately with soap and water and flush thoroughly • Avoid suturing wound unless indicated for functional or cosmetic reasons Report all patients suspected of rabies infection to public health authorities
Rubella	Rubella Ig	Does not prevent infection or viremia For use in rubella-susceptible women exposed to confirmed rubella early in pregnancy when termination is not being considered.[40] Routine use of rubella Ig in early pregnancy is not recommended.
Tetanus	Vaccine TIG	See Table 16.9 for details Give to any child with HIV infection or other severe immunodeficiency for any tetanus-prone wound, regardless of vaccination status Dosing: 1× 250 units IM

Continued

TABLE 16.5—cont'd

Disease	Prophylaxis Type	Indication/Administration Details
Varicella See Fig. 3.12 of the 2018 Red Book for details[29]	Vaccine	Vaccinate immunocompetent, nonimmune people ≥12 months as soon as possible after exposure, preferably within 3 days Vaccination should still be given after this time for protection against subsequent exposures Do not give vaccine concurrently with or for 5 months after VariZIG Avoid antivirals for 21 days after vaccination
	VariZIG: Prepared from plasma containing high-titer antivaricella antibodies	Give for significant exposures in individuals with no immunity and a high likelihood of complications from infection including: • Immunocompromised • Pregnant women • Certain newborn infants Give as soon as possible within 10 days of exposure Dosing (Weight-based, IM, 125 units = 1 vial): • 62.5 units for ≤2 kg • 125 units for 2.1–10 kg • 250 units for 10.1–20 kg • 375 units for 20.1–30 kg • 500 units for 30.1–40 kg • 625 units for >40 kg
	IVIG	May be used if VariZIG is not available Dosing: 400 mg/kg IV
	Chemoprophylaxis	If VariZIG or IVIG are not available, consider prophylaxis with 7 days of acyclovir or valacyclovir beginning 7–10 days after exposure in immunocompromised, nonimmune patients

CDC, Centers for Disease Control and Prevention; *HBIG*, hepatitis B immune globulin; *HBsAg*, hepatitis B surface antigen; *Hib, Haemophilus influenzae* type b; *HIV*, human immunodeficiency virus; *Ig*, immunoglobulin; *IM*, intramuscular; *IMIG*, intramuscular immunoglobulin; *IVIG*, intravenous immunoglobulin; *LAIV*, live, attenuated influenza vaccine; *MMR*, measles, mumps, rubella; *PEP*, postexposure prophylaxis; *RIG*, rabies immune globulin; *TIG*, tetanus immune globulin; *TMP-SMX*, trimethoprim-sulfamethoxazole; *VariZIG*, varicella zoster immune globulin.

(2) Obtaining titers and revaccinating those with unprotective levels.

c. Timing of resumption of immunization varies based on the patient's specific treatment regimen (from 3 months to ≥24 months).
   (1) Inactivated vaccines are generally delayed until ≥6 months after the end of chemotherapy.
   (2) Live vaccines are generally delayed until ≥12 months after the end of chemotherapy.

d. Inactivated influenza vaccine (IIV) should be given annually, even during chemotherapy.

7. **Hematopoietic stem cell transplant (HSCT) recipients**
   a. After transplant, HSCT recipients are considered to have lost immunity to all vaccines. Reimmunize against all vaccine-preventable illnesses.
      (1) Inactivated vaccines are safe to administer 6 to 12 months after HSCT. Our center starts the pneumococcal series at 6 months and the remainder at 12 months.
      (2) IIV may be given as early at 6 months post-HSCT. Children ≤8 years should receive two doses. Do not administer LAIV. During a community outbreak, IIV may be given 3 to 4 months post-HSCT, with a second dose 4 weeks later regardless of age.
      (3) Avoid live vaccines during the first 24 months post transplant.
      (4) For specific vaccine recommendations, see Table EC 16.B.
   b. Consider passive immunoprophylaxis or chemoprophylaxis after exposures (see Table 16.5).
   c. Household contacts should receive routine immunizations. Only exception is LAIV if the HSCT recipient's level of immunocompromise is severe (e.g., HSCT in last 3 months). HSCT recipients should avoid contact with body fluids or skin eruptions of household contact who received rotavirus or varicella vaccines, respectively.
8. **Solid organ transplant recipients**
   a. See Section IV.B.3 for pneumococcal vaccination recommendations.
   b. Before transplant: Give all routinely recommended vaccines. Give live vaccines ≥4 weeks prior to transplantation.
      (1) Children 6 to 11 months can receive MMR if not immunosuppressed and if transplant is ≥4 weeks away.
      (2) Children 6 to 11 months (or without evidence of varicella immunity) can receive varicella vaccine if not immunosuppressed and if transplant is ≥4 weeks away.
   c. After transplant: Inactivated vaccines, including those indicated for immunocompromised hosts, should resume 2 to 6 months after transplant. Live vaccines are generally not given after transplant. For specific vaccine recommendations, see Table EC 16.C.
9. **Patients on corticosteroids**
   a. Only live vaccines are potentially contraindicated.
   b. See Table 16.6 for details.

TABLE EC 16.B

VACCINATIONS AFTER HSCT[41-44]

Vaccine	Timing Posttransplant (# of recommended doses)[c]
DTaP, DT, Td, Tdap	Age <7 years: 12 months (3 doses of DTaP) Age ≥7 years: 12 months (3 doses of DTaP OR 1 dose of Tdap, followed by 2 doses of either DT or Td)
HepA	12 months (2 doses)
HepB	12 months (3 doses)
Hib	12 months (3 doses)
HPV	Age 11–26 years: 6–12 months (3 doses)
IIV	6 months, or 4 months during outbreak (1 dose annually; 2 doses if age 6 months–8 years and receiving for first time or if given prior to 6 months post-HSCT)
IPV	12 months (3 doses)
LAIV[a]	Contraindicated
Meningococcal	Age 11–18 years: 12 months (2 doses; booster at 16–18 years if first post-transplant dose given at age 11–15 years)
MMR[a]	24 months (2 doses)[b]
PCV13	6 months (3 doses; a fourth dose should be added at 14 months instead of PPSV23 in patients with chronic GVHD)
PPSV23	14 months if no chronic GVHD
Rotavirus[a]	Contraindicated
Varicella[a]	24 months (2 doses)[b]

[a]Do not administer live vaccines to patients with active GVHD or ongoing immunosuppression.
[b]Should only be administered to patients without ongoing immunosuppression, no chronic GVHD, and 8–12 months after last dose of IVIG.
[c]Some variation in recommended timing of administration post-HSCT. These recommendations reflect our center's practice.
DT, Diphtheria and tetanus vaccine; *DTaP,* diphtheria, tetanus, acellular pertussis vaccine; *GVHD,* graft versus host disease; *HepA,* hepatitis A; *HepB,* hepatitis B; *Hib, Haemophilus influenzae* type b; *HPV,* human papilloma virus; *IIV,* inactivated influenza vaccine; *IPV,* inactivated polio vaccine; *LAIV,* live, attenuated influenza vaccine; *MMR,* measles, mumps, rubella; *PCV13,* pneumococcal 13-valent conjugate vaccine; *PPSV23,* pneumococcal 23-valent polysaccharide vaccine; *Td,* tetanus and diphtheria vaccine; *Tdap,* tetanus, diphtheria, acellular pertussis vaccine.

TABLE EC 16.C

VACCINATIONS AFTER SOLID ORGAN TRANSPLANT[43-46]

Vaccine	Administration Recommendations (Starting 2–6 Months Posttransplant)
DTaP, DT, Td, Tdap	Routine schedule
HepA	Routine schedule
HepB	Routine schedule
Hib	Routine schedule
HPV	Routine schedule
IIV	Routine schedule (can be administered ≥1 month after transplant during outbreak)
IPV	Routine schedule
LAIV	Contraindicated
Meningococcal	Routine schedule
MMR	Contraindicated
MMRV	Contraindicated
PCV13	Recommended, if not given pretransplant (high risk for pneumococcal disease)

TABLE EC 16.C—cont'd

Vaccine	Administration Recommendations (Starting 2–6 Months Posttransplant)
PPSV23	Recommended for age ≥2 years, if not given pretransplant (high risk for pneumococcal disease)
Rotavirus	Contraindicated
Varicella	Contraindicated[a]

[a]Exception: Select nonimmune patients with renal or liver transplant receiving minimal or no immunosuppression and without recent graft rejection.

NOTE: Vaccination should not be withheld because of concern about transplant rejection.

DT, Diphtheria and tetanus vaccine; *DTaP,* diphtheria, tetanus, acellular pertussis vaccine; *HepA,* hepatitis A; *HepB,* hepatitis B; *Hib, Haemophilus influenzae* type b; *HPV,* human papilloma virus; *IIV,* inactivated influenza vaccine; *IPV,* inactivated polio vaccine; *LAIV,* live, attenuated influenza vaccine; *MMR,* measles, mumps, rubella; *MMRV,* measles, mumps, rubella, varicella; *PCV13,* pneumococcal 13-valent conjugate vaccine; *PPSV23,* pneumococcal 23-valent polysaccharide vaccine; *Td,* tetanus and diphtheria vaccine; *Tdap,* tetanus, diphtheria, acellular pertussis vaccine.

TABLE 16.6

LIVE VACCINE IMMUNIZATION FOR PATIENTS RECEIVING CORTICOSTEROID THERAPY

Steroid Dose	Recommended Guidelines
Topical, inhaled, or local injection of steroids. Low-dose steroids (<2 mg/kg/day or <20 mg/day of prednisone equivalent[a]), including physiologic doses	Live vaccines can generally be given unless there is clinical evidence of immunosuppression.
High-dose steroids (≥2 mg/kg/day or ≥20 mg/day of prednisone equivalent[a]) duration of therapy <14 days	Live vaccines may be given immediately after cessation of therapy (but consider 2-week delay).
High-dose steroids (≥2 mg/kg/day or ≥20 mg/day of prednisone equivalent[a]) duration of therapy ≥14 days	Delay live vaccines until 4 weeks after discontinuation of therapy.
Systemic or local steroids in patients with underlying disease affecting immune response (e.g., lupus) or receiving other immunosuppressant medication	Do not administer live vaccines.

[a]20 mg/day cutoff for children weighing more than 10 kg.
Adapted from pages 84–85 of the 2018 Red Book.[29]

10. **Patients on biologic response modifiers**
    a. See Table 1.20 of the 2018 Red Book for details.[29]
    b. Antibodies to proinflammatory cytokines or proteins that bind to cytokine receptors (e.g., tumor necrosis factor [TNF]-α inhibitors) are considered highly immunosuppressive.
    c. Prior to initiating therapy:
        (1) Perform serologic testing for hepatitis B virus and vaccinate/revaccinate if hepatitis B surface antibody (HBsAb) is <10 mIU/mL.
        (2) Give inactivated vaccines (including IIV) ≥2 weeks prior to starting therapy.
        (3) Give live-virus vaccines ≥4 weeks prior, unless contraindicated by condition or other therapies.
    d. During/after therapy:
        (1) Live-virus vaccines: Contraindicated during therapy. Interval after therapy for safe administration has not been established.
        (2) Inactivated vaccines (including IIV): Give according to schedule.
11. **Patients treated with immunoglobulin or other blood products**
    See Table EC 16.D for suggested intervals between blood product and MMR or varicella administration.

B. Disease-Specific Considerations

1. **Children at high risk of Hib[10]**
    a. Indications: Functional or anatomic asplenia (including sickle cell disease), HIV infection, immunoglobulin deficiency, early component complement deficiency, or chemotherapy/radiation.

Table EC 16.D

RECOMMENDED INTERVALS BETWEEN ADMINISTRATION OF ANTIBODY-CONTAINING PRODUCTS AND MMR/VARICELLA VACCINES

Product/Indication (Dosing)	Interval (Months)
BLOOD TRANSFUSION (ALL 10 ML/KG IV)	
Washed RBCs	0
RBCs, adenine-saline added	3
Packed RBCs	6
Whole blood	6
Plasma/platelet products	7
INTRAMUSCULAR IMMUNOGLOBULIN	
Hepatitis A IgG (0.1–0.2 mL/kg IM)	3
Hepatitis B IgG (HBIG) (0.06 mL/kg IM)	3
Tetanus IgG (TIG) (250 units IM)	3
Rabies IgG (RIG) (20 units/kg IM)	4
Palivizumab (RSV monoclonal Ab) (15 mg/kg IM)	0
Varicella IgG (VariZIG) (125 units/10 kg IM; max 625 units)	5
Measles prophylaxis IgG (immunocompetent contacts; 0.5 mL/kg IM)	6
INTRAVENOUS IMMUNOGLOBULIN	
Cytomegalovirus IVIG (150 mg/kg max)	6
Botulinum IVIG (BabyBIG) (1.0 mL/kg IV)	6
IVIG	
• Replacement therapy for immune deficiencies (300-400 mg/kg)	8
• Postexposure measles prophylaxis (immunocompromised contacts) (400 mg/kg)	8
• Postexposure varicella prophylaxis (400 mg/kg)	8
• ITP treatment (400 mg/kg)	8
• ITP treatment (1000 mg/kg)	10
• Kawasaki disease (2 g/kg)	11

IM, Intramuscular; *ITP,* immune; *IV,* intravenous; *IVIG,* intravenous immunoglobulin; *RBCs,* red blood cells; *RSV,* respiratory syncytial virus.

Modified from Appendix A from Centers for Disease Control and Prevention. *Epidemiology and Prevention of Vaccine-Preventable Diseases.* In: Hamborsky J, Kroger A, Wolfe S, eds. 13th ed. Washington, DC: Public Health Foundation; 2015. Available online at: www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/a/mmr_ig.pdf

b. Age <12 months: Give primary series.
c. Age 12 to 59 months:
   (1) Received 0 to 1 dose(s) before 12 months: Give 2 doses at 8-week intervals.
   (2) If ≥2 doses were received <12 months: Give 1 additional dose at least 8 weeks after previous dose.
d. Age ≥5 years and not fully immunized with asplenia or HIV: Give 1 dose at least 8 weeks after previous dose.

2. **Children at high risk of meningococcal disease**[11-13]
   a. Indications: Functional or anatomic asplenia, HIV infection, persistent complement deficiency (including Eculizumab use), travel to or residence in areas with hyperendemic or epidemic meningococcal disease, or residence in a community with a meningococcal outbreak.
   b. Age <2 years:
      (1) MenACWY-CRM (Menveo): If age 8 weeks to 6 months, give 4 doses at 2, 4, 6, and 12 months. If age 7 to 23 months and unvaccinated, give 2 doses with second dose ≥12 weeks after first dose and after first birthday.
      (2) MenACWY-D (Menactra): Can use for persistent complement component deficiency or travel, but not for anatomic/functional asplenia, sickle cell disease, or HIV infection before age 2 years. If age 9 to 23 months, give two doses 12 weeks apart (8-week interval acceptable if needed prior to travel).
   c. Age ≥2 year: Give two doses of Menactra or Menveo (min. 8-week interval). Only one dose is needed for children who are traveling, live in hyperendemic regions, or during an outbreak. Give Menactra ≥4 weeks after completing PCV13 series.
   d. Boosters:
      (1) Most recent dose given <7 years old: Give one booster dose 3 years after completion of the primary series, then every 5 years thereafter.
      (2) Most recent dose given ≥7 years old: Give one booster dose every 5 years.
   e. Age ≥10 years with asplenia or persistent complement deficiency:
      (1) Give two-dose MenB-4C (Bexsero) or three-dose MenB-FHbp (Trumenba) in addition to MCV4 series.
      (2) The two MenB vaccines are **not** interchangeable; use the same product for all doses in a series.

3. **Children at high risk for pneumococcal disease**[14,15]
   a. Indications:
      (1) Immunocompromised: Functional or anatomic asplenia (including sickle cell disease), primary immunodeficiencies, HIV infection, malignancy, immunosuppressive or radiation therapy, solid organ transplant, chronic renal failure or nephrotic syndrome

(2) Other chronic conditions: Chronic heart disease, chronic lung disease, diabetes mellitus, CSF leak, cochlear implant, chronic liver disease, or alcoholism

b. All recommended doses of PCV13 should be given prior to PPSV23, if possible.
c. Age <6 years at high risk: Complete primary series with PCV13.
d. Age ≥2 years at high risk: Give one dose of PPSV23 ≥8 weeks after last PCV13 dose.
e. Age ≥6 years with immunocompromise, CSF leak, or cochlear implant with no history of PCV13: Give one dose of PCV13 ≥8 weeks after any prior PPSV23. Wait ≥8 weeks before giving PPSV23 if patient has never received PPSV23.
f. Age ≥6 years with immunocompromise: Give one PPSV23 booster dose 5 years after the first dose (do not repeat).

C. Preterm Infants

1. **Immunize according to chronologic age, using regular vaccine dose.** Defer risk of rotavirus vaccine until hospital discharge.
2. **Hepatitis B**:
   a. For infants <2 kg born to hepatitis B surface antigen (HBsAg) negative mothers, delay first vaccine dose until 1 month of age or hospital discharge (whichever is first).
   b. For management of preterm and low-birth-weight infants of mothers with positive or unknown HepB status, see Fig. 16.1.
3. See Table 16.2 for indications for respiratory syncytial virus (RSV) immunoprophylaxis.

D. Pregnant Women

1. **Tdap (tetanus, diphtheria, acellular pertussis)**: Give during each pregnancy, preferably at 27 to 36 weeks gestation, regardless of prior immunization status.
2. **Give IIV** regardless of trimester. Do not give LAIV.
3. **Other inactivated vaccines**: Considered precautionary and generally deferred until after the pregnancy.
4. **Live vaccines**: Generally contraindicated during pregnancy.

E. Immigration, Emigration, and Travel

1. **Travelers**:
   a. See CDC's Travelers' Health site for destination-specific recommendations: http://www.cdc.gov/travel/destinations/list.
   b. Consider referral to a travel clinic.
2. **Immigrants from outside the United States.**
   See CDC's Immigrant and Refugee Health site for recommendations for immigrants, refugees, and international adoptees: http://www.cdc.gov/immigrantrefugeehealth/.

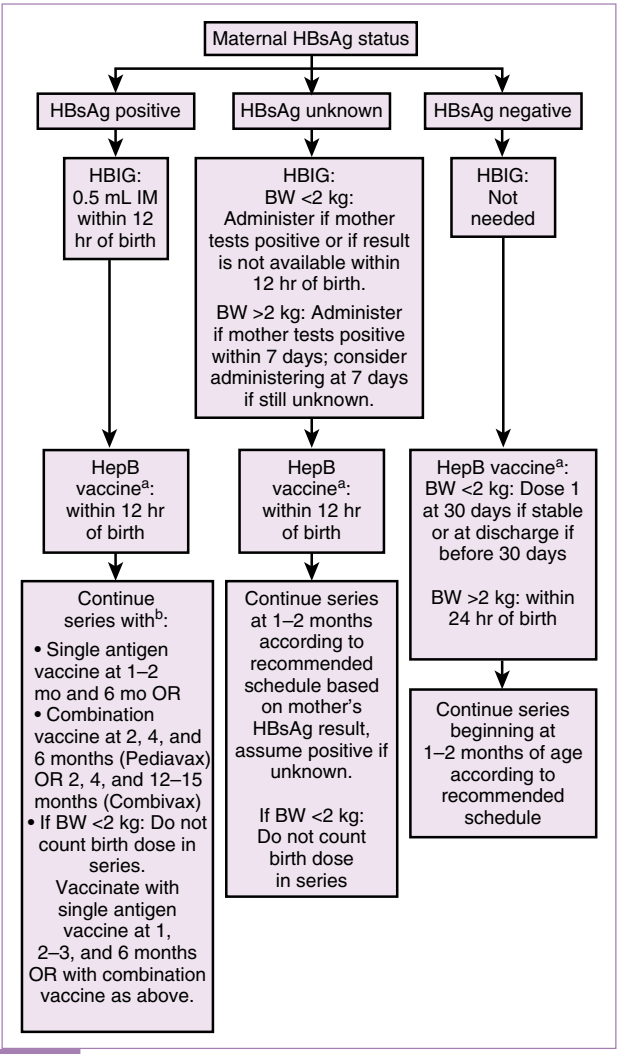

FIGURE 16.1

Management of neonates born to mothers with unknown or positive hepatitis B surface antigen *(HBsAg)* status. [a]Only single antigen vaccine should be used. [b]Reimmunization may be required based on anti-HBs; test for HBsAg and anti-HBs at age 9 to 12 months or 1 to 2 months after completion of HepB series if delayed. HBsAg-negative infants with anti-HBs levels ≥10 mIU/mL are protected. HBsAg-negative infants with anti-HBs levels <10 mIU/mL should be reimmunized with a fourth dose and retested. If still <10 mIU/mL, two additional doses should be given. If after six doses the levels are <10 mIU/mL, no additional doses of HepB vaccine are indicated. *BW,* birth weight; *HBIG,* hepatitis B immune globulin; *HepB,* hepatitis B. (Modified from American Academy of Pediatrics. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Elk Grove Village, IL: AAP; 2018.)

V. COUNSELING AND COMMUNICATION ABOUT VACCINES[16-26]

A. Vaccine Hesitancy

1. **Definition**: Delay in the acceptance or refusal to vaccinate despite the availability of vaccine services. Not a dichotomous behavior, but a continuum. Vaccine-hesitant parents may accept all vaccines but remain concerned, accept some vaccines and refuse others, or refuse all vaccines. Approximately 3% of parents in the United States refuse all vaccines.[20]
2. The AAP recommends continued engagement with vaccine-hesitant parents while providing other health services and attempting to modify opposition to vaccines.
3. **Determinants of vaccine acceptance**
   a. The 3C Model: Confidence, Complacency, Convenience. Key determinants of vaccine acceptance in global populations as determined by the World Health Organization (WHO) SAGE Working Group on Vaccine Hesitancy. See Online Content for more details.
   b. Parental concerns about vaccines (Box 16.1)

BOX 16.1

PARENTAL CONCERNS ABOUT VACCINES

Vaccine Safety
Too many vaccines
Development of autism
Vaccine additives (thimerosal, aluminum)
Overload of the immune system
Serious adverse reactions
Potential for long-term adverse events
Inadequate research performed before licensure
May cause pain to the child
May make the child sick
Necessity of Vaccines
Disease is more "natural" than vaccine
Parents do not believe diseases being prevented are serious
Vaccine-preventable diseases have disappeared
Not all vaccines are needed
Vaccines do not work
Freedom of Choice
Parents have the right to choose whether to immunize their child
Parents know what's best for their child
Believe that the risks outweigh the benefits of vaccine
Do not trust organized medicine, public health
Do not trust government health authorities
Do not trust pharmaceutical companies
Ethical, moral, or religious reasons

Adapted from Table 2 of Edwards KM, Hackell JM, AAP Committee on Infectious Diseases, The Committee on Practice and Ambulatory Medicine. Countering vaccine hesitancy. *Pediatrics*. 2016;138(3):e20162146.

TABLE 16.7

HEPATITIS B VIRUS PROPHYLAXIS AFTER PERCUTANEOUS EXPOSURE TO BLOOD

Exposed Person	HBsAg Status of Source of Blood: Positive	Negative	Unknown
Unimmunized	HBIG and HBV series	HBV series	HBV series
PREVIOUSLY IMMUNIZED			
Known responder	No treatment	No treatment	No treatment
Known nonresponder	HBIG and HBV series (or HBIG ×2 at 1-month interval if already received two HBV series without response)	No treatment	Treat as if positive if known high-risk source
Response unknown	Test exposed person for anti-HBs[a]: If adequate, no treatment If inadequate, HBIG ×1 and HBV booster	No treatment	Test exposed person for anti-HBs[a]: If adequate, no treatment If inadequate, HBV booster dose and recheck titer in 1–2 months

[a]Adequate anti-HBs is ≥10 mIU/mL.

Anti-HBs, hepatitis B surface antibody; *HBIG,* hepatitis B immune globulin; *HBV,* hepatitis B vaccine.

Adapted from Table 3.23 of the 2018 Red Book.[29]

TABLE 16.8

RABIES POSTEXPOSURE PROPHYLAXIS BASED ON ANIMAL

Animal Type	Evaluation and Disposition of Animal	Postexposure Prophylaxis Recommendations
Dog, cat, ferret	Healthy and available for 10 days' observation	Do not begin prophylaxis unless animal develops signs of rabies
	Rabid or suspected rabid: euthanize animal and test brain	Provide immediate immunization and RIG[b]
	Unknown (escaped)	Consult public health officials
Skunk, raccoon, bat,[a] fox, woodchuck, most other carnivores	Regard as rabid unless geographic area is known to be free of rabies or until animal is euthanized and proven negative by testing	Provide immediate immunization and RIG[b]
Livestock, rodents, rabbit, other mammals	Consider individually	Consult public health officials; these bites rarely require treatment

[a]In the case of direct contact between a human and a bat, consider prophylaxis even if a bite, scratch, or mucous membrane exposure is not apparent.

[b]Treatment may be discontinued if animal fluorescent antibody is negative.

RIG, Rabies immune globulin.

Adapted from Table 3.63 of the 2018 Red Book.[29]

TABLE 16.9

INDICATIONS FOR TETANUS PROPHYLAXIS

Prior Tetanus Toxoid Doses	Clean, Minor Wounds		All Other Wounds	
	Tetanus Vaccine[a]	TIG	Tetanus Vaccine[a]	TIG
Unknown or <3	Yes	No	Yes	Yes
≥3, last <5 years ago	No	No	No	No
≥3, last 5–10 years ago	No	No	Yes	No
≥3, last ≥10 years ago	Yes	No	Yes	No

[a]DTaP preferred under age 7 years; Tdap preferred over age 7 years. DT or Td if pertussis is contraindicated.
DT, Diphtheria and tetanus vaccine; *DTaP,* diphtheria, tetanus, acellular pertussis vaccine; *Td,* tetanus and diphtheria vaccine; *Tdap,* tetanus, diphtheria, acellular pertussis vaccine; *TIG,* tetanus immune globulin.
Adapted from Table 3.78 of the 2018 Red Book.[29]

B. Countering Vaccine Hesitancy

1. Parent and/or patient-specific concerns should be acknowledged and addressed while correcting misconceptions in a nonconfrontational manner.
2. Relationship with primary care provider/pediatrician is a strong influence on decision to vaccinate. Mutual desire to do what is best for the child should be emphasized.
3. See Section VII: Online Content, for more information on specific communication strategies and interventions, as well as online provider resources.

VI. WEB RESOURCES[27-33]

- **Advisory Committee on Immunization Practices (ACIP) Vaccine Recommendations and Guidelines**: www.cdc.gov/vaccines/hcp/acip-recs/index.html
- **Epidemiology and Prevention of Vaccine-Preventable Diseases (Pink Book)**: www.cdc.gov/vaccines/pubs/pinkbook/index.html
- **AAP Report of the Committee on Infectious Diseases (Red Book)**: http://redbook.solutions.aap.org/
- **CHOP Vaccine Education Center**: http://www.chop.edu/centers-programs/vaccine-education-center
- **WHO Immunization, Vaccines and Biologicals**: www.who.int/immunization/
- **VaxView**: www.cdc.gov/vaccines/vaxview/index.html
  Data for ACIP-recommended vaccine coverage across the United States.
- **Vaccine Adverse Event Report System (VAERS)**: http://vaers.hhs.gov/
  National vaccine safety surveillance program run by the CDC and U.S. Food and Drug Administration (FDA) that collects information about post-vaccination adverse events.
- **Vaccines for Children (VFC) Program**: www.cdc.gov/vaccines/programs/vfc/about/index.html
  Provides vaccines to children who parents/guardians may not be able to afford them.
- **Centers for Disease Control and Prevention (CDC) Vaccine Shortages and Delays**: www.cdc.gov/vaccines/hcp/clinical-resources/shortages.html

REFERENCES

A complete list of references can be found online at www.expertconsult.com.

VII. ONLINE CONTENT

A. Additional Vaccine Recommendations

1. Vaccine Information for Patients with Immunodeficiencies (Table EC 16.A)
2. Vaccinations After HSCT (Table EC 16.B)
3. Vaccinations After Solid Organ Transplant (Table EC 16.C)
4. Recommended Intervals Between Administration of Antibody-Containing Products and MMR/Varicella Vaccines (Table EC 16.D)

B. The 3C Model: Key Barriers to Vaccine Use Worldwide[16]

1. Confidence: Trust in healthcare professionals, vaccines, and their effectiveness. Includes concerns regarding vaccine safety, quality of interactions with healthcare providers, religious beliefs, and media influence.
2. Complacency: Low awareness of the risks of vaccine-preventable diseases and the importance of vaccines. Includes resistance to introduction of new vaccines, resistance to mode of vaccine delivery, and lack of knowledge about the risks of now uncommon diseases.
3. Convenience: Availability of and accessibility to vaccines and healthcare services (rural areas, low-middle income countries). Includes vaccine supply issues, lack of education or medical literacy, geographic barriers, political conflicts and instability, and immigration.

C. Strategies to Address Vaccine Hesitancy[18-19,22-26]

1. Communication
   a. Studies have found that parents want more information than they are getting, want balanced information about potential benefits and harms, struggle to find unbiased, trustworthy sources of information, and view healthcare workers as an important source of information.
   b. Consider the timing for making vaccination information available to parents, the settings where information is available, the provision of impartial and clear information tailored to parental needs, and parents' perceptions of health workers and the information provided.
   c. AAP Communication Highlights (Box EC 16.A)
2. Interventions
   a. SAGE Working Group assessed systematic reviews and meta-analyses of worldwide strategies to address vaccine hesitancy. No convincing evidence that any specific intervention to address parental vaccine hesitancy/refusal is effective across populations.
   b. Most effective interventions were tailored to specific populations and addressing specific concerns, pointing to the importance of understanding the drivers of vaccine hesitancy to inform the interventions.
   c. Most successful interventions were multicomponent strategies that directly targeted unvaccinated/under vaccinated populations, aimed to increase vaccine knowledge and awareness, improved convenience and access to vaccination, mandated vaccination, and engaged religious or other influential leaders to promote vaccination.

BOX EC 16.A

VACCINE COMMUNICATION HIGHLIGHTS

Vaccines are safe and effective, and serious disease can occur if your child and family are not immunized.

Vaccine-hesitant individuals are a heterogeneous group, and their individual concerns should be respected and addressed.

Vaccines are tested thoroughly before licensure, and vaccine safety assessment networks exist to monitor vaccine safety after licensure.

Nonmedical vaccine exemptions increase rates of unvaccinated children.

Unvaccinated children put vaccinated children and medically exempt children who live in that same area at risk.

Pediatricians and other healthcare providers play a major role in educating parents about the safety and effectiveness of vaccines.

Strong provider commitment to vaccination can influence hesitant or resistant parents. Personalizing vaccine acceptance is often an effective approach.

The majority of parents accepted the provider's vaccine recommendations when they were presented as required immunizations to maintain optimal disease prevention.

The current vaccine schedule is the only one recommended by the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP). Alternative schedules have not been evaluated.

Adapted from Table 4 of Edwards KM, Hackell JM, AAP Committee on Infectious Diseases, The Committee on Practice and Ambulatory Medicine. Countering vaccine hesitancy. *Pediatrics*. 2016;138(3):e20162146.

D. Provider Resources for Vaccine Communication

1. WHO guide to addressing vaccine hesitancy: www.who.int/immunization/programmes_systems/vaccine_hesitancy/en
2. CDC resources for effective communication with parents regarding vaccines
   a. Vaccine conversations with parents: https://www.cdc.gov/vaccines/hcp/conversations/conv-materials.html
   b. List of public health, policy, and clinical studies for helping providers increase vaccination rates in their communities: www.cdc.gov/vaccines/hcp/admin/reminder-sys.html
3. The Community Guide: www.thecommunityguide.org/topic/vaccination Regularly publishes evidence-based recommendations on interventions intended to improve routine delivery of universally recommended vaccinations in the United States (in collaboration with the CDC).
4. AAP Tools
   a. AAP refusal to vaccinate form: https://www.aap.org/en-us/Documents/immunization_refusaltovaccinate.pdf
   b. Risk communication videos: https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/immunization/Pages/vaccine-hesitant-parents.aspx#Video

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Chapter 17

Microbiology and Infectious Disease

Kevin Klembczyk, MD and Samuel McAleese, MD

I. COMMON NEONATAL AND PEDIATRIC INFECTIONS: GUIDELINES FOR DIAGNOSIS AND INITIAL MANAGEMENT

Tables 17.1–17.6 and Figs. 17.1–17.3 present the most common neonatal and pediatric infections, organized by site of infection or by organism, when applicable. These recommendations are based on national guidelines and recent literature. They are not meant to replace clinical judgment.

For recommendations on preliminary identification of bacteria and antibiotic selection based on spectrum of activity for commonly used antibiotics, please see Sections II–III. Please note that local resistance pattern should guide antibiotic selection. Follow published institutional guidelines and culture results for individual patients and infections. When possible, always use the agent with the narrowest spectrum of activity, particularly when organism susceptibilities are known.

A. Congenital, Perinatal, and Neonatal Infections (Table 17.1)

B. Pediatric Infections by System (Table 17.2)

C. Pediatric Viral Illnesses (Table 17.3)

D. Pediatric Tick-Borne Diseases (Table 17.4)

E. Tuberculosis: Diagnosis and Treatment (Boxes 17.1 and 17.2)[1,2]

1. Diagnosis
   a. See Box 17.1 for screening guidelines and Box 17.2 for information on interpretation of tuberculin skin tests (TSTs) and interferon gamma release assays (IGRAs).
   b. If positive screening test, obtain chest X-ray.
   c. If symptoms indicate active tuberculosis (TB) disease, determine source.
      (1) Consider pediatric protocol chest CT over X-ray when available.
      (2) Specimen sources include sputum, bronchial washings, gastric aspirates (morning aspirate before feeding/ambulation x 3 specimens), pleural fluid, cerebrospinal fluid, urine, tissue biopsy.
      (3) Acid-fast smear and/or nucleic acid amplification testing may provide rapid diagnosis. The latter may also detect rifampin resistance. Solid media culture can take as long as 10 weeks, liquid media 1 to 6 weeks.
   d. Lumbar puncture is recommended in children less than 12 months with confirmed TB and should be considered in children 12 to 24 months. (Cont'd on pg. 433.)

TABLE 17.1

CONGENITAL, PERINATAL, AND NEONATAL INFECTIONS

	Presentation	Etiology	Diagnosis	Treatment
CONGENITAL AND PERINATAL INFECTIONS				
Cytomegalovirus[1]	**Congenital**: 90% asymptomatic at birth. IUGR, jaundice, thrombocytopenia, petechiae, hepatosplenomegaly, transaminitis, microcephaly, intracranial calcifications, sensorineural hearing loss, and retinitis. **Perinatal**: sepsis, pneumonitis, hepatosplenomegaly, transaminitis	Herpes virus. Congenital infection is transmitted in utero. Perinatal infection may be transmitted via birth canal or breastmilk.	PCR or rapid viral culture of saliva, urine, blood, sputum, or CSF. Variable practice of screening infants (urine or saliva). May target those who fail newborn hearing screen or with low birth weight.	Congenital: PO valganciclovir for 6 months if symptomatic. Affected infants should have hearing tested at regular intervals. Perinatal: IV ganciclovir for 2–3 weeks. Follow CMV serum viral load.
Group B Strep[3,48]	Early-onset: 0–6 days, typically within 24 hr. Most commonly pneumonia, bacteremia, or meningitis. Late-onset: 7–89 days, typically 3–4 weeks. Most commonly bacteremia or meningitis. Also septic arthritis, osteomyelitis, UTI, and cellulitis.	Transmitted by mother with genitourinary GBS colonization OR in setting of maternal infection (bacteremia, endometritis, chorioamnionitis). Intrapartum antibiotics decrease transmission (at least 1 dose ≥4 hr prior to delivery).	Multiple accepted approaches for risk assessment among infants born >35 weeks of gestation. Example of common, categorical approach shown in Fig. 17.1. Newer, multivariate risk assessment (Neonatal Early-Onset Sepsis Calculator) is available at: https://neonatalsepsiscalculator.kaiserpermanente.org. Diagnosis made by culture.	Penicillin G. Presumptive early-onset GBS sepsis: ampicillin and gentamicin. Empiric treatment for late-onset GBS meningitis: ampicillin and cefotaxime. Ceftriaxone if >30 days. Consider inclusion of vancomycin for *Streptococcus pneumoniae* meningitis.
Hepatitis B[1]	90% of infants infected perinatally or in first year of life develop chronic HBV infection, leading to: 1. Chronic low-grade hepatitis 2. Progression to cirrhosis and HCC 3. Risk of reactivation acute hepatitis	Hepadnavirus usually transmitted perinatally (rather than in utero), from mother with acute or active chronic infection. 95% of transmission prevented with appropriate immunoprophylaxis at birth.[4]	If mother HBsAg-positive, test infant for HBsAg and anti-HBsAg between 9 and 12 months (or 1–2 months after final HBV vaccine). Monitor HBV DNA and ALT in chronic HBV. Infection cleared at ~1% per year. See Table 17.5 for interpretation of serologies.	See Chapter 16 for immunoprophylaxis with HBV vaccine and HBIG. Breastfeeding is safe. Refer for treatment if active HBV replication with elevated ALT for 6 months.

Continued

TABLE 17.1—cont'd

CONGENITAL, PERINATAL, AND NEONATAL INFECTIONS

	Presentation	Etiology	Diagnosis	Treatment
Hepatitis C[1]	80% of acute infections become chronic. Syndrome less pronounced than in hepatitis B.	Flavivirus transmitted in utero or perinatally from about 5% of infected (RNA-positive) mothers.	HCV antibody at 18 months (maternal HCV antibodies persist 12+ months). Monitor ALT.	Rapidly evolving field. New oral antiviral regimens approved for 12+ years. Breastfeeding safe.
Herpes simplex virus[1]	Presents within first 4 weeks as: 1. Localized to skin, eyes, and mouth (45%) 2. Localized CNS (30%) 3. Disseminated (25%) with sepsis, pneumonitis, hepatitis, consumptive coagulopathy, and CNS involvement.	Herpes virus transmitted most commonly via maternal genital tract with active HSV lesions. Less commonly ascending (in utero) and postnatal (via caregivers) transmission.	Surface culture or PCR from active vesicles, mouth, nasopharynx, conjunctivae, and anus. PCR or culture of blood and CSF. Viremia can be seen in nondisseminated disease.	IV acyclovir: 14 days for skin, eye, and mouth disease; 21 days for CNS or disseminated disease. CSF clearance must be proven. Treat eye involvement with additional topical antiviral. All types receive 6 months PO prophylaxis.
Rubella[1]	IUGR, cataracts, glaucoma, cardiac anomalies (PDA and PPS), deafness, "blueberry muffin rash."	Togavirus transmitted via primary maternal infection (85% chance of transmission if maternal infection before 12 weeks gestation).	IgM at birth. Level typically would increase within first 6 months of life. Diagnosis can be confirmed by stable or increasing IgG level over first 7 to 11 months. RNA PCR and viral culture also used.	Supportive care, with evaluation by ophthalmology and cardiology.
Syphilis[1]	May be asymptomatic at birth. Oro/nasophraryngeal secretions ("snuffles"), mucocutaneous lesions, maculopapular rash, hepatosplenomegaly, hemolytic anemia, thrombocytopenia. If untreated, CNS, bones/joints/teeth, eyes, and skin affected by late disease.	*Treponema pallidum* is a spirochete transmitted in utero at any stage of maternal syphilis.	If maternal nontreponemal serology positive (RPR or VDRL), obtain maternal treponemal test (STT) and screen infant nontreponemal tests. Reverse sequence testing is also practiced. Full evaluation includes: CBC, transaminases, CSF analysis, long-bone x-rays, adnominal US neuro-imaging, ophtho exam, ABR testing.	Full evaluation and treatment indicated for infants at high risk: Abnormal exam or infant RPR or VDRL titer fourfold greater than maternal or mother inadequately treated. Full treatment: IV aqueous penicillin G or IM procaine penicillin G for 10 days. If less likely (normal exam, RPR/VDRL ≤ fourfold maternal titer, and mother

			Refer to Red Book for interpretation of screening tests, diagnostic approach, and treatment algorithms.	treated during pregnancy >4 weeks before delivery): benzathine penicillin G single dose. If unlikely (normal exam, RPR/VDRL ≤ fourfold maternal titer, mother treated before pregnancy, and maternal titer low and stable before and throughout pregnancy): ensure titer returns to negative. Some experts give benzathine penicillin G single dose.
Toxoplasmosis[1]	May be asymptomatic at birth. Major: chorioretinitis, cerebral calcifications, hydrocephalus. Other: IUGR, microcephaly, seizures, hearing loss, strabismus, maculopapular rash, cytopenias.	Intracellular parasite transmitted via primary infection during pregnancy (contracted from cat feces or undercooked meat).	Serologies and PCR. Positive IgM after 5 days or IgA after 10 days is diagnostic. Positive PCR in CSF, blood, or urine is diagnostic. Eye exam for chorioretinitis. CT is most sensitive for cerebral calcifications.	Pyrimethamine + sulfadiazine with folinic acid for at least 12 months.
Varicella[1]	Congenital infection → varicella embryopathy = limb hypoplasia, cutaneous scarring, eye/CNS damage. Maternal disease onset at 5 days pre-through 2 days postpartum confers high risk of disseminated infection in infant, with high mortality, due to lack of sufficient maternal antibodies.	Herpes virus transmitted via primary maternal infection, most commonly during 1st or early 2nd trimester. Also via active lesions peripartum.	PCR of vesicle or scab swab is gold standard. PCR of saliva less sensitive.	Acyclovir 10 days in disseminated disease. Immunoprophylaxis with VariZIG (or IVIG): 1. Mother develops primary varicella between 5 days pre- and 2 days postpartum. 2. Hospitalized preterm infants with known exposure.[5]

Continued

TABLE 17.1—cont'd

CONGENITAL, PERINATAL, AND NEONATAL INFECTIONS

	Presentation	Etiology	Diagnosis	Treatment
Zika virus[6]	Microcephaly, CNS or ocular anomalies, deafness, congenital contractures.	Flavivirus transmitted in utero after primary maternal infection.	Workup: RNA PCR of blood/urine, IgM in serum, and neuroimaging. Test if: 1. Clinical findings with possible maternal infection in pregnancy based on stay in endemic areas. 2. Lab-proven maternal infection in pregnancy, even without clinical findings.	Supportive. Head ultrasound, audiology evaluation, and full ophthalmologic exam by 1 month. See Red Book and latest WHO/CDC algorithms.
NEONATAL INFECTIONS				
Fever in infant[7,8]	Serious bacterial infections (UTI, bacteremia, meningitis) are common in febrile infants. Risk is significant even if well-appearing without a clear source. Unimmunized infants, premature infants, or infants who received antibiotics recently are at higher risk for serious bacterial infection.	0–28 days: *Escherichia coli, Klebsiella pneumoniae, GBS.* Rarely, *Listeria.* 29+ days: The marked decline in invasive infections due to *Haemophilus influenzae type b* and *S. pneumoniae* since introduction of conjugate vaccines has reduced the likelihood of serious bacterial infection in this age group. In neonates under 90 days, vast majority of bacterial infections are UTIs.	Ill-appearing infant or <28 days, require full sepsis workup and admission. Goal with well-appearing infants >28 days is identifying those who can be safely discharged and monitored as outpatient with or without antibiotics. Well-established algorithms often rely on the Rochester, Philadelphia, and Boston criteria. Step-by-Step approach is a newer model that is also generally accepted. Our approach is outlined in Fig. 17.2.	Empiric therapy: 0–28 days: ampicillin + gentamicin or cefotaxime when meningitis is suspected. Add acyclovir as clinically indicated. 29+ days: ceftriaxone In well-appearing infants with negative cultures, treatment and admission can be shortened to 24–36 hr (blood cultures positive by 24 hr in 91% of cases of bacteremia[7]). Macrolide antibiotic if confirmed chlamydia pneumonia.

Neonatal exudative conjunctivitis[1,9]	*Neisseria gonorrhoeae* Onset 2–5 days. *Chlamydia trachomatis* Onset 5–12 days.	Culture is gold standard. DFA is FDA-approved. NAAT often used. Culture secretions. Gonococcal ophthalmia should prompt hospitalization and evaluation for disseminated disease.	Gonorrhea: ceftriaxone or cefotaxime single dose. Chlamydia: oral azithromycin × 3 days or erythromycin × 14 days. Saline irrigation.

ABR, Auditory brainstem response; *ALT*, alanine aminotransferase; *CBC*, complete blood count; *CDC*, Centers for Disease Control; *CMV*, cytomegalovirus; *CNS*, central nervous system; *CSF*, cerebrospinal fluid; *CT*, computed tomography; *DFA*, direct fluorescent antibody; *DNA*, deoxyribonucleic acid; *FDA*, Food and Drug Administration; *GBS*, group B streptococcus; *HBIG*, hepatitis B immunoglobulin; *HBsAg*, hepatitis B surface antigen; *HBV*, hepatitis B virus; *HCC*, hepatocellular carcinoma; *HCV*, hepatitis C virus; *HSV*, herpes simplex virus; *Ig*, immunoglobulin; *IM*, intramuscular; *IUGR*, intrauterine growth restriction; *IV*, intravenous; *IVIG*, intravenous immunoglobulin; *NAAT*, nucleic acid amplification test; *PCR*, polymerase chain reaction; *PDA*, patent ductus arteriosus; *PO*, by mouth; *PPS*, peripheral pulmonic stenosis; *RNA*, ribonucleic acid; *RPR*, rapid plasma regain; *SNHL*, sensorineural hearing loss; *UTI*, urinary tract infection; *VDRL*, venereal disease research laboratory test; *WHO*, World Health Organization.

TABLE 17.2

PEDIATRIC INFECTIONS BY SYSTEM

	Presentation	Etiology	Diagnosis	Treatment
CENTRAL NERVOUS SYSTEM				
Meningitis[11,12]	Infant: ill-appearing, fever, hypothermia, lethargy, vomiting, poor feeding, seizures, bulging fontanelle. Child and adolescent: fever, headache, altered mental status, nuchal rigidity, photophobia, nausea, vomiting. Can be progressive or acute and fulminant.	<1 month: *Group B Streptococcus, Escherichia coli, Klebsiella, Listeria* 1–23 months: *Streptococcus pneumoniae, Neisseria meningitidis, S. agalactiae* (GBS), *Haemophilus influenzae.* 2+ years: *S. pneumoniae, N. meningitidis.* Brain abscess: *Streptococcus* spp., anaerobes, *Staphylococcus aureus*	Indication for head CT prior to LP: immunocompromised, known CNS disease, papilledema, focal neurologic deficit (not including CN VI/VII palsy). LP for Gram stain, culture, and analysis. See Table 17.6.	If hemodynamically unstable, do not delay antibiotics for head CT or LP. <1 month: ampicillin + cefotaxime. 1+ month: vancomycin + ceftriaxone Adjunctive dexamethasone may reduce hearing loss in children >6 weeks with *H. influenzae* type B meningitis. Brain abscess: vancomycin + ceftriaxone + metronidazole.
VP shunt infection[11]	Similar to meningitis.	*Staphylococcus epidermidis, S. aureus,* Gram-negative bacilli, *Cutibacterium acnes.*	MRI with gadolinium. CSF analysis and culture (shunt sampling/tap or LP).	Vancomycin and cefepime. Removal of infected hardware and shunt externalization.
HEAD AND NECK				
Conjunctivitis[12]	Foreign body sensation, itching, burning, photophobia, hyperemia.	Viruses (~80% of cases, especially adenovirus), *S. pneumoniae, H. influenzae,* *Neisseria gonorrhoeae, Chlamydia trachomatis.* Noninfectious: allergic, toxic, inflammatory, dry eyes.	Clinical diagnosis is nonspecific, and individual symptoms are unreliable. Allergic: watery, pruritic. Viral: fever, bilateral conjunctivitis, lymphadenopathy. Bacterial: fever, purulent discharge, pain.	Viral: supportive care. Bacterial: ophthalmic polymyxin B/TMP drops for bacterial infection. Ointments preferred in young children. Ophthalmology consult if photophobia, vision loss, severe pain, recurrent episodes, or suspected gonorrhea.

Acute otitis media[13]	Nonspecific symptoms and signs, including fever, irritability, apathy, poor feeding, vomiting, and diarrhea. May have ear pain and/or rubbing.	*S. pneumoniae, H. influenzae, Moraxella catarrhalis.*	Moderate-to-severe bulging of the tympanic membrane, mild bulging with signs of inflammation, or new-onset otorrhea.	High-dose amoxicillin × 10 days. If amoxicillin in past 30 days, give amoxicillin/clavulanate. Consider watchful waiting if: 6–23 months—unilateral AOM without otorrhea or severe symptoms.[a] 24+ months—unilateral or bilateral AOM without otorrhea or severe symptoms.[a] [a](Toxic-appearing, T ≥39°C, otalgia >48 hr.) If treatment failure after 48–72 hr: amoxicillin-clavulanate × 10 days or IM ceftriaxone × 1–3 days.
Mastoiditis[14]	Complication of AOM. Tender mastoid, protruding auricle.	*S. pneumoniae, Streptococcus pyogenes, H. influenzae.*	Clinical. Contrast CT or MRI if complications suspected (CNS signs, ill-appearing, treatment failure).	Empiric ceftriaxone and vancomycin. Often requires surgical management.
Otitis externa[15]	Ear pain, pruritus, discharge, auricle and tragus tenderness and erythema.	*Pseudomonas, S. aureus.*	Culture in severe cases.	Otic drops × 7 days: ciprofloxacin or polymyxin-neomycin. Wick if outer canal swollen.
Group A strep pharyngitis[16]	Classic signs: fever, tonsillar exudates, lymphadenopathy, absence of cough. Higher concern between age 3 and 15. Scarlet fever (from exotoxin production) involves diffuse, finely papular, erythematous rash 24–48 hr after onset of symptoms.	Group A strep.	Rapid antigen detection test. If negative, confirm with culture. IDSA recommends testing if 3+ years old, without viral symptoms (cough, rhinorrhea, hoarseness, oral ulcers).	Amoxicillin × 10 days or benzathine penicillin IM × 1 dose. Nonsevere PCN allergy: cephalexin × 10 days. PCN-allergic: clindamycin × 10 days. Second line: azithromycin × 5 days.

Continued

TABLE 17.2—cont'd

PEDIATRIC INFECTIONS BY SYSTEM

	Presentation	Etiology	Diagnosis	Treatment
Peritonsillar abscess[17,18]	Sore throat, trismus, uvular deviation. Can be bilateral. Most common in adolescents.	Often polymicrobial: *S. pyogenes,* viridians group streptococci, *S. aureus,* oral anaerobes.	Clinical. Consider imaging if diagnosis unclear.	Ampicillin/sulbactam or ceftriaxone/cefotaxime + clindamycin. Often requires aspiration or I&D.
Retropharyngeal/parapharyngeal abscess[17,18]	Sore throat, fever, dysphagia, neck stiffness, medial deviation of wall of oropharynx (parapharyngeal abscess). Most common at age 2–4 years.	Often polymicrobial: *S. pyogenes,* viridians group streptococci, *S. aureus,* oral anaerobes.	Clinical. Consider imaging if diagnosis unclear.	Ampicillin/sulbactam or ceftriaxone/cefotaxime + clindamycin. If no airway compromise, can trial antibiotics × 48–72 hr, prior to obtaining CT and surgical management.
Ludwig angina (submandibular cellulitis)[19]	Rapidly progressive, bilateral cellulitis, often originating as dental infection. Causes elevation of the tongue, risk of airway compromise.	Often polymicrobial: viridians group streptococci, oral anaerobes.	Clinical. Consider imaging if diagnosis unclear.	(Ampicillin/sulbactam or aqueous penicillin) + metronidazole. Consider surgical drainage.
Lemierre syndrome[20]	Thrombophlebitis of internal jugular vein seeded from primary oropharyngeal infection, bacteremia, or distant site(s) of infection. High grade fever (>39.5), neck swelling/tenderness, exudative tonsillitis, or grayish pseudomembranes.	*Fusobacterium necrophorum*, *Bacteroides*, nongroup A streptococci.	WBC count, CRP, and ESR often are markedly elevated. CT with contrast is most useful imaging. An unremarkable oropharyngeal appearance at the time of septicemia does not rule out Lemierre syndrome.	Aqueous penicillin G AND metronidazole. Surgical management often required.
Preseptal cellulitis[21]	May follow external trauma, spread from sinuses or hematogenous infection.	*S. aureus, Streptococcus spp.*	Clinical.	Amoxicillin/clavulanate × 7 days.
Orbital cellulitis[21]	Proptosis, ophthalmoplegia, pain on extraocular movements, and blurred vision.	*Streptococcus spp, S. aureus, H. influenzae, M. catarrhalis.* Most commonly extension of rhinosinusitis.	CT with contrast; ophthalmology and ENT consultation.	(Ampicillin/sulbactam or ceftriaxone or cefotaxime) + vancomycin. Often requires abscess drainage.

Sinusitis (bacterial)[22]	Rhinorrhea, inflammation of septum and turbinates, tenderness over sinuses.	*S. pneumoniae, H. influenzae* (nontypeable), *M. catarrhalis*. If chronic, also *S. aureus,* anaerobes.	Clinical: persistent sinusitis 10+ days without improvement, worsening course after initial improvement, or severe symptoms (purulent discharge, fever ≥39°C) for 3+ days.	Amoxicillin/clavulanate × 10–14 days. If uncomplicated and persistent >10 days, can opt to observe with close follow-up. In chronic sinusitis, consider culture to guide antibiotics.
Cervical lymphadenitis[1,23]	Distinguished from reactive lymphadenopathy by fluctuance, warmth, overlying erythema.	Acute (<2 weeks) - Unilateral: most commonly *S. aureus, S. pyogenes*. Bilateral: consider EBV, CMV. Chronic (>2 weeks) - Consider *Bartonella henselae* (cat scratch disease), atypical mycobacteria, Toxoplasmosis, HIV, TB.	Consider ultrasound if diagnosis unclear. Consider FNA and culture if no improvement in 48–72 hr. If >2 weeks, consider tuberculin skin test.	PO cephalexin or amoxicillin/clavulanate or clindamycin × 7 days. IV ampicillin/sulbactam, or cefazolin or clindamycin. Azithromycin × 5 days shown to have mild effect on cat scratch disease.
Oral candidiasis (thrush)	White plaques on tongue, buccal mucosa, and/or palate.	*Candida albicans* is most common.	Clinical.	Nystatin swish and swallow or clotrimazole troches for 7-14 days. Nystatin for infants.
PULMONARY				
Community-acquired pneumonia[24]	Fever, respiratory distress, cough. On exam, tachypnea, hypoxia, diminished breath sounds, crackles asymmetric breath sounds.	Bacterial: *S. pneumoniae,* nontypeable *H. influenzae, M. catarrhalis.* *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* may be considered in subacute presentations. Viral: influenza, parainfluenza, human metapneumovirus, adenovirus.	Clinical diagnosis for mild disease. Chest x-ray if hypoxic, respiratory distress, or hospitalized. CBC or inflammatory markers (CRP, ESR, procalcitonin) are not reliable to differentiate bacterial vs viral pneumonia. Blood culture not required for mild disease.	Outpatient: high-dose amoxicillin × 5 days. Inpatient: ampicillin × 5 days. ICU: ceftriaxone plus TMP/SMX. Small parapneumonic effusions treated with antibiotics alone.

Continued

TABLE 17.2—cont'd

PEDIATRIC INFECTIONS BY SYSTEM

	Presentation	Etiology	Diagnosis	Treatment
Pertussis[1]	Mild URI symptoms (catarrhal stage). Progresses to whooping cough (paroxysmal stage). Duration 6–10 weeks. Atypical presentation in neonates with cyanosis, gasping and posttussive emesis.	*Bordetella pertussis*. Droplet transmission. Incubation 7–10 days.	NAAT performed on posterior nasopharynx specimen. Sensitivity is not significantly affected by antibiotic treatment.	Azithromycin × 5 days. Alt: TMP-SMX. Treatment during paroxysmal stage unlikely to affect clinical course but reduces transmission. Postexposure prophylaxis recommended for household and other close contacts (including children in daycare).
Tuberculosis	See Section 17.I.E.			
GASTROINTESTINAL				
Appendicitis[25]	Right lower quadrant pain, anorexia, fever. More difficult to diagnose in females or those <3 years of age.	Enteric pathogens + anaerobes.	Clinical diagnosis. Imaging now standard (ultrasound if available, otherwise CT with contrast or MRI).	Ceftriaxone + metronidazole + source control. Nonoperative management only considered if symptoms <48 hr and no abscess or fecalith.
Gastroenteritis[1,26]	Typically mild disease that does not require hospitalization. Worrisome signs include: age <2 months, underlying disease, persistent vomiting, high output diarrhea (>8×/day), family reported signs of severe dehydration.	Etiologies without treatment: toxin-mediated *S. aureus*, *Bacillus cereus*, *Clostridium perfringens*; viral: norovirus, rotavirus, astrovirus, adenovirus.	If suspect inflammatory bacterial enteritis: stool culture or bacterial NAAT panel. Depending on exposures and chronicity, consider stool for ova and parasites.	Enteral rehydration is preferred to intravenous regardless of etiology.
		Nontyphoid *Salmonella* spp.		If <3 months, immunocompromised, hemoglobinopathy, or severe disease, treat with ceftriaxone x 2-5 days or azithromycin x 3 days. For invasive infection, evaluate for focal infection to guide duration of treatment.

		Shigella spp. *Campylobacter* spp. *E. coli*		If <3 months, immunocompromised, or severe disease, treat with ceftriaxone x 2-5 days, azithromycin x 3 days, or ciprofloxacin x 3 days. If severe disease, age <3 months, relapse, immunocompromised: azithromycin × 3 days or ciprofloxacin × 5 days. In most cases there is no need for antibiotics. Azithromycin × 3 days or ciprofloxacin × 3 days if severe or prolonged (>7 days); no antibiotics for STEC O157:H7, as antibiotics increase risk of hemolytic uremic syndrome.[27]
Clostridium difficile colitis[28]	Diarrhea, pseudomembranous colitis with fever and abdominal pain. Severe disease present with shock, ileus, or megacolon. Asymptomatic colonization is common through 12 months of age.		Stool *C. difficile* toxin gene NAAT. Do not test unless ≥3 unformed stools within 24 hr. Make sure patient is not receiving laxatives.	Discontinue antibiotics if possible. Nonsevere: PO metronidazole or PO vancomycin. Severe (shock, ileus, or toxic megacolon): PO vancomycin + IV metronidazole.
Giardia[1]	Intermittent cramps, watery diarrhea, anorexia. Can be asymptomatic, acute, or chronic.	Flagellate protozoan. Fecal-oral transmission of cysts. Incubation period 1–3 weeks.	Stool EIA or DFA. Stool NAAT panel if available.	Metronidazole × 5–7 days. Alternatives: nitazoxanide × 3 days or tinidazole × 1 dose.

Continued

TABLE 17.2—cont'd

PEDIATRIC INFECTIONS BY SYSTEM

	Presentation	Etiology	Diagnosis	Treatment
Helicobacter pylori[29]	Chronic gastritis, duodenal ulcer. Can often be asymptomatic. Warning signs include severe chronic abdominal pain, anorexia and failure to thrive, or persistent vomiting. Sequelae: iron deficiency anemia, short stature, and chronic immune thrombocytopenia.	Fecal-oral transmission. Up to 80% prevalent in resource-poor countries.	Diagnosis should aim to find the underlying cause of symptoms and not solely look for *H. pylori* infection. Diagnostic testing for *H. pylori* not recommended in children with functional abdominal pain. Gold standard: gastric biopsy with culture (also yields susceptibilities). Test of cure (stool EIA or urea breath test) 4–6 weeks after treatment.	Triple therapy: PPI + amoxicillin + clarithromycin × 14 days. Subsequent regimens should be guided by susceptibilities. If none are available, PPI + amoxicillin + metronidazole +/− bismuth × 14 days.
GENITOURINARY				
Cystitis (UTI)[30]	Dysuria, urgency, fever of unknown source. Foul smelling urine is not sensitive for UTI. Risk factors for infants less than 2 years: Nonblack Temp >39°C Uncircumcised Fever >2 days Young age (<12 mo if female, <6 mo if male)	*E. coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*. The following are not considered pathogens in healthy children: *Lactobacillus spp*, coagulase-negative staphylococci, and *Corynebacterium spp*.	Diagnosis requires pyuria (≥10 WBCs/hpf or positive leukocyte esterase) and culture of ≥50,000 colony forming units for infants and children and ≥100,000 for adolescents. In infants, bagged urine specimen can be used for screening urinalysis, and if positive, should send catheterized sample for culture and repeat urinalysis.	PO cephalexin or nitrofurantoin: 3 days (7 days if <2 years). In young (<2 years) patients with 1st time UTI: renal bladder ultrasound; VCUG if abnormal. There is controversy around the timing of VCUG. AAP guidelines support waiting until second UTI. AAP Section on urology (based on RIVUR study) supports VCUG after 1st febrile UTI.[31]

Pyelonephritis[30]	Symptoms of cystitis, plus fever or flank pain (costovertebral angle tenderness). All neonatal UTIs are considered pyelonephritis.		Diagnosis of cystitis (see above), PLUS fever, flank pain, or ill appearance.	If tolerating PO, cephalexin or cefadroxil. If not tolerating PO, cefazolin or ceftriaxone. Cefepime if history of pseudomonas or catheter-dependent. Duration: 7 days. Longer treatment up to 14 days can be considered if not improving after 3 days. Transition to oral antibiotics once clinically improving.
Sexually transmitted infections	See Chapter 5.			
OSTEOARTICULAR				
Osteomyelitis[32]	Majority in long bones: pain, limping, swelling, erythema, fever. Spinal infection in infants involving the discs: gradual irritability, refusal to crawl/sit. Spinal infection involving vertebra (more common in adolescents): back pain.	Hematogenous spread. *S. aureus* (>80% cases), GAS, *S. pneumoniae*, GBS (<3 months), *Kingella kingae (<5 years), Salmonella* spp. (if history of sickle cell disease).	Blood cultures, consider bone cultures. Inflammatory markers: CRP and ESR. Imaging: X-ray, MRI.	Consider empiric coverage based on local resistance patterns. For children <5 years: cefazolin or oxacillin ± TMP/SMX. For children >5 years: cefazolin or oxacillin or clindamycin or TMP/SMX. (Clindamycin monotherapy is ineffective for *K. kingae*. In unstable or ill-appearing, IV vancomycin. Switch to oral therapy when clinically improved. Duration 3-4 weeks for acute infection.

Continued

TABLE 17.2—cont'd

PEDIATRIC INFECTIONS BY SYSTEM

	Presentation	Etiology	Diagnosis	Treatment
Hardware-associated bone infection[32]	Pain, limping, swelling, erythema, fever.	Coagulase-negative *Staphylococci, S. aureus, C. acnes,* Gram-negative bacilli including *Pseudomonas* spp.	Same as osteomyelitis plus deep tissue/bone sample.	Cefepime and vancomycin; add rifampin if *S. aureus*. Prolonged duration of treatment.
Septic arthritis[1,33]	Pain, swelling of joint, inability to bear weight, gait abnormality, fever.	*S. aureus* (>80% cases). GAS, *S. pneumoniae, K. kingae* (<5 years), *Salmonella* (if history of sickle cell disease). *Borrelia burgdorferi* (Lyme disease; if subacute presentation involving large joint). *Neisseria gonorrhoeae* (adolescents with migratory arthritis).	Kocher criteria used to differentiate septic joint from transient synovitis. Designed for hips, but often applied to knee/ankle. If 3 of 4 criteria met, 93% chance of septic joint: 1. Non–weight bearing 2. Fever 3. ESR >40 mm/hr 4. WBC >12,000/mm^3 If criteria met or high-risk: Knee—X-ray Hip—ultrasound. Joint aspiration suggests septic arthritis if >50,000 WBC/mm^3. For Lyme disease: two-tier test with serology and confirmation western blot and/or PCR from joint fluid.	Early drainage relieves discomfort, prevents synovial damage. Consider empiric coverage based on local resistance patterns. For children <5 years: cefazolin or oxacillin ± TMP/SMX. For children >5 years: cefazolin or oxacillin or clindamycin or TMP/SMX. If unstable or ill-appearing, IV vancomycin. Duration 3-4 weeks for acute infection. Lyme disease is treated empirically with ceftriaxone or doxycycline. *N. gonorrhea* is treated with ceftriaxone. Should also treat for chlamydia and test for other STIs.
SKIN AND SOFT TISSUE				
Nonpurulent cellulitis/erysipelas[34]	Intact skin, erythema, warmth, swelling, tenderness, nonpurulent.	Beta-hemolytic *streptococci*. Less common *S. aureus*.	Clinical. Blood or wound culture not routinely recommended.	Cephalexin × 5 days.

Purulent cellulitis/abscess[34]	Erythema, warmth, fever, tenderness, fluctuance, induration, history of purulent drainage.	*S. aureus*	Clinical. Ultrasound can confirm drainable collection. Wound cultures for hospitalized or immunocompromised children.	Mild/moderate: I&D Add TMP/SMX if any of the following: Abscess >2 cm, extensive cellulitis, fever, hypotension, septic phlebitis, immunocompromised. Severe: I&D + vancomycin.
Animal/human bites[34]	Higher risk injury with puncture wounds.	Often polymicrobial: *S. aureus,* Streptococci, *Pasteurella multocida* (animal), *Capnocytophaga* spp., oral anaerobes, *Eikenella corrodens* (human).	Clinical: puncture vs. nonpuncture.	Antibiotic prophylaxis is indicated if moderate/severe wound especially of hand or face, immunocompromise, possible penetration of periosteum or joint capsule, or edema of the area. Prophylaxis: amoxicillin/clavulanate x 5 days. See Chapter 2 for additional management. See Chapter 16 for post-exposure prophylaxis recommendations for tetanus and rabies.

Continued

TABLE 17.2—Cont'd

PEDIATRIC INFECTIONS BY SYSTEM

	Presentation	Etiology	Diagnosis	Treatment
Dermatophyte (tinea) infections[1]	Tinea capitis - Multiple scaly patches with alopecia and patches of alopecia with black dots at follicular orifices that represent broken hairs. May also present with widespread scaling, kerion, or favus. Tinea pedis (athlete's foot) - Interdigital hyperkeratotic or vesiculobullous eruption. Tinea cruris (jock itch) - Involving the inguinal fold. Tinea corporis - Dermatophyte infection occurring in sites other than feet, groin, face, or hand.	Dermatophytes	Tinea capitis, pedis, cruris, corporis: Clinical. Can confirm with skin scrapings in 10% potassium hydroxide (KOH).	Tinea capitis: Oral griseofulvin or terbinafine × 4–8 weeks or 2 weeks after clinical resolution. Fungal shedding decreased with selenium sulfide or ketoconazole shampoo. Tinea pedis, cruris, corporis: Topical antifungal. Tinea pedis: 2–4 weeks. Tinea cruris: 4–6 weeks. Tinea corporis: 4 weeks.
	Tinea unguium (onychomycosis) - White or yellow discoloration of finger- or toe-nail, often with thickening, splitting, or deformity.		Tinea unguium: Confirm with nail clippings in 10% KOH or culture.	Topical ciclopirox 8% once daily for 4–8 weeks preferred (no lab monitoring). Alternative: oral terbinafine 6 weeks if fingernail; 12 weeks if toenail.
BLOODSTREAM				
Catheter-related bloodstream infections[35]	Fever, erythema around catheter site; pain with infusion.	*S. aureus*, Gram-negative bacilli, Coagulase-negative *Staphylococci* (usually requires two positive cultures to exclude contaminant), *Enterococcus* species.	Two sets of cultures (one peripheral, one from suspected catheter) prior to antibiotics. If unable to draw peripheral culture, draw two sets from same line several minutes apart.	Vancomycin and cefepime. Remove line whenever possible.

Malaria[1]	Paroxysmal fevers and malaise. Severe malaria: 5+% parasitemia, CNS involvement, shock, hypoglycemia, anemia, thrombocytopenia, acidosis.	*Plasmodium falciparum, vivax, ovale.* *P. vivax* and *ovale* form hypnozoites in liver, difficult to eradicate. Incubation period 7 days to months.	Thick and thin blood smears. If high suspicion with negative smears, repeat every 12–24 hr for 72 hr. Rapid antigen detection tests exist. Speciation is performed by microscopy, with confirmation by PCR in specialized labs.	Severe: IV artesunate complemented by either artemether-lumefantrine, clindamycin, or doxycycline. Non-severe (chloroquine-resistant or unknown resistance): artemether-lumefantrine x 3 days. Alternative: quinine + (clindamycin or doxycycline). Non-severe (chloroquine-sensitive): chloroquine or hydroxychloroquine. *P. vivax* or *ovale*: add primaquine × 14 days. Travel prophylaxis varies by region due to chloroquine resistance. See CDC Yellow Book for resistance info and specific regimens.
Other				
Fever of unknown origin[36]	Defined as temperature greater than 38.3 for at least 2 weeks. Often an uncommon presentation of a common disease.	Localized or systemic infections are most commonly identified etiology.	No specific guidelines exist; stepwise approach is recommended.	Consider discontinuing all nonessential medications to aid in diagnosis.

Continued

TABLE 17.2—Cont'd

PEDIATRIC INFECTIONS BY SYSTEM

Presentation	Etiology	Diagnosis	Treatment
	Other etiologies include: rheumatologic, neoplastic, collagen vascular disease (e.g., juvenile idiopathic arthritis), drug fever, and Kawasaki disease.	First line: blood count, peripheral smear, renal/hepatic function tests, lactate dehydrogenase, inflammatory markers, blood cultures, urinalysis, chest x-ray. Second line: TB testing, CMV, EBV, echocardiogram. Third line: abdominal/pelvis CT, ANA, C3/C4, HIV, thyroid studies.	Treatment depends on etiology identified.

AAP, American Academy of Pediatrics; *ANA*, antinuclear antibody; *AOM*, acute otitis media; *AUA*, American Urologic Association; *CBC*, complete blood count; *CDC*, Centers for Disease Control; *CMV*, cytomegalovirus; *CN*, cranial nerve; *CNS*, central nervous system; *CRP*, C-reactive protein; *CSF*, cerebrospinal fluid; *CT*, computed tomography; *DFA*, direct fluorescent antibody; *EBV*, Epstein-Barr virus; *EIA*, enzyme immunoassay; *ENT*, ear-nose-throat physician (otolaryngologist), *ESR*, erythrocyte sedimentation rate; *FNA*, fine needle aspiration; *GBS*, group B streptococcus; *HIV*, human immunodeficiency virus; *hpf*, high-power field; *ICU*, intensive care unit; *I&D*, incision and drainage; *IDSA*, Infectious Disease Society of America; *IM*, intramuscular; *IV*, intravenous; *LP*, lumbar puncture; *MRI*, magnetic resonance imaging; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *NAAT*, nucleic acid amplification test; *PCN*, penicillin; *PCR*, polymerase chain reaction; *PO*, by mouth; *RIVUR*, randomized intervention for children with vesicoureteral reflux; *STEC*, Shiga toxin–producing *Escherichia coli*; *T*, temperature; *TB*, tuberculosis; *TMP*, trimethoprim; *TMP/SMX*, trimethoprim sulfamethoxazole; *URI*, upper respiratory infection; *UTI*, urinary tract infection; *VCUG*, voiding cystourethrography; *VP*, ventriculoperitoneal, *WBC*, white blood cell.

TABLE 17.3

PEDIATRIC VIRAL ILLNESSES

	Presentation	Transmission and Incubation	Diagnosis	Treatment
Cytomegalovirus (CMV)[1]	Infectious mononucleosis-like syndrome with fever and hepatitis. Immunocompromised: pneumonia, retinitis, colitis, leukopenia, thrombocytopenia. See Table 17.1 for congenital CMV.	Primary infection from respiratory droplets or vertical transmission. Persists after primary infection with intermittent shedding.	PCR for CMV DNA, histopathology for definitive diagnosis of tissue invasive disease. Gold standard is CMV culture in affected organ system. Quantitative CMV DNA and pp65 antigen are used in immunocompromised, and to monitor response to treatment. IgG to screen for risk of reactivation (e.g., organ transplant donors and recipients).	Ganciclovir or valganciclovir for disseminated or organ-specific CMV (typically immunosuppressed), serodiscordant transplant recipients, and CMV retinitis. Alternative antiviral: foscarnet (nephrotoxic).
Dengue[1]	Febrile phase (2–7 days) with myalgias, arthralgias, retro-orbital headache. Critical phase (24–48 hr) follows defervescence with increased vascular permeability. Convalescent phase with gradual improvement. Severe dengue (hemorrhagic fever): severe abdominal pain, bleeding, shock.	Four virus subtypes; severe dengue more common with second or subsequent infections. Transmitted by *Aedes* mosquitoes. Incubation period 3–14 days.	RT-PCR or anti-dengue virus IgM EIA.	Supportive. Avoid NSAIDs (bleeding risk).

Continued

TABLE 17.3—cont'd

PEDIATRIC VIRAL ILLNESSES

	Presentation	Transmission and Incubation	Diagnosis	Treatment
Epstein-Barr virus (EBV)[1]	Infectious mononucleosis: fever, pharyngitis with petechiae or exudates, hepatosplenomegaly, atypical lymphocytosis. Variable presentation in young children. Associated with post-transplant lymphoproliferative disease, Burkitt lymphoma, nasopharyngeal carcinoma, and other malignancies.	Transmitted via oral secretions or sexual contact. Incubation period 30–50 days.	Heterophile antibody positive by 2 weeks postexposure; though low sensitivity in children under 4 years. IgM/IgG to viral capsid antigen if heterophile negative and suspicion high. See Fig. 17.3.	Supportive. No strenuous activity or contact sports × 21 days, or until symptoms and splenomegaly resolve. Steroids if tonsillar swelling threatens airway, massive splenomegaly, myocarditis, hemolytic anemia, or HLH.
Human immunodeficiency virus (HIV)	See Section 17.I.F.			
Influenza[1]	Often abrupt onset of systemic symptoms (fever, myalgias, chills, headache, malaise, anorexia) with URI, croup, bronchiolitis, pneumonia. Complications include AOM, secondary bacterial pneumonia (especially *Staphylococcus aureus* and *Streptococcus pneumoniae*); rarely myositis, myocarditis, or CNS complications, including encephalitis, myelitis, Guillain-Barre syndrome.	Incubation 1–4 days.	Clinical diagnosis; lab confirmation not required for treatment. Multiple rapid antigen and PCR tests exist.	Oseltamivir for 5 days. Alternatives include inhaled zanamivir, IV peramivir, and PO baloxavir. Most effective within 48 hr of onset of symptoms. Treat all patients who are hospitalized, have severe illness, or are at high risk for complications. Consider treating patients who could transmit to elderly or unvaccinated contacts. Counsel families on influenza vaccination. Recommendations change yearly. See http://www.cdc.gov/flu.

Measles[1]	Fever, cough, coryza, conjunctivitis, Koplik spots, descending maculopapular rash. At risk for acute encephalitis and subacute sclerosing panencephalitis.	Droplet and airborne precautions. Incubation period 8–12 days.	RT-PCR from throat swab or urine or serum IgM.	Supportive. Counsel families on measles vaccination. Vitamin A reduces morbidity and mortality.
Mumps[1]	Swelling of 1+ salivary glands, often parotid. Orchitis more common after puberty.	Droplet precautions until 5 days after onset of parotid swelling. Incubation period 12–25 days.	RT-PCR from buccal swab or serum IgM.	Supportive.
Parvovirus B19 (Fifth disease)[1]	Mild viral syndrome followed by slapped cheek rash with circumoral pallor. Symmetric, macular, reticular rash on trunk, spreads peripherally. Polyarthropathy. Transient aplastic crisis. Can cause chronic infection and anemia in immunocompromised.	Droplet precautions. Incubation period 4–14 days.	Serum IgM. PCR required if immunocompromised.	Supportive. RBC transfusion in aplastic crisis. IVIG used in chronic infections of immunodeficient patients.
Rubella[1]	Descending, erythematous, maculopapular rash. See Table 17.1 for congenital rubella.	Droplet precautions until 7 days after onset of the rash. Incubation period 14–21 days.	Serum IgM.	Supportive.
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2)	Most children with SARS-CoV-2 may be asymptomatic or with mild to moderate symptoms including fever, cough and pharyngeal erythema. Less often GI symptoms.[48] In contrast with infected adults, most infected children appear to have a milder clinical course, although infants may have more severe disease.[49]	Respiratory transmission, likely droplet. Shedding can start 1-2 days prior to symptoms and continue >2 weeks. Incubation period: 5 days (2-14). Virus detected in stool with implications for fecal-oral transmission.[50] Perinatal transmission has not been reported.	Nasopharyngeal swab for PCR per CDC criteria.[51] Serological tests are being developed. Although imaging is often not performed, CT shows patchy peripheral ground glass opacities.[52,53]	Supportive care. No current FDA-approved directed therapies. Therapeutics being considered: remdesivir, lopinavir/ritonavir, hydroxychloroquine, nitazoxamine, tocilizumab, and others.

Continued

TABLE 17.3—cont'd

PEDIATRIC VIRAL ILLNESSES

	Presentation	Transmission and Incubation	Diagnosis	Treatment
Varicella zoster virus (VZV)[1]	Primary varicella (chickenpox): pruritic macules that progress to vesicles, plus fever and malaise. Herpes zoster: painful, vesicular, dermatomal rash. See Table 17.1 for congenital VZV.	Airborne spread or direct contact. Incubation period 10–21 days. Reactivation of latent VZV from sensory ganglia.	Clinical. PCR of vesicular fluid.	Supportive care if healthy host. Treat with acyclovir/valacyclovir if chronic skin or lung disease, unvaccinated and 12+ years old, or immunocompromised. Acyclovir/valacyclovir reduce duration and risk of postherpetic neuralgia.

DNA, Deoxyribonucleic acid; *EIA*, enzyme immunoassay; *HLH*, hemophagocytic lymphohistiocytosis; *Ig*, immunoglobulin; *IVIG*, intravenous immunoglobulin; *NSAIDs*, nonsteroidal antiinflammatory drugs; *RBC*, red blood cell; *RT-PCR*, reverse-transcriptase polymerase chain reaction.

TABLE 17.4

PEDIATRIC TICK-BORNE DISEASES

	Presentation	Etiology	Diagnosis	Treatment
Lyme disease[1]	Early localized: <1 month after tick bite. Erythema migrans. Early disseminated: 3–10 weeks after bite. Secondary erythema migrans with multiple smaller target lesions, cranioneuropathy (especially facial nerve palsy), systemic symptoms, rarely carditis with heart block or aseptic meningitis. Late disease: 2–12 months after bite. Pauciarticular arthritis of large joints, peripheral neuropathy, encephalopathy.	Spirochete *Borrelia burgdorferi* (*B. afzelii* and *B. garinii* in Europe and Asia). Requires 24–48 hr of tick attachment. Incubation 3–32 days (median 11 days). Most common in New England and Mid-Atlantic. Less common in Upper Midwest and Northwest.	Early: Clinical. No testing indicated. Early disseminated and late disease: EIA or IFA for antibodies. If positive, Western blot to confirm. IgM detectable for first 30 days. IgG detectable by week 4–6. False positives occur with viral infections, other spirochetes, and autoimmune disease. Perform LP as clinically indicated for CNS involvement.	Early localized: amoxicillin (14 days) or cefuroxime (14 days) or doxycycline (10 days). Early disseminated: any of above x 14 days. Late disease: any of above x 28 days. Doxycycline relatively contraindicated in children < 8 years. If cranioneuropathy, doxycycline preferred (any age). For meningitis, use ceftriaxone. In high-risk areas, can consider one-time dose of prophylactic doxycycline following removal of engorged tick for children > 8 years.
Rocky Mountain spotted fever[1]	Rash initially erythematous and macular, progresses to maculopapular and petechial. Classically spreads proximally from ankles and wrists, with involvement of palms and soles.	*Rickettsia rickettsii.* Incubation 3–12 days. Widespread; most common in South Atlantic, Southeastern, and South Central United States.	Clinical, with lab confirmation. Gold standard is indirect fluorescent antibody; IgG and IgM increase around 7–10 days. Serum PCR if available. Negative result (PCR or antibody testing) does not rule out the diagnosis.	Doxycycline recommended for children of any age. Should be started as soon as the diagnosis is suspected. Duration: continue until patient is afebrile for ≥3 days, with clinical improvement.

Continued

TABLE 17.4—cont'd

PEDIATRIC TICK-BORNE DISEASES

	Presentation	Etiology	Diagnosis	Treatment
Ehrlichiosis[1]	Systemic febrile illness. More severe disease: pulmonary infiltrates, bone marrow hypoplasia, respiratory failure, encephalopathy, meningitis, DIC, spontaneous hemorrhage, and renal failure.	*Ehrlichia chaffeensis* and *Ehrlichia ewingii*. Incubation period 5–14 days. Southeastern, South Central, East Coast, and Midwestern United States.	Identification of DNA by PCR from whole blood is highly sensitive and specific. Isolation in culture must be done at CDC specialty labs from samples prior to initiation of antibiotics.	Doxycycline for at least 3 days after defervescence, for a minimum total course of 7 days.
Anaplasmosis[1]	Same as *Ehrlichia*.	*Anaplasma phagocytophilum*. Incubation 5–21 days. Upper Midwest and Northeastern United States, Northern California.	Same as *Ehrlichia*.	Same as *Ehrlichia*.

CDC, Centers for Disease Control and Prevention; *CNS*, central nervous system; *DIC*, disseminated intravascular coagulation; *DNA*, deoxyribonucleic acid; *EIA*, enzyme immunoassay; *Hr*, hour; *IFA*, immunofluorescent assay; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M; *LP*, lumbar puncture; *PCN*, penicillin; *PCR*, polymerase chain reaction.

TABLE 17.5

INTERPRETATION OF THE SEROLOGIC MARKERS OF HEPATITIS B IN COMMON SITUATIONS

Serologic Marker				
HB*s*Ag	**Total HB*c*Ab**	**IgM HB*c*Ab**	**HB*s*Ab**	**Interpretation**
–	–	–	–	No prior infection, not immune.
–	–	–	+	Immune after hepatitis B vaccination (if concentration ≥10 IU/mL) or passive immunization from HBIG administration.
–	+	–	+	Immune after recovery from HBV infection.
+	+	+	–	Acute HBV infection.
+	+	–	–	Chronic HBV infection.

HBsAg, Hepatitis B surface antigen; *HBcAb*, antibody to hepatitis B core antigen; *HBsAb*, antibody to hepatitis B surface antigen; *HBIG*, hepatitis B immune globulin; *HBV*, hepatitis B virus; *IgM*, immunoglobulin M.
From Davis AR, Rosenthal P. Hepatitis B in Children. *Pediatr Rev.* 2008;29(4);111–120.

TABLE 17.6

CEREBROSPINAL FLUID ANALYSIS IN SUSPECTED MENINGTITIS

	Bacterial meningitis	**Viral meningitis**	**No CNS infection**
WBC (cells/mm^3)	>10; typically >100, but wide range	10–100	<10
Cell type	PMN predominance (80+%)	Mononuclear	Mononuclear
Protein (mg/dL)	>100	60–100	<60
Glucose (mg/dL)	<40	40–80	40–80

CNS, Central nervous system; *PMN*, polymorphonuclear neutrophil; *WBC*, white blood cell.
Adapted from Tunkel 2004. Analysis of cerebrospinal fluid is necessary to differentiate various types of meningitis. Initial studies such as cell counts and gram stain can be helpful, but culture of cerebrospinal fluid remains diagnostic. Opening pressure is generally in the range of 200 to 500 mm H_2O, although values may be lower in neonates, infants, and children with acute bacterial meningitis.

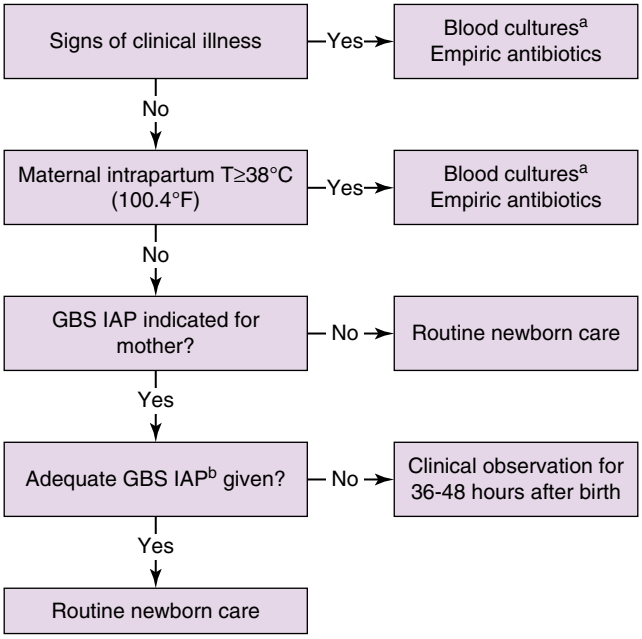
2. Treatment of latent TB infection (Cont'd from pg. 408)
   a. Rule out active TB.
   b. Treatment regimens
      (1) 12 weeks of weekly isoniazid and rifapentine if above 2 years.
      (2) 9 months of isoniazid daily.
      (3) Rifampin daily for 4 months (preferred regimen if isoniazid-resistant).
   c. If young (<4 years) or immunocompromised, treat recent contacts of people with active TB, even if testing (TST/IGRA) is negative. Some experts would discontinue treatment if repeat testing is negative at 8-12 weeks.
3. Treatment of active TB
   a. High rates of resistance in endemic countries. Treatment should be initiated in consultation with an infectious disease specialist.

b. Pulmonary TB: 6-month regimen, including 2 months RIPE (rifampin, isoniazid, pyrazinamide, ethambutol), followed by 4 months of rifampin/isoniazid.
c. Extra-pulmonary or drug-resistant TB: Consult infectious disease specialist.
d. Pyridoxine supplementation if breastfed, meat-/milk-deficient diet, symptomatic HIV, or pregnant.

F. Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

Please see the National Institutes of Health (NIH) guidelines on the diagnosis and management of children with HIV infection at www.aidsinfo.nih.gov/ for the most up-to-date recommendations.

1. Diagnosis
   a. Perinatal: See Table 17.8 for diagnosis in perinatal period.[37]
   b. Infants and children[38]: HIV nucleic acid testing must be used under 18 months to avoid confounding from maternal antibodies. Antigen/antibody testing can be performed after 18 months. If concern for breastmilk exposure, test immediately, then at 4 to 6 weeks, 3 months, and 6 months after stopping breastfeeding.
   c. Adolescents[39]: HIV screening with fourth-generation antigen/antibody assay with opt-out consent as part of routine clinical care. If positive, confirm with HIV-1/HIV-2 immunoassay; if indeterminate, HIV-1 nucleic acid testing.
2. Management[37–40]
   a. See Table 17.7 for management during perinatal period.
   b. Initiation of therapy for all children with HIV is recommended by the Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents and the World Health Organization (WHO).
   c. Therapy: Combination antiretroviral therapy (ART) of at least three drugs from at least two different classes. Go to http://www.aidsinfo.nih.gov/ for most current therapy recommendations.
3. Monitoring[38]
   a. At diagnosis: CD4 count, plasma HIV RNA viral load, genotype resistance. If starting therapy, HLA-B*5701 (screening for hypersensitivity to abacavir) and hepatitis B serology.
   b. Follow-up not on ART: Every 3 to 4 months, CD4 count, plasma HIV RNA viral load, CBC with differential, complete metabolic panel with glucose, renal function, albumin, transaminases, lipid panel. Every 6 to 12 months, obtain urinalysis to evaluate for nephropathy.
   c. Follow-up on ART: At 2 to 4 weeks after initiation or switching therapy, CD4, viral load, and labs according to possible toxicities of ART. Then similar testing as above every 3 to 4 months.
   d. Once viral suppression achieved, CD4 improved, good adherence, and otherwise stable for 2 to 3 years, can space labs to every 6 to 12 months.
   e. Latent TB skin testing starting at age 3 to 12 months, and then annually.



[a] Consider lumbar puncture and CSF culture before initiation of empiric antibiotics for infants who are at the highest risk of infection, especially those with critical illness. Lumbar puncture should not be performed if the infant's clinical condition would be compromised, and antibiotics should be administered promptly and not deferred because of procedure delays.

[b] Adequate GBS IAP is defined as the administration of penicillin G, ampicillin, or cefazolin ≥4 hours before delivery.

FIGURE 17.1

Example of categorical risk factor assessment for infants ≥35 weeks gestation. The risk of infection is highly variable among the newborn infants depending on the gestational age, duration of ROM, and timing and content of administered intrapartum antibiotics. This approach likely results in empirical treatment of many relatively low-risk infants. Newer, multivariate approaches are available online. (From Puopolo KM, Lynfield R, Cummings JJ, COMMITTEE ON INFECTIOUS DISEASES. Management of Infants at Risk for Group B Streptococcal Disease. *Pediatrics*. 2019 Aug 1;144(2):e20191881)

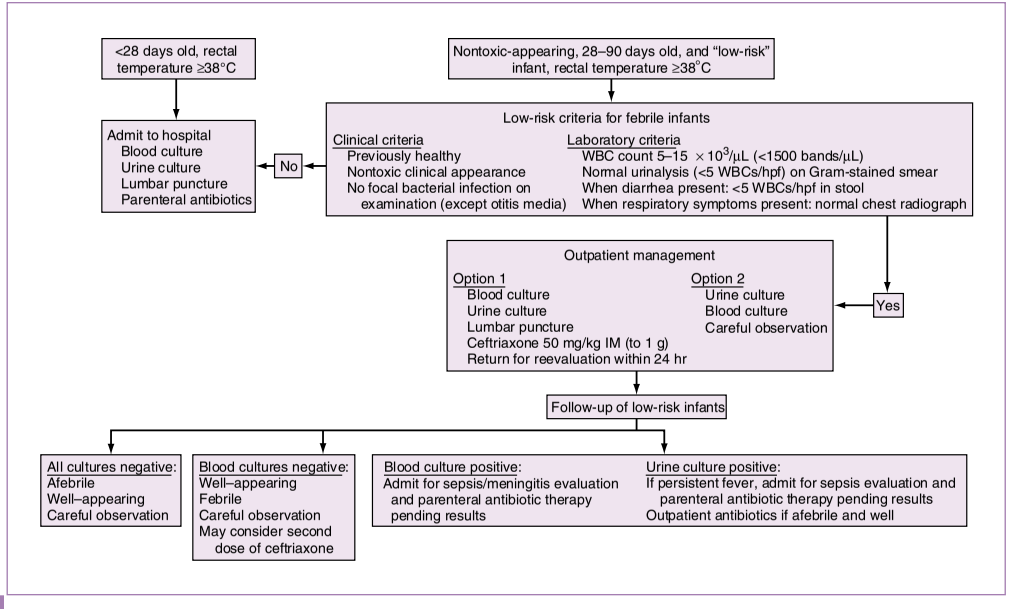


FIGURE 17.2

Algorithm for management of a previously healthy infant aged ≤90 days with a fever without localizing signs. This algorithm is a suggested but not exhaustive approach. *hpf*, High-power field. (Modified from Baraff LJ. Management of fever without source in infants and children. *Ann Emerg Med.* 2000;36:602–614; and Baraff LJ. Management of infants and young children with fever without source. *Pediatr Ann.* 2008;37:673–679.)

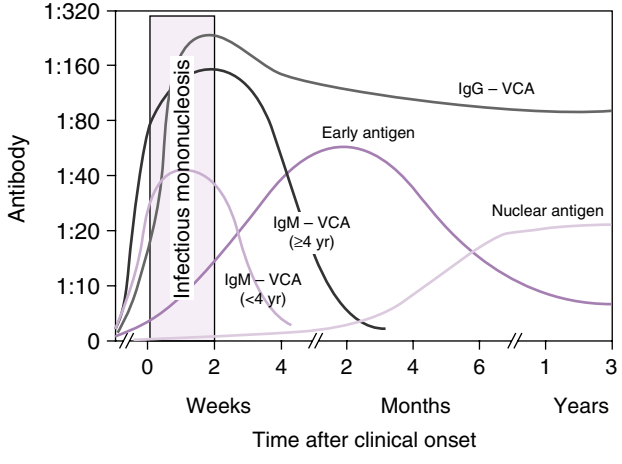


FIGURE 17.3

Graphic representation of the development of antibodies to Epstein–Barr virus antigens as a function of time from infection. Antibody titers are calculated as geometric mean values expressed as reciprocals of the serum dilution. The immunoglobulin M *(IgM)* response to viral capsid antigen *(VCA)* varies according to age of the patient. *IgG*, Immunoglobulin G. (From Jenson HB. Epstein-Barr Virus. In: Kliegman RE, Stanton B, St Geme J, et al., eds. *Nelson Textbook of Pediatrics.* 20th ed. Philadelphia: Elsevier; 2016.)

BOX 17.1

TUBERCULOSIS SCREENING GUIDELINES[1,41]

The American Academy of Pediatrics recommends treatment for at-risk individuals. Clinicians should complete at-risk assessment questionnaire at first well-child visit, then every 6 months in 1st year of life, and then routine care (at least annually). Screening questions include:

- Born outside the United States in countries with endemic infection
- Traveled outside United States in countries with endemic infection
- Family member with positive tuberculin skin test (TST)
- Exposed to someone who had tuberculosis disease
- Special populations including children with HIV, organ transplant, and those on immunosuppressive therapies including tumor necrosis factor blockers/antagonists

f. Vaccines[1] (see Chapter 16 and Red Book for details):
   (1) Meningococcal conjugate ACWY (can start at 2 months; 2 or 4 doses depending on age).
   (2) 23-valent polysaccharide pneumococcal vaccine at 2 years.
   (3) MMR can be given if CD4 >15% (any age) and CD4 count > 200 lymphocytes/mm^3 (if >5 years).
   (4) Some experts would consider monovalent varicella vaccine for children >12 months with CD4 >15%. Combined MMRV should not be given.

BOX 17.2

DEFINITIONS OF POSITIVE TUBERCULIN SKIN TESTING[1]

Induration ≥5 mm

- Children in close contact with known or suspected contagious cases of tuberculosis
- Children suspected to have tuberculosis based on clinical or radiographic findings
- Children on immunosuppressive therapy or with immunosuppressive conditions (including HIV infection)

Induration ≥10 mm

- Children at increased risk for dissemination based on young age (<4 years) or with other medical conditions (cancer, diabetes mellitus, chronic renal failure, or malnutrition)
- Children with increased exposure: Those born in or whose parents were born in endemic countries; those with travel to endemic countries; those exposed to HIV-infected adults, homeless persons, illicit drug users, nursing home residents, or incarcerated or institutionalized persons

Induration ≥15 mm

- Children ≥4 years without any risk factors

A tuberculin skin testing **(TST)** should be read in 48 to 72 hours. The measles vaccine can suppress TST reactivity for 4 to 6 weeks. An **interferon gamma release assay (IGRA)** can be used instead of TST in children older than 2 years. It has a higher specificity than TST because antigens used are not found in Bacillus Calmette-Guérin (BCG) vaccine or most pathogenic nontuberculous mycobacteria.

4. Pre-exposure prophylaxis (PrEP)[7]
   a. Common indications
      (1) Men who have sex with men: HIV-positive partner, bacterial STI (gonorrhea, chlamydia, syphilis) in past 6 months, history of inconsistent or condomless anal intercourse with an unknown status or nonmonogamous partner, commercial (or exchange) sex, history of high number of sex partners
      (2) Heterosexual men and women: HIV-positive partner, bacterial STI (gonorrhea, syphilis) in past 6 months, history of inconsistent condom use, commercial (or exchange) sex, history of high number of sex partners, living in a high HIV prevalence setting.
   b. Initiating
      (1) Labs: fourth generation HIV test, syphilis, gonorrhea, chlamydia, HBV, HCV (if ever used IV drugs), and renal function. Pregnancy test if indicated. Counsel on condom use.
      (2) Use emtricitabine/tenofovir alafenamide (Descovy) for biological males. Effective only after 7 days. Emtricitabine/tenofovir disoproxil (Truvada) for biological females. Effective only after 21 days. Consult infectious disease expert for initiation of PrEP unless provider has extensive experience.

TABLE 17.7

DIAGNOSIS AND MANAGEMENT FOR INFANTS WITH *IN UTERO* HIV EXPOSURE

Age	Laboratory Tests[a]	Next Steps
Prenatal/Labor	Opt-out testing of all pregnant women. HIV antibody testing in third trimester, before 36 weeks gestation preferred. Rapid HIV testing with confirmation if unknown HIV status during labor.	Start ART in mother. If viral load RNA >1000 copies/mL or unknown at labor, start IV zidovudine (ZDV) and consider cesarean section if greater than 38 weeks gestation.
Newborn	HIV nucleic acid test (DNA or RNA) if maternal status unknown, or high risk of infection. Baseline CBC with differential.	Start ZDV within 6–12 hr of delivery. If low-risk, continue ZDV for 4 weeks. If maternal viral load detectable and <1000 copies/mL near delivery, give nevirapine x 3 doses (within 48hr of birth, 48hr after first dose, 96hr after second dose). Continue zidovudine for 6 weeks. Some experts add lamivudine for 1 week. If mother did not receive antepartum ART or has acute/primary HIV in the 3rd trimester or has viral load >1000 copies/mL near delivery, start empiric ART with zidovudine, lamivudine, and either nevirapine or raltegravir.
2–3 weeks	HIV nucleic acid test (DNA or RNA). CBC with differential.	Check ZDV dosing and administration. Assess psychosocial needs, consider case management referral.
4–6 weeks	HIV nucleic acid test (DNA or RNA). CBC with differential.	Discontinue ZDV monotherapy regardless of PCR result (ZDV monotherapy is used during first 6 weeks for prophylaxis only). If positive, start ART according to guidelines. Presumptively exclude HIV infection if results of ≥2 weeks PCR and ≥4 weeks PCR both negative. No TMP-SMX needed. If PCR results not yet known, begin *Pneumocystis jirovecii* pneumonia prophylaxis, such as TMP-SMX.
2 months		Discontinue TMP-SMX if DNA or RNA testing negative.
4–6 months	HIV nucleic acid test (DNA or RNA).	Definitively exclude HIV infection: two negative PCRs at ≥1 month and ≥4 months, as long as no signs/symptoms of HIV infection.
18–24 months	Antibody testing may be performed to confirm clearance of maternal HIV antibodies. If present, need to use nucleic acid testing.	

[a]Any abnormal result requires prompt pediatric HIV specialist consultation.

ART, Antiretroviral therapy; *CBC*, complete blood cell count; *DNA*, deoxyribonucleic acid; *HIV*, human immunodeficiency virus; *IV*, intravenous; *PCR*, polymerase chain reaction; *RNA*, ribonucleic acid; *TMP-SMX*, trimethoprim–sulfamethoxazole; *ZDV*, zidovudine.

Modified from Department of Health and Human Services guidelines for pediatric and perinatal HIV infection (see www.aidsinfo.nih.gov for more detailed information). National Perinatal HIV Hotline: 1-888-448-8765.

(3) Descovy and Truvada are FDA-approved for adolescents > 35kg. Descovy is not approved to prevent transmission via vaginal sex.

c. Follow-up

(1) Every 3 months: HIV test and syphilis/gonorrhea/chlamydia if patient is symptomatic, engaging in anal intercourse, has prior history of STIs, or has multiple partners. Counsel on condom use at every visit.

(2) Every 6 months: Same as above, plus routine STI screening (including oral and/or anal testing, if applicable) and renal function.

5. Post-exposure prophylaxis (PEP)[42,43]

a. Indications for occupational PEP: Consider with percutaneous, mucosal, or skin exposure to blood or bodily fluids from a patient with known HIV or in whom there is high suspicion. See Section IV. for further non-HIV details.

b. Indications for nonoccupational (nPEP): Unprotected vaginal/anal intercourse, oral sex with ejaculation or blood exposure, needle sharing, or injuries with blood exposure from an individual with known HIV or unknown status.

c. Labs: 4th-generation HIV test, HBV surface antigen and antibody, HCV antibody. Depending on exposure, consider tetanus prophylaxis and STI testing.

d. Regimen: Initiate as soon as possible (lower likelihood of efficacy at greater than 72 hours); three-drug (or more) ART regimen for 28 days. Regimen: tenofovir and emtricitabine with raltegravir. For nPEP, dolutegravir may be used instead of raltegravir. Consult infectious disease expert for any initiation of PEP.

e. Follow-up testing can occur at 6 weeks, 12 weeks, and 6 months; for occupational exposures, if 4th-generation testing available, follow-up testing can be done at 6 weeks and 4 months.

f. Clinicians' PEP Line: 1-888-448-4911.

II. MICROBIOLOGY

A. Collection of Specimens for Blood Culture

1. Preparation: To minimize contamination, clean venipuncture site with 70% isopropyl ethyl alcohol. Apply tincture of iodine or 10% povidone-iodine and allow skin to dry for at least 1 minute, or scrub site with 2% chlorhexidine for 30 seconds and allow skin to dry for 30 seconds. Clean blood culture bottle injection site with alcohol only.
2. Collection: Two sets of cultures from two different sites of equal blood volume should be obtained for each febrile episode, based on patient weight: less than 8 kg, 1 to 3 mL; 8 to 13 kg, 4 to 5 mL; 14 to 25 kg, 5 to 6 mL; greater than 25 kg, 10 mL. Peripheral sites preferred. If concern for central line infection, collect one from central access site, second from peripheral. Consider anaerobe blood cultures if concern for the following: head and neck infections, intra-abdominal infections, immunodeficiency, trauma or pressure sore.[44,45]

B. Rapid Microbiologic Identification of Common Aerobic Bacteria (Fig. 17.4) and Anaerobic Bacteria (Fig. 17.5)

Note: Molecular assays for identification of bacteria and antibiotic resistance are increasingly available.

III. SPECTRA OF ACTIVITY FOR COMMONLY USED ANTIBIOTICS (FIG. 17.6)

IV. EXPOSURES TO BLOOD BORNE PATHOGENS AND PROPHYLAXIS

A. General Practice[46]

1. Regardless of status of patient, if you experience a needlestick or splash exposure, immediately wash with soap/water, irrigate, report to supervisor, and seek medical assistance.
2. There is an increased risk of transmission with larger volume of blood, prolonged exposure, high viral titer, deep injury, or if patient has advanced disease.
3. Source should be tested for HIV, hepatitis C antibody, and hepatitis B surface antigen. Exposed person should be tested for HIV, hepatitis C antibody, hepatitis B surface antibody, and hepatitis B surface antigen.

B. Disease-Specific Post-Exposure Management

1. Hepatitis B[47]: High risk of transmission if surface antigen and e-antigen positive. Lower risk of transmission if surface antigen positive, e-antigen negative. Post-exposure management includes hepatitis B immune globulin and initiation of hepatitis B vaccine series, depending on immune status. For details, see Chapter 16.
2. Hepatitis C[47]: Lower risk of transmission. No preventative therapy is currently recommended, but this is an evolving field. Follow-up testing essential.
3. See Section I.F for information on post-exposure management for HIV.

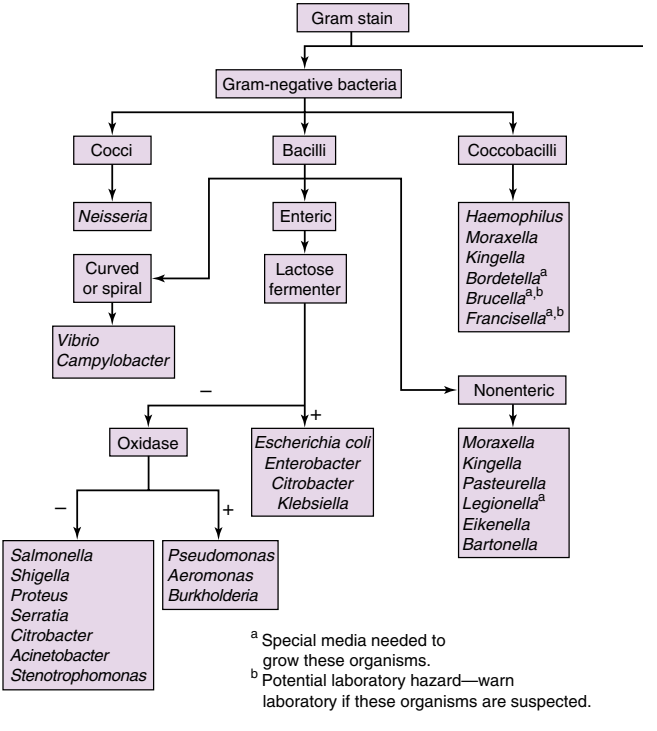
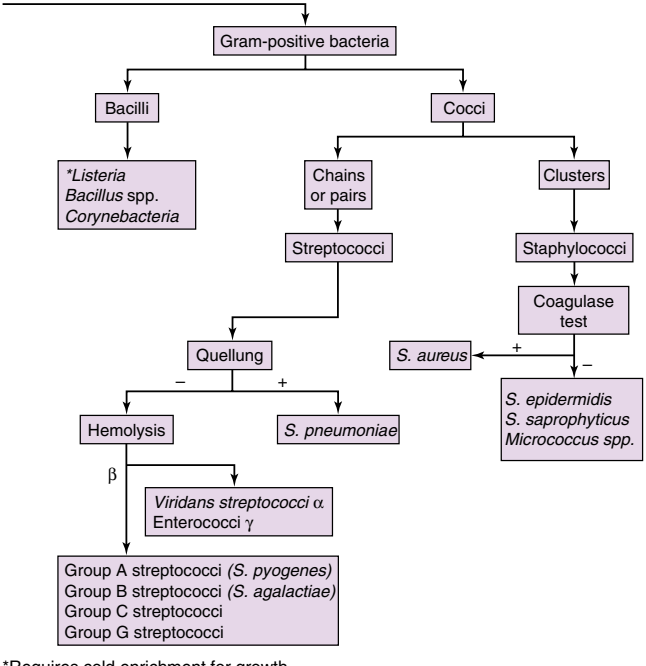


FIGURE 17.4
Algorithm demonstrating identification of aerobic bacteria.



*Requires cold enrichment for growth.

FIGURE 17.4, cont'd

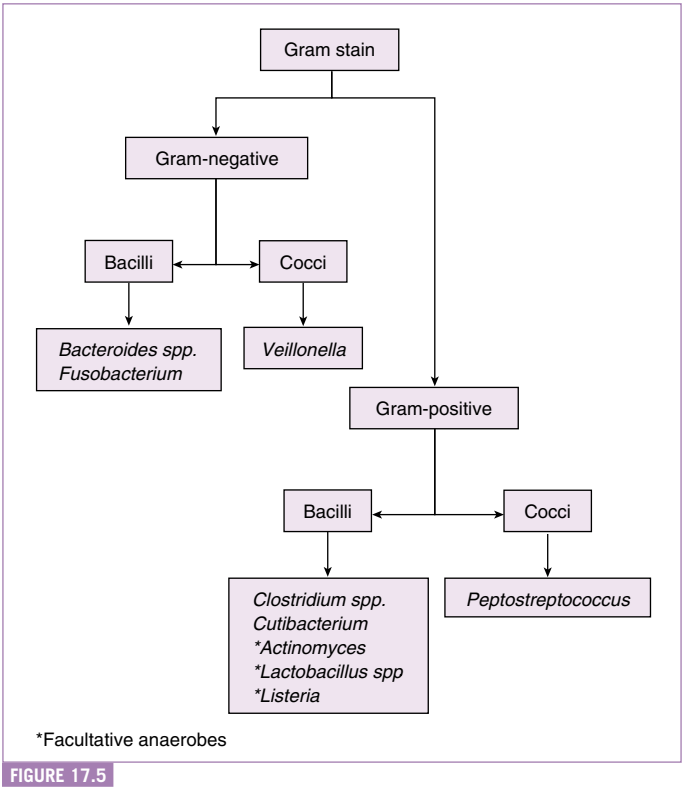


FIGURE 17.5
Algorithm demonstrating identification of anaerobic bacteria.

FIGURE 17.6

Approximation for the spectrum of activity for commonly used antibiotics and common pediatric infections. Exact sensitivities will change with different local resistance patterns. For antibiotic recommendations for specific infections, refer to relevant part of Section I.

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Chapter 18

Neonatology

Niana Carter, MD and Bethany Sharpless Chalk, PharmD

See additional content on Expert Consult

I. NEWBORN RESUSCITATION

A. Algorithm for Neonatal Resuscitation (Fig. 18.1)

1. Essential functional equipment: Radiant warmer, prewarmed blankets, hat, bag-mask/NeoPIP ventilator, appropriately sized laryngoscope, appropriately sized endotracheal tube (ETT) +/–stylet, suction device and bulb syringe, emergency medications, and vascular access supplies.
2. Meconium stained fluids: Per Neonatal Resuscitation Program (NRP) 7th edition, routine intrapartum oropharyngeal/nasopharyngeal suctioning and endotracheal intubation are not recommended.[2]
3. Cord clamping should be delayed for at least 30 to 60 seconds for vigorous term and preterm infants, given no maternal or fetal indications for immediate clamping.[3] See Box EC 18.A for exclusions. There is insufficient evidence to support or refute use of umbilical cord milking.

B. Endotracheal Tube Size and Depth of Insertion (Table 18.1)

1. **Quick estimations:**
   a. ETT size: 2.5 mm for infants <30 weeks gestational age (wGA); 3.0 mm for 30 to 34 wGA; 3.5 mm for >35 wGA.
   b. ETT depth: Infant's weight (kg) + 6 cm

C. Vascular Access (See Chapter 4 for Umbilical Venous/Artery Catheter Placement)

NOTE: During the initial resuscitation, an umbilical venous catheter (UVC) should be inserted just far enough to obtain blood return; no measurement or verified placement is needed.

II. ROUTINE NEWBORN CARE OF A TERM INFANT

A. General Care for the Full-Term Healthy Newborn with Uncomplicated Delivery

NOTE: Protocols vary by hospital.

1. Drying, removal of wet blankets. Then, preferably skin-to-skin contact with mother[4] or otherwise placed under warmer.
2. Feeding: Preferably breastfeeding soon after birth and on demand thereafter. Breastfed newborns should feed 8 to 12 times daily. Formula-fed newborns should be offered a bottle soon after birth.

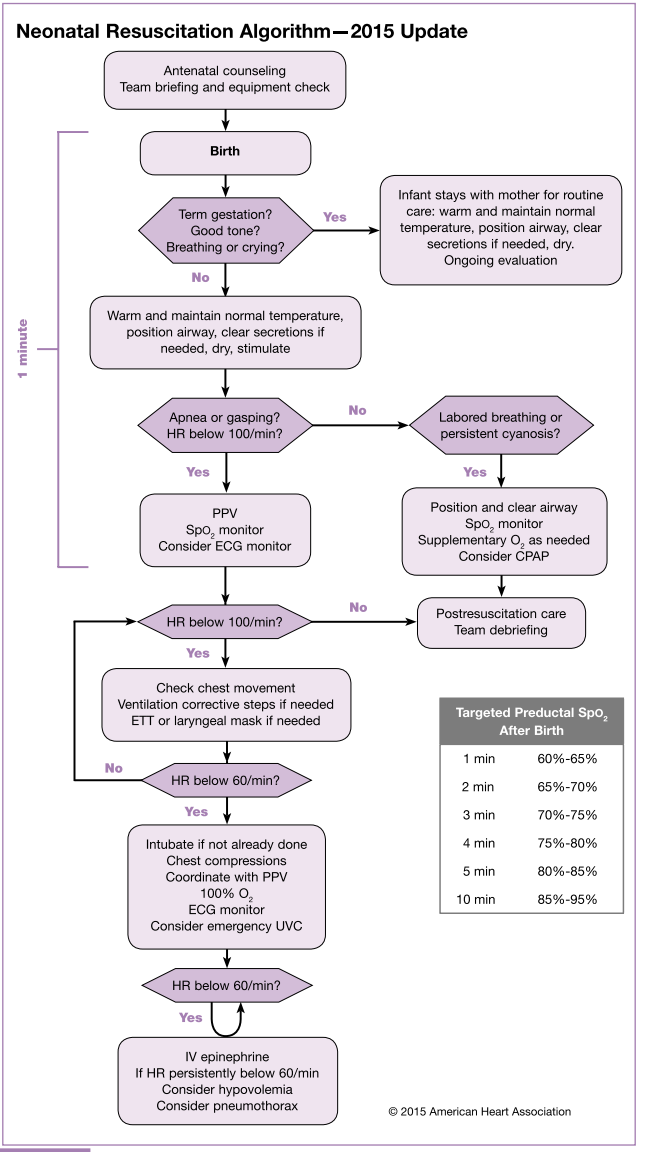


FIGURE 18.1

Overview of resuscitation in the delivery room. *CPAP*, Continuous positive airway pressure; *HR*, heart rate; *IV*, intravenous; *PPV*, positive pressure ventilations; *SpO_2*, oxygen saturation by pulse oximetry. (From Wykoff M, Aziz K, Escobedo M. et al. Part 15: neonatal resuscitation: 2015 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132(2):S543–560.)

BOX EC 18.A

EXCLUSION CRITERIA FOR DELAYED CORD CLAMPING

Absolute Exclusions Prior to Birth[2,3]

Fetal

- Monochorionic twins
- Discordant twins >25%
- IUGR <3rd percentile with reversed end-diastolic flow
- Poorly controlled maternal diabetes
- Congenital diaphragmatic hernia
- Abdominal wall defects
- Infant requiring immediate resuscitation

Maternal

- Known carrier of G6PD
- Placental abruption
- Velamentous cord insertion
- Incision through placenta
- Uterine rupture
- Placental delivery prior to infant

Individualized Considerations—Not Absolute Exclusions

- Hydrops fetalis
- RBC alloimmunization
- History of sibling with double volume exchange transfusion

Note: Presence of meconium-stained amniotic fluid does not automatically exclude delayed cord clamping.

G6PD, Glucose-6-phosphate dehydrogenase; *IUGR*, intrauterine growth retardation; *RBC*, red blood cell

TABLE 18.1

PREDICTED ENDOTRACHEAL TUBE SIZE AND DEPTH BY BIRTH WEIGHT AND GESTATIONAL AGE

Gestational Age (weeks)	Weight (g)	ETT Size (mm)	ETT Depth of Insertion (cm from Upper Lip)
23–24	500–600	2.5	5.5
25–26	700–800	2.5	6
27–29	900–1000	2.5	6.5
30–32	1100–1400	2.5–3.0	7
33–34	1500–1800	3.0	7.5
35–37	1900–2400	3.0–3.5	8
38–40	2500–3100	3.5	8.5

ETT, Endotracheal tube.

Data from Peterson J, Johnson N, Deakins K, et al. Accuracy of the 7-8-9 rule for endotracheal tube placement in the neonate. *J Perinatol.* 2006;26:333–336.

3. Vitamin K injection for prevention of hemorrhagic disease of the newborn.
4. Antibiotic ophthalmic ointment for prophylaxis against gonococcal infection.
5. Monitor clinically for jaundice, accounting for newborn's risk factors for hyperbilirubinemia. Transcutaneous bilirubin monitoring may be useful as a screening tool but does not replace plasma level.[5] Obtain plasma bilirubin level if warranted. See Section IX for more information and management.
6. Consider blood glucose monitoring if infant is at increased risk or is symptomatic of hypoglycemia (see Fig. 18.2 for management).
7. Monitor for stool/urine output. Most infants should have 1 void and 1 meconium stool within first 24 hours.[6]
8. Monitor for excessive weight loss.

B. Prior to Discharge[7]

1. Newborn metabolic screening: First screen typically performed within first 72 hours of life, at least 24 hours after initiation of feeding (see Chapter 13).
2. Vaccinations: Hepatitis B vaccine (see Chapter 16).
3. Critical congenital heart disease screening: Measure pre- and/or post-ductal oxygen saturation (see Chapter 7).
4. Newborn hearing screening.
5. Document red reflex.
6. Establish primary care.

III. NEWBORN ASSESSMENT

A. Vital Signs and Birth Weight

1. **Mean arterial blood pressure:** Related to birth weight, gestational age.

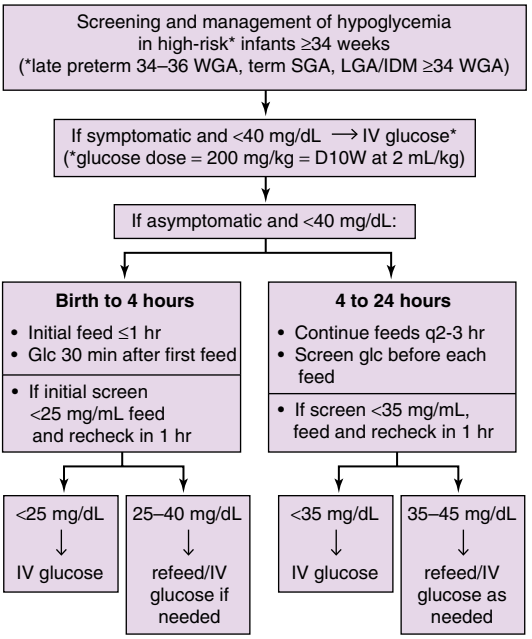


FIGURE 18.2

Screening for and management of postnatal glucose homeostasis. *D10W*, 10% dextrose in water; *glc*, glucose; *IDM*, infant of diabetic mother; *IV*, intravenous; *LGA*, large for gestational age; *SGA*, small for gestational age; *WGA*, weeks gestational age (Modified from Adamkin D, Committee on the Fetus and Newborn. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics*. 2011;127:575–579.)

2. **Birth weight:**
   a. Extremely low birth weight (ELBW): <1000 g, very low birth weight (VLBW): <1500 g, low birth weight (LBW): <2500 g.
   b. Small for gestational age (SGA): <10% for gestational age, large for gestational age (LGA): >90% for gestational age.

B. APGAR Scores (Table 18.2)

Assess at 1 and 5 minutes. Repeat at 5-minute intervals if score at 5 minutes is <7.[8]

C. Gestational Age Estimation

The Ballard Score is most accurate between the age of 12 and 20 hours, and approximates gestational age based on neuromuscular and physical maturity ratings (Fig. EC 18.A).

TABLE 18.2

APGAR SCORES

Score	0	1	2
Heart rate	Absent	<100 bpm	>100 bpm
Respiratory effort	Absent, irregular	Slow, crying	Good
Muscle tone	Limp	Some flexion of extremities	Active motion
Reflex irritability (nose suction)	No response	Grimace	Cough or sneeze
Color	Blue, pale	Acrocyanosis	Completely pink

Data from Apgar V. Proposal for a new method of evaluation of the newborn infant. *Anesth Analg.* 1953;32:260.

1. Posture: Observe infant quiet and supine. Score 0 for arms, legs extended; 1 for starting to flex hips and knees, arms extended; 2 for stronger flexion of legs, arms extended; 3 for arms slightly flexed, legs flexed and abducted; and 4 for full flexion of arms and legs.
2. Square window: Flex hand on forearm enough to obtain fullest possible flexion without wrist rotation. Measure angle between hypothenar eminence and ventral aspect of forearm.
3. Arm recoil: With infant supine, flex forearms for 5 seconds, fully extend by pulling on hands, then release. Measure the angle of elbow flexion to which arms recoil.
4. Popliteal angle: Hold infant supine with pelvis flat, thigh held in knee-chest position. Extend leg by gentle pressure and measure popliteal angle.
5. Scarf sign: With baby supine, pull infant's hand across the neck toward opposite shoulder. Determine how far elbow will reach across. Score 0 if elbow reaches opposite axillary line, 1 if past midaxillary line, 2 if past midline, and 3 if elbow unable to reach midline.
6. Heel-to-ear maneuver: With baby supine, draw foot as near to head as possible without forcing it. Observe distance between foot and head and degree of extension at knee.

D. Birth Trauma

1. **Extradural fluid collections:** See Table 18.3 and Fig. 18.3.
2. **Fractured clavicle:** Possible crepitus/deformity/decreased movement on day 1 ± swelling/discomfort on day 2.
3. **Brachial plexus injuries:** See Section XI.

E. Selected Anomalies, Syndromes, and Malformations (see Chapter 13 for genetic disorders)

1. **VACTERL association: V**ertebral defects, **A**nal atresia, **C**ardiac defects, **T**racheo-**E**sophageal fistula, **R**enal anomalies, and **L**imb abnormalities.
2. **CHARGE syndrome**: **C**oloboma, **H**eart disease, choanal **A**tresia, **R**etarded growth and development (may include central nervous system anomalies), **G**enital anomalies (may include hypogonadism), and **E**ar abnormalities or deafness.
3. **Infant of a diabetic mother:** Increased risk of hypoglycemia, polycythemia, transient tachypnea of the newborn (TTN), sacral agenesis,

Neuromuscular maturity

Neuromuscular maturity sign	Score							Record score here
	–1	0	1	2	3	4	5	
Posture								
Square window (wrist)	> 90°	90°	60°	45°	30°	0°		
Arm recoil		180°	140–180°	110–140°	90–110°	<90°		
Popliteal angle	180°	160°	140°	120°	100°	90°	<90°	
Scarf sign								
Heel to ear								
							TOTAL NEUROMUSCULAR MATURITY SCORE	

Physical maturity

Physical maturity sign	Score							Record score here
	–1	0	1	2	3	4	5	
Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Superficial peeling and/or rash, few veins	Cracking, pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled	
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald		
Plantar surface	Heel-toe: 40–50 mm: –1 <40 mm: –2	>50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases anterior two thirds	Creases over entire sole		
Breast	Imper-ceptible	Barely perceptible	Flat areola, no bud	Stippled areola, 1–2 mm bud	Raised areola, 3–4 mm bud	Full areola, 5–10 mm bud		
Eye/ear	Lids fused: loosely: –1 tightly: –2	Lids open, pinna flat, stays folded	Sl. curved pinna, soft, slow recoil	Well-curved pinna, soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff		
Genitals (male)	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae		
Genitals (female)	Clitoris prominent and labia flat	Prominent clitoris and small labia minora	Prominent clitoris and enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora		
							TOTAL PHYSICAL MATURITY SCORE	

Score
Neuromuscular_____
Physical_____
Total_____

Maturity rating														
Score	–10	–5	0	5	10	15	20	25	30	35	40	45	50
Weeks	20	22	24	26	28	30	32	34	36	38	40	42	44

Gestational age (weeks)
By dates_____
By ultrasound_____
By exam_____

FIG. EC 18.A

Neuromuscular and physical maturity (New Ballard Score). (Modified from Ballard JL et al. New Ballard Score, expanded to include extremely premature infants. *J Pediatr*. 1991;119:417–423.)

TABLE 18.3

BIRTH-RELATED EXTRADURAL FLUID COLLECTIONS

	Caput Succedaneum	Cephalohematoma	Subgaleal Hemorrhage
Location	At point of contact; can extend across sutures	Usually over parietal bones; does not cross sutures	Beneath epicranial aponeurosis; may extend to orbits or nape of neck
Findings	Vaguely demarcated; pitting edema, shifts with gravity	Distinct margins; initially firm, more fluctuant after 48 hr	Firm to fluctuant, ill-defined borders; may have crepitus or fluid waves
Timing	Maximal size/firmness at birth; resolves in 48–72 hr	Increases after birth for 12–24 hr; resolution over weeks	Progressive after birth; resolution over weeks
Severity	Minimal	Rarely severe	May be severe, especially in the setting of associated coagulopathy

Data from DJ Davis. Neonatal subgaleal hemorrhage: diagnosis and management. *CMAJ.* 2001;164:1452.

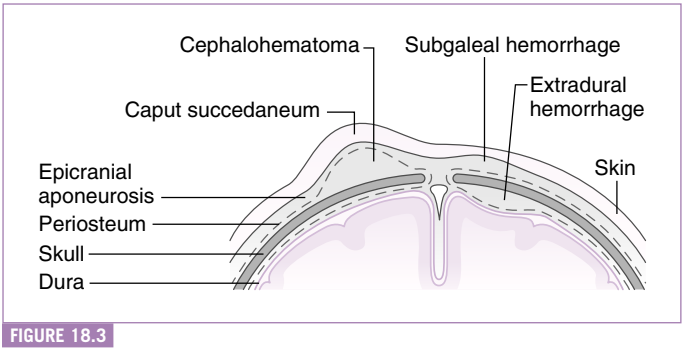


FIGURE 18.3

Types of extradural fluid collections seen in newborn infants.

femoral hypoplasia, cardiac defects, cleft palate/lip, preaxial radial defects, microtia, microphthalmos, holoprosencephaly, microcephaly, anencephaly, spina bifida, hemivertebrae, urinary tract defects, and polydactyly.

4. **Fetal alcohol syndrome:** SGA, short palpebral fissures, epicanthal folds, flat nasal bridge, long philtrum, thin upper lip, small hypoplastic nails. May be associated with cardiac defects.

IV. FLUIDS, ELECTROLYTES, AND NUTRITION

A. Fluids

1. **Fluid requirements of newborns** (Table 18.4)
2. **Insensible water loss in preterm infants** (Table EC 18.A)

TABLE 18.4

ESTIMATED MAINTENANCE FLUID REQUIREMENTS OF NEWBORNS

Birth Weight (g)	Fluid Requirements (mL/kg/24 hr) by Age			
	Day 1	Day 2	Day 3–6	Days 7+
<750	100–140	120–160	140–200	140–160
750–1000	100–120	100–140	130–180	140–160
1000–1500	80–100	100–120	120–160	150
>1500	60–80	80–120	120–160	150

Data from Gleason CA, Juul SE, eds. *Avery's Diseases of the Newborn.* 10th ed. Philadelphia: Elsevier; 2018.

B. Glucose

1. **Glucose infusion rate (GIR):** Preterm neonates require approximately 5 to 6 mg/kg/min of glucose (40 to 100 mg/dL).[9] Term neonates require approximately 3 to 5 mg/kg/min of glucose. Calculate as follows:

$$\text{GIR (mg/kg/min)} = 0.167 \times [\,\%\ \text{dextrose concentration}] \left[\text{infusion rate} \left(\frac{\text{mL}}{\text{hr}}\right)\right] / [\text{Weight (kg)}]$$

2. **Management of hyperglycemia and hypoglycemia:** Table 18.5 and Fig. 18.2 (see Chapters 1 and 10).

C. Electrolytes, Minerals, and Vitamins

1. **Electrolyte requirements** (Table 18.6)
2. **Mineral and vitamin requirements:**
   a. Infants born at <34 weeks gestation have higher calcium, phosphorus, sodium, iron, and vitamin D requirements and require breastmilk fortifier or special preterm formulas with iron. Fortifier is generally added to breast milk after the 2nd week of life.
   b. Iron: Preterm infants tolerating full enteral feeds require an elemental iron supplementation of 2 to 4 mg/kg/day. Timing of initiation remains controversial, generally after age 2 weeks.
   c. Vitamin D: Infants fed breast milk without fortifier require 400 IU daily. Infants fed preterm formula require 200 IU/day. Infants fed full term formula should be supplemented 400 IU/day until consuming 1 liter daily.
   d. ADEK: Indicated for infants with malabsorption and/or cholestasis tolerating full enteral feeds.

D. Nutrition

1. **Growth and caloric requirements: Table 18.7**
2. **Total parenteral nutrition (see Chapter 21)**

TABLE EC 18.A

INSENSIBLE WATER LOSS IN PRETERM INFANTS

Body Weight (g)	Insensible Water Loss (mL/kg/day)
<1000	60–70
1000–1250	60–65
1251–1500	30–45
1501–1750	15–30
1751–2000	15–20

Estimates of insensible water loss at different body weights during the first few days of life
Data from Veille JC. Management of preterm premature rupture of membranes. *Clin Perinatol.* 1988;15:851–862.

TABLE 18.5

MANAGEMENT OF HYPERGLYCEMIA AND HYPOGLYCEMIA

	Hypoglycemia	Hyperglycemia
Definition	Serum glucose <40 mg/dL in term and late preterm infants	Serum glucose >125 mg/dL in term infants, >150 mg/dL in preterm infants
Differential diagnosis	Insufficient glucose delivery Decreased glycogen stores Increased circulating insulin (e.g., infant of a diabetic mother, maternal drugs, Beckwith-Wiedemann syndrome, tumors) Endocrine and metabolic disorders Sepsis or shock Hypothermia, polycythemia, or asphyxia	Excess glucose administration Sepsis Hypoxia Hyperosmolar formula Neonatal diabetes mellitus Medications
Evaluation	Assess for symptoms and calculate glucose delivery to infant. Confirm bedside glucose with laboratory serum glucose. Consider other laboratory evaluations: Complete blood cell count with differential; electrolytes; blood, urine, ±cerebrospinal fluid cultures; urinalysis; insulin and C-peptide levels.	
Management	See Fig. 18.3. If glucose <40 and symptomatic, treat with intravenous glucose (dose = 200 mg/kg, which is equivalent to dextrose 10% at 2 mL/kg). Change dextrose infusion rates gradually. Generally, no more than 2 mg/kg/min in a 2-hr interval (see Chapter 1) . Monitor glucose levels every 30–60 min until normal.	Gradually decrease glucose infusion rate if receiving >5 mg/kg/min Monitor glucosuria. Consider insulin infusion for persistent hyperglycemia.

TABLE 18.6

ELECTROLYTE REQUIREMENTS

	Before 24 hr of Life	Transitional, After 24 hr of Life[a]	Growing Premature Infant	Growing Term Infant
Sodium (mEq/kg/day)	0–1	2–5	3–5	2–4
Potassium (mEq/kg/day)	0	0–2	2–3	2–3

[a]Pending postnatal diuresis has been established. Period to physiologic and metabolic stability, generally occurring between 2 and 7 days.

TABLE 18.7

AVERAGE CALORIC REQUIREMENTS AND GROWTH FOR PRETERM AND TERM INFANTS

	Preterm Infant	Term Infant
Caloric requirements (kcal/kg/day) [Parental/Enteral]	PN: 85–110 EN: 105–130 *Up to 150 for infants with cardiac conditions or BPD	PN: 90–100 EN: 100–120
Growth after 10 days of life	<2 kg: 15–20 g/kg/day >2 kg: 25–35 g/day	20–30 g/day

*Signifies an exception for infants with cardiac conditions or BPD.

V. CYANOSIS IN THE NEWBORN

A. Differential Diagnosis

1. **General:** Hypothermia, hypoglycemia, sepsis
2. **Cardiac:** Congestive heart failure, congenital cyanotic heart disease
3. **Respiratory:** Persistent pulmonary hypertension of the newborn (PPHN), diaphragmatic hernia, pulmonary hypoplasia, choanal atresia, pneumothorax, respiratory distress syndrome (RDS), TTN, pneumonia, meconium aspiration
4. **Neurologic:** Central apnea, central hypoventilation, intraventricular hemorrhage (IVH), meningitis
5. **Hematologic:** Polycythemia, methemoglobinemia
6. **Medications:** Respiratory depression from maternal medications (e.g., magnesium sulfate, narcotics, general anesthesia)

B. Evaluation

1. **Physical examination:** Note central vs. peripheral and persistent vs. intermittent cyanosis, respiratory effort, single vs. split S_2, presence of heart murmur. Acrocyanosis is often a normal finding in newborns.
2. **Clinical tests:** Hyperoxia test (see Chapter 7) , preductal/postductal arterial blood gases or pulse oximetry to assess for right-to-left shunt, and transillumination of chest for possible pneumothorax.
3. **Other data:** Complete blood cell count (CBC) with differential, serum glucose, chest radiograph, electrocardiogram (ECG), echocardiography. Consider blood, urine, and cerebrospinal fluid cultures if sepsis is suspected and methemoglobin level if cyanosis is out of proportion to hypoxemia.

VI. RESPIRATORY DISEASES

A. General Respiratory Considerations

1. **Exogenous surfactant therapy:**
   a. Indications: RDS in preterm infants, meconium aspiration, pneumonia, persistent pulmonary hypertension.
   b. Administration: If infant is ≤26 weeks gestation, first dose is typically given in delivery room or as soon as stabilized; repeat dosing can be considered based on ongoing oxygen requirements and level of respiratory support.
   c. Complications: Pneumothorax, pulmonary hemorrhage.
2. **Supplemental O_2:** Adjust inspired oxygen to maintain O_2 saturation. Ideal target oxygen saturations vary based on factors such as gestational age, chronologic age, and underlying conditions, and aims to minimize adverse outcomes from hypoxemia and hyperoxemia. Higher targets (>94%) can be used when the retinas are mature (see Section XIII) and in cases of pulmonary hypertension.[10]

B. Respiratory Distress Syndrome

1. **Etiology:** Deficiency of pulmonary surfactant resulting in increased surface tension and alveolar collapse. Surfactant is produced in increasing quantities after 32 weeks gestation.

TABLE 18.8

INCIDENCE OF RESPIRATORY DISTRESS SYNDROME BY GESTATIONAL AGE AND ANTENATAL STEROID ADMINISTRATION[11-14]

Gestational Age (week)	Antenatal Steroids Administered	Antenatal Steroids Not Administered
<30	35%	60%
30–34	10%	25%
34–36	1.4%[a]; 5.5%	2.3%[a]; 6.4%
>37	2.6%	5.4%

[a]Neonates with severe respiratory distress syndrome.

Note: The use of antenatal corticosteroids in >34 weeks gestational age is controversial due to inconsistent data regarding efficacy and limited data regarding long-term effects.

2. **Prevention:**
   a. Antenatal maternal administration of steroids >24 hours and <7 days prior to delivery, has been shown to decrease neonatal morbidity and mortality.[11-14]
      (1) Generally, either two doses of betamethasone administered 24 hours apart or four doses of dexamethasone given every 12 hours.
      (2) A single repeat course considered in women <34 weeks gestation and whose previous steroid course was administered >14 days prior. Serial courses not currently recommended.
   b. Other factors that accelerate lung maturity include maternal hypertension, sickle cell disease, narcotic addiction, intrauterine growth retardation, prolonged rupture of the membranes, and fetal stress.
3. **Incidence:** Table 18.8
4. **Risk factors:** Prematurity, maternal diabetes, cesarean section without antecedent labor, perinatal asphyxia, second twin, previous infant with RDS.
5. **Clinical presentation:**
   a. Respiratory distress worsens during first few hours of life, progresses over 48 to 72 hours, and subsequently improves.
   b. Recovery is accompanied by brisk diuresis.
   c. See Chapter 26 for imaging findings.
6. **Management:**
   a. Ventilatory and oxygenation support
   b. Surfactant therapy

C. Persistent Pulmonary Hypertension of the Newborn

1. **Etiology:** Idiopathic or secondary to conditions leading to increased pulmonary vascular resistance. PPHN is most commonly seen in term or postterm infants, infants born by cesarean section, and infants with a history of fetal distress and low APGAR scores. It usually presents within 12 to 24 hours of birth:
   a. Vasoconstriction secondary to hypoxemia and acidosis
   b. Interstitial pulmonary disease (meconium aspiration syndrome, pneumonia)
   c. Hyperviscosity syndrome (polycythemia)

d. Pulmonary hypoplasia, either primary or secondary to congenital diaphragmatic hernia or renal agenesis

2. **Diagnostic features:**
   a. Severe hypoxemia (Pao_2 <35 to 45 mmHg in 100% O_2) disproportionate to radiologic changes.
   b. Structurally normal heart with right-to-left shunt at foramen ovale and/or ductus arteriosus; pre/postductal oxygenation gradient (≥7 to 15 mmHg is significant).
   c. Must be distinguished from cyanotic heart disease. Infants with cyanotic heart disease will have an abnormal cardiac examination and show little to no improvement in oxygen therapy or hyperventilation. See Chapter 7 for interpretation of hyperoxia test.
3. **Principles of therapy:**
   a. **Improve oxygenation:** Supplemental oxygen administration and optimization of oxygen-carrying capacity with blood transfusions as indicated.
   b. **Minimize pulmonary vasoconstriction:**
      (1) Minimal handling of infant or noxious procedures. Sedation and occasionally paralysis of intubated neonates may be necessary.
      (2) Avoid severe hyperventilation associated hypocarbia (PCO_2 <30 mmHg), which can be associated with myocardial ischemia and decreased cerebral blood flow. Hyperventilation may result in barotrauma and predispose to chronic lung disease. Consider high-frequency ventilation.
   c. **Maintenance of systemic blood pressure and perfusion:** Reversal of right-to-left shunt through volume expanders and/or inotropes.
   d. **Consider pulmonary vasodilator therapy: see Chapter 1**
      (1) Inhaled nitric oxide (NO): Reduces pulmonary vascular resistance (PVR). Typical starting dose is 20 parts per million (ppm). Unlikely to have additional benefit at >40 ppm. Complications include methemoglobinemia (reduce NO dose for methemoglobin >4%), NO_2 poisoning (reduce NO dose for NO_2 concentration >1 to 2 ppm).
      (2) Prostacyclin analog (e.g., epoprostenol): Pulmonary vasodilator, normally produced by lung when lung vessels are constricted.
      (3) Sildenafil: Cyclic cGMP-specific phosphodiesterase type 5 (PDE5) inhibitor; results in pulmonary vasodilation.
   e. **Broad-spectrum antibiotics:** Sepsis is a common underlying cause of PPHN.
   f. **Consider extracorporeal membrane oxygenation (ECMO):** Reserved for cases of severe cardiovascular instability, oxygenation index (OI) >40 for >3 hour, or alveolar-arterial gradient ($A\text{-}aO_2$) ≥610 for 8 hours (see Chapter 1 for OI and A-a gradient equations). Infants typically need to be >2000 g and at >34 weeks gestation to be ECMO candidates. Obtain head ultrasound and consider EEG before initiating ECMO.
4. **Mortality depends on underlying diagnosis:** Mortality rates are generally lower for RDS and meconium aspiration, but higher in sepsis and diaphragmatic hernia.

D. Transient Tachypnea of the Newborn

1. **Etiology:** Incomplete or delayed resorption of amniotic fluid from the lungs.
   a. Immaturity of respiratory epithelial Na^+ transport.
2. **Risk factors:** Birth by cesarean section, male sex, macrosomia, lower gestational age, maternal diabetes, maternal asthma, maternal smoking.
3. **Diagnostic features:**
   a. Symptoms present within first 6 hours of delivery and resolve within first postnatal week, usually within 72 hours.
   b. Tachypnea: greater than 60 breaths/min, often in the range of 80 to 100 breaths/min.
   c. Retractions, grunting, or nasal flaring may be present. Cyanosis and hypoxia rare.
   d. CXR consistent with retained fluid: congestion, perihilar streaking, fluid in the interlobar fissure.
   e. Exclusion of other diagnoses, i.e. pneumonia, aspiration, congenital malformations, subarachnoid hemorrhage, hypoxic-ischemic encephalopathy (HIE), pneumothorax, acidosis, RDS.
4. **Management:**
   a. NPO with gavage feedings or 10% dextrose-containing fluids via IV.
   b. Supplemental oxygen and/or CPAP as indicated.
   c. No proven benefit of adjuncts including diuretics or racemic epinephrine.

E. Pneumothorax

1. Seen in 1% to 2% of normal newborns.
2. Associated with use of high ventilatory pressures and underlying diseases such as RDS, meconium aspiration, and pneumonia.
3. Consider monitoring in a neonatal intensive care unit (NICU).
4. Consider needle thoracostomy or chest tube placement (see Chapter 4).

VII. APNEA AND BRADYCARDIA

A. Apnea[15]

1. **Definition:** Respiratory pause >20 seconds or a shorter pause associated with cyanosis, pallor, hypotonia, or bradycardia <100 bpm. May be central (no diaphragmatic activity), obstructive (upper airway obstruction), or mixed.
2. **Etiology:** See Fig. 18.4. Apnea of prematurity occurs in most infants born at <28 weeks gestation, ~50% of infants born at 30 to 32 weeks gestation, and <7% of infants born at 34 to 35 weeks gestation. Usually resolves by 34 to 36 weeks postmenstrual age, but may persist after term in infants born at <25 weeks gestation.
3. **Management:**
   a. Consider pathologic causes for apnea (e.g., meningitis, seizures).
   b. Pharmacotherapy with caffeine or other stimulants.

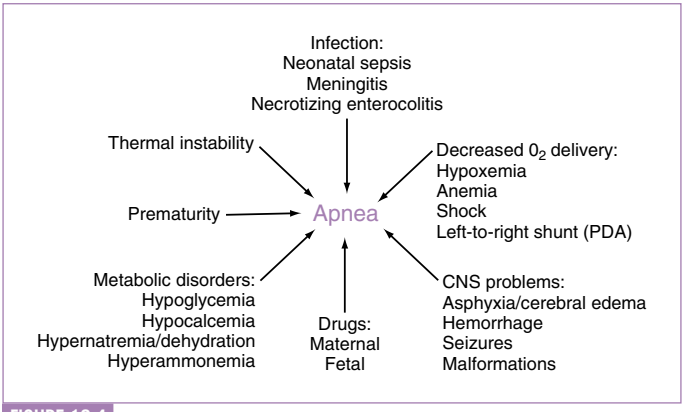


FIGURE 18.4

Causes of apnea in the newborn. *CNS*, Central nervous system; *PDA*, patent ductus arteriosus. (From Klaus MH, Fanaroff AA. *Care of the High-Risk Neonate*. 5th ed. Philadelphia: WB Saunders; 2001:268.)

c. Continuous positive airway pressure or mechanical ventilation (see Chapter 1).

B. Bradycardia without Central Apnea

Etiologies include obstructive apnea, mechanical airway obstruction, gastroesophageal reflux, increased intracranial pressure, increased vagal tone (defecation, yawning, rectal stimulation, and placement of nasogastric [NG] tube), electrolyte abnormalities, heart block.

VIII. CARDIAC DISEASES

A. Patent Ductus Arteriosus

1. **Definition:** Failure of ductus arteriosus to close in first 72 hours of life or reopening after functional closure. Typically results in left-to-right shunting of blood once PVR has decreased. If PVR remains high, blood may be shunted right to left, resulting in hypoxemia (see Section VI.C).
2. **Epidemiology:** Up to 60% in preterm infants weighing <1500 g and higher in those weighing <1000 g. Female-to-male ratio is 2:1.
3. **Diagnosis:**
   a. Examination: Systolic murmur may be continuous and best heard at the left upper sternal border or left infraclavicular area. Bounding peripheral pulses with widened pulse pressure if large shunt. Hyperactive precordium and palmar pulses may be present.
   b. ECG: Normal or left ventricular hypertrophy in small to moderate patent ductus arteriosus (PDA); biventricular hypertrophy in large PDA.
   c. Chest radiograph: May show cardiomegaly and increased pulmonary vascular markings, depending on size of shunt.

d. Echocardiogram

4. **Management:**
   a. Indications for treatment, timing of intervention, and best management strategy remain controversial.[16,17]
   b. Indomethacin/Ibuprofen: Prostaglandin synthetase inhibitor; 80% closure rate in preterm infants
      (1) Ibuprofen is as effective as indomethacin but fewer renal adverse effects.[18]
      (2) Complications[16-18]: Transient decrease in glomerular filtration rate and decreased urine output, transient gastrointestinal bleeding (no increased incidence of necrotizing enterocolitis [NEC]), prolonged bleeding time, and disturbed platelet function for 7 to 9 days independent of platelet count (no increased incidence of intracranial hemorrhage). Spontaneous isolated intestinal perforations are seen with indomethacin use. Rates are higher with concomitant hydrocortisone use.
   c. Acetaminophen[19-22]: Insufficient evidence but thought to be as effective as indomethacin/ibuprofen without effects on the kidneys and platelets.
   d. Surgical ligation of the duct.

B. Cyanotic Heart Disease (See Chapter 7)

IX. HEMATOLOGIC DISEASES

A. Unconjugated Hyperbilirubinemia in the Newborn[23]

1. **Overview:**
   a. During first 3 to 4 days of life, total serum bilirubin (TSB) increases to 6.5 ± 2.5 mg/dL.
   b. Maximum rate of bilirubin increase for normal infants with nonhemolytic hyperbilirubinemia: 5 mg/dL/24 hr or 0.2 mg/dL/hr.
   c. Always consider clinical jaundice or TSB >5 mg/dL on first day of life pathologic.
   d. Risk factors: Birth weight <2500 g, exclusive breastfeeding, prematurity, ABO incompatibility, cephalohematoma or significant bruising, predischarge bilirubin in high-risk zone, observed jaundice in first 24 hours, gestational age 35 to 36 weeks, infant of a diabetic mother, previous sibling requiring phototherapy, low albumin, infection, race.
2. **Evaluation:**
   a. Maternal prenatal testing: ABO and Rh (D) typing and serum screen for isoimmune antibodies.
   b. Infant or cord blood: Blood and Rh typing (if maternal blood type is O, Rh negative, or prenatal blood typing was not performed). Consider hemoglobin, blood smear, glucose-6-phosphate dehydrogenase (GPD) testing, direct Coombs test.

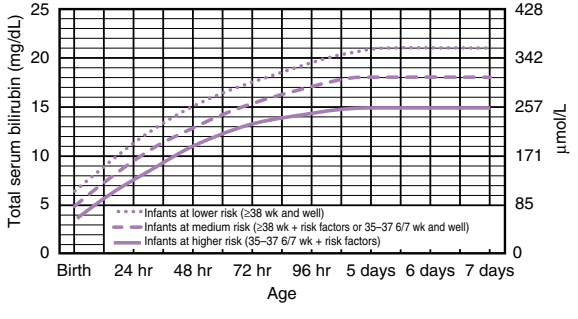
3. **Management:**
   a. Phototherapy: Ideally, intensive phototherapy should produce a TSB decline of 1 to 2 mg/dL within 4 to 6 hours, with further subsequent decline. Guidelines:
      (1) Preterm newborn (Table 18.9)
      (2) Term newborn (Fig. 18.5)
   b. Intravenous immunoglobulin (IVIG) (>35 weeks gestational age): In isoimmune hemolytic disease, IVIG administration (0.5 to 1 g/kg over 2 hours) is recommended if TSB is rising despite intensive phototherapy or TSB is within 2 to 3 mg/dL of exchange transfusion level (see Chapter 15 for discussion of IVIG).

TABLE 18.9

GUIDELINES FOR MANAGEMENT OF HYPERBILIRUBINEMIA IN PRETERM INFANTS AGED <1 WEEK

Gestational age (weeks)	Phototherapy (mg/dL)	Consider Exchange Transfusion (mg/dL)
<28 0/7	5–6	11–14
28 0/7–29 6/7	6–8	12–14
30 0/7–31 6/7	8–10	13–16
32 0/7–33 6/7	10–12	15–18

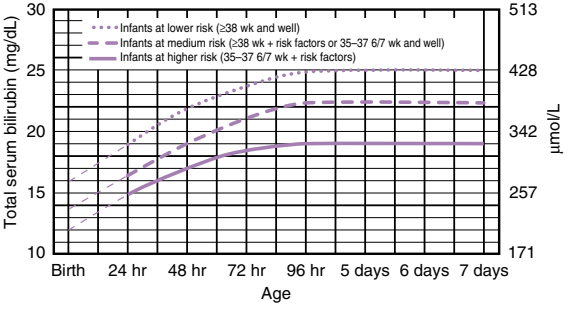
Data from Maisels MJ, Watchko JF, Bhutani V. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. *J Perinatol*. 2012;32(9):660–4.



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors: Isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin <3.0 g/dL (if measured)
- For well infants 35–37 6/7 wk, can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wk and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2–3 mg/dL (35–50 mmol/L) below those shown, but home phototherapy should not be used in any infant with risk factors.

FIGURE 18.5

Guidelines for phototherapy in infants born at 35 weeks of gestation or more. *G6PD*, Glucose-6-phosphate dehydrogenase; *TSB*, total serum bilirubin.



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry) or if TBS is ≥5 mg/dL (85 μmol/L) above these lines.
- Risk factors: Isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio.
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35–37 6/7 wk (median risk), can individualize TSB levels for exchange based on actual gestational age.

FIGURE 18.6

Guidelines for exchange transfusion in infants born at 35 weeks of gestation or more. *B/A*, Bilirubin/albumin; *G6PD*, glucose-6-phosphate dehydrogenase; *TSB*, total serum bilirubin.

c. Neonatal double-volume exchange transfusion (see Table 18.9 and Fig. 18.6):
   (1) Volume: 160 mL/kg for full-term infant, 160 to 200 mL/kg for preterm infant.
   (2) Route: During exchange, blood is removed through umbilical arterial catheter (UAC) and an equal volume is infused through UVC. If UAC is unavailable, use a single venous catheter.
   (3) Procedure: Replaces up to 85% of infant's circulation. Exchange in 15-mL aliquots for full-term infants. Exchange at 2 to 3 mL/kg/min in premature/less stable infants to avoid hemolysis.
   (4) Complications: Emboli, thromboses, hemodynamic instability, electrolyte disturbances, coagulopathy, infection, death.

NOTE: CBC, reticulocyte count, peripheral smear, bilirubin, Ca^{2+}, glucose, total protein, infant blood type, Coombs test, and newborn screen should be performed on a preexchange sample of blood; they are of no diagnostic value with postexchange blood. **If indicated, save preexchange blood for serologic or genetic studies.**

B. Conjugated Hyperbilirubinemia (See Chapter 12)

1. **Definition:** Direct bilirubin >2.0 mg/dL and >10% of TSB.

2. **Etiology:** Biliary obstruction/atresia, choledochal cyst, hyperalimentation, α_1-antitrypsin deficiency, hepatitis, sepsis, infections (especially urinary tract infections), hypothyroidism, inborn errors of metabolism, cystic fibrosis, red blood cell abnormalities.
3. **Management:** Ursodiol for infants on full feeds; consider supplementation with fat-soluble vitamins (A, D, E, K); otherwise depends on etiology. Phototherapy is not contraindicated but poses the risk for "bronze baby" syndrome.

C. Polycythemia

1. **Definition:** Venous hematocrit >65% confirmed on two consecutive samples. May be falsely elevated when obtained by heel stick or falsely lower when obtained by arterial stick.
2. **Etiologies:** Delayed cord clamping, twin-twin transfusion, maternal-fetal transfusion, intrauterine hypoxia, Beckwith-Wiedemann syndrome, maternal diabetes, neonatal thyrotoxicosis, congenital adrenal hyperplasia, trisomies.
3. **Clinical findings:** Plethora, respiratory distress, cardiac failure, tachypnea, hypoglycemia, irritability, lethargy, seizures, apnea, jitteriness, poor feeding, thrombocytopenia, hyperbilirubinemia.
4. **Complications:** Hyperviscosity predisposes to venous thrombosis and CNS injury. Hypoglycemia may result from increased erythrocyte utilization of glucose.
5. **Management:** Partial exchange transfusion for symptomatic infants, with isovolemic replacement of blood with isotonic fluid. Blood is exchanged in 10- to 20-mL increments to reduce hematocrit to <55%.

$$\text{Estimated blood volume} = \text{birth weight (kg)} \times 90 \text{ mL/kg}$$

X. GASTROINTESTINAL DISEASES

A. Necrotizing Enterocolitis

1. **Definition:** Serious intestinal inflammation and injury thought to be secondary to bowel ischemia, immaturity, and infection. Occurs principally in infants who have been fed.
2. **Risk factors:** Prematurity, asphyxia, African American race, hypotension, polycythemia–hyperviscosity syndrome, umbilical vessel catheterization, exchange transfusion, bacterial and viral pathogens, enteral feeds, PDA, congestive heart failure, cyanotic heart disease, RDS, intrauterine cocaine exposure.
3. **Clinical findings:** See Table EC 18.B.
   a. Systemic: Temperature instability, apnea, bradycardia, metabolic acidosis, hypotension, disseminated intravascular coagulopathy.
   b. Intestinal: Blood in stool, absent bowel sounds, and/or abdominal tenderness or mass. Elevated pregavage residuals in the absence of other clinical symptoms rarely raise a suspicion of NEC.
   c. Radiologic: Ileus, intestinal pneumatosis, portal vein gas, ascites, pneumoperitoneum (see Chapter 26).

TABLE EC 18.B

MODIFIED BELL'S STAGING SYSTEM FOR NECROTIZING ENTEROCOLITIS

Stage	Findings
IA (NEC suspected)	Temperature instability, apnea, bradycardia, lethargy, mild abdominal distention, gastric residuals, poor feeding, bilious emesis, occult blood in stool, x-ray findings: normal to mild ileus
IB (NEC suspected)	As for Stage IA, but with gross blood in stool
IIA (definite NEC, mildly ill)	As for stage IB with pneumatosis intestinalis, absent bowel sounds ± abdominal tenderness
IIB (definite NEC, moderately ill)	As for Stage IIA with metabolic acidosis, mild thrombocytopenia; definite abdominal tenderness; ± abdominal cellulitis or right lower quadrant mass; ± ascites or portal venous gas
IIIA (advanced NEC, severely ill infant, bowel intact)	As for stage IIB, but with hypotension, bradycardia, apnea, metabolic and respiratory acidosis, neutropenia, disseminated intravascular coagulation, peritonitis, abdominal distention and tenderness, abdominal erythema; definite ascites
IIIB (severely ill, perforated bowel)	As for Stage IIIA with pneumoperitoneum

NEC, Necrotizing enterocolitis.

Modified from Kleigman RM, Walsh MC. Neonatal necrotizing enterocolitis: pathogenesis, classification and spectrum of illness. *Curr Prob Pediatr.* 1987;17(4):219–288.

4. **Management:** Nothing by mouth, NG tube decompression, maintain adequate hydration and perfusion, broad spectrum antibiotics for 7 to 10 days based on hospital antibiogram, surgical consultation. Surgery is performed for signs of perforation or necrotic bowel.
5. **Minimizing risk of NEC:**
   a. Several studies link the use of probiotics and a decreased risk of NEC.[24] However, variations among formulations of probiotics, dosing, and lack of long-term studies on outcome have prevented the standard use of probiotics in the NICU.[25]
   b. There have been additional studies on supplements including L-arginine and lactoferrin.[26-28] Data remains insufficient to support a practice recommendation.[29]
   c. The exclusive use of human milk, including donor breast milk, has been shown to decrease the risk of NEC and associated mortality.[30]

B. Bilious Emesis

See Table EC 18.C and Chapter 12.

1. **Mechanical:** Annular pancreas, intestinal atresia/duplication/malrotation/obstruction (including adjacent organomegaly), meconium plug or ileus, Hirschsprung disease, imperforate anus.
2. **Functional (i.e., poor motility):** NEC, electrolyte abnormalities, sepsis.

NOTE: Must eliminate malrotation as an etiology because volvulus is a surgical emergency.

C. Abdominal Wall Defects (Table EC 18.D)

D. Gastroesophageal Reflux Disease (See Chapter 12)

XI. NEUROLOGIC DISEASES

A. Neonatal Hypoxic-Ischemic Encephalopathy:

1. **Initial Management**[31]
2. **Hypothermia protocol:** Infants with evidence of HIE shortly after birth who are >36 weeks gestation should be considered for hypothermia. Protocol should be initiated within 6 hours of delivery.
3. **Criteria for hypothermia vary by center but typically include one or more of the following:**
   a. Cord gas or blood gas in the first hour of life with a pH of <7.0 or base deficit of >16. For infants with a pH of 7.01 to 7.15 or base deficit of 10 to 15.9, additional criteria should be met (e.g., significant perinatal event).
   b. 10-minute APGAR ≤5.
   c. Evidence of moderate to severe encephalopathy.
   d. Need for assisted ventilation at birth for at least 10 minutes.
4. Severity and outcome of HIE in full-term neonate: Table 18.10.

B. Intraventricular Hemorrhage

1. **Definition:** IVH usually arises in the germinal matrix and periventricular regions of the brain.

TABLE EC 18.C

CONSIDERATIONS IN BILIOUS EMESIS

	Proximal Intestinal Obstruction	Distal Intestinal Obstruction
Differential diagnosis	Duodenal atresia Annular pancreas Malrotation with or without volvulus Jejunal obstruction/atresia	Ileal atresia Meconium ileus Colonic atresia Meconium plug—hypoplastic left colon syndrome Hirschsprung disease
Physical exam	Abdominal distention not prominent	Abdominal distention
Diagnosis	Abdominal X-ray: "Double bubble" Upper gastrointestinal series	Abdominal x-ray: Dilated loops of bowel Contrast enema Sweat test Mucosal rectal biopsy

Modified data from: Shields TM and Lightdale JR. Vomiting in children. *Pediatr Rev.* 2018;39:342–358.

TABLE EC 18.D

DIFFERENCES BETWEEN OMPHALOCELE AND GASTROSCHISIS

	Omphalocele	Gastroschisis
Position	Central abdominal	Right paraumbilical
Hernia sac	Present	Absent
Umbilical ring	Absent	Present
Umbilical cord insertion	At the vertex of the sac	Normal
Herniation of other viscera	Common	Rare
Extraintestinal anomalies	Frequent	Rare
Intestinal infarction, atresia	Less frequent	More frequent

BOX 18.1

SIGNS AND SYMPTOMS OF OPIOID WITHDRAWAL

W	Wakefulness
I	Irritability, insomnia
T	Tremors, temperature variation, tachypnea, twitching (jitteriness)
H	Hyperactivity, high-pitched cry, hiccups, hyperreflexia, hypertonia
D	Diarrhea (explosive), diaphoresis, disorganized suck
R	Rub marks, respiratory distress, rhinorrhea, regurgitation
A	Apnea, autonomic dysfunction
W	Weight loss
A	Alkalosis (respiratory)
L	Lacrimation (photophobia), lethargy
S	Seizures, sneezing, stuffy nose, sweating, sucking (nonproductive)

TABLE 18.10

SEVERITY AND OUTCOME OF HYPOXIC-ISCHEMIC ENCEPHALOPATHY IN FULL-TERM NEONATE

	Mild	Moderate	Severe
Level of consciousness	Increased irritability, hyperalert	Lethargic	Stupor or coma
Seizures	Rare	Common	Uncommon
Primitive reflexes	Exaggerated	Suppressed	Absent
Brain stem dysfunction	Rare	Rare	Common
Elevated intracranial pressure	Rare	Rare	Variable
Duration	<24 hr	>24 hr (variable)	>5 days
Poor outcome (%)[a]	0	20–40	100

[a]Poor outcome is defined by presence of intellectual disability, cerebral palsy, or seizures.

Data from MacDonald M, Mullett, M. Severity and outcome of hypoxic-ischemic encephalopathy in full term neonate. In: *Avery's Neonatology.* 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2005.

2. **Incidence:**
   a. 30% to 40% of infants <1500 g; 50% to 60% of infants <1000 g
   b. Highest incidence within first 72 hours of life: 60% within 24 hours, 85% within 72 hours, and <5% after 1 week of age
3. **Diagnosis and classification:**
   a. Ultrasonography; grade is based on maximum amount of hemorrhage seen by age 2 weeks:
      (1) Grade I: Hemorrhage in germinal matrix only
      (2) Grade II: IVH without ventricular dilation
      (3) Grade III: IVH with ventricular dilation
      (4) Grade IV: Periventricular hemorrhagic infarct with or without IVH.

   NOTE: Many institutions use descriptive data (as opposed to the grading system) to denote severity of IVH.
4. **Screening:** Indicated in infants <32 weeks gestational age within 72 hours of life; repeat in 1 to 2 weeks.
5. **Outcome:** Infants with grade III and intraparenchymal hemorrhages have an increased risk for neurodevelopmental disabilities and posthemorrhagic hydrocephalus.

TABLE 18.11

BRACHIAL PLEXUS INJURIES

Plexus Injury	Spinal Level Involved	Clinical Features
Erb-Duchenne palsy (90% of cases)	C5–C6 Occasionally involves C4	Adduction and internal rotation of arm. Forearm is pronated; wrist is flexed. Diaphragm paralysis may occur if C4 is involved.
Total palsy (8%–9% of cases)	C5–T1 Occasionally involves C4	Upper arm, lower arm, and hand involved. Horner syndrome (ptosis, anhidrosis, and miosis) exists if T1 is involved.
Klumpke paralysis (<2% of cases)	C7–T1	Hand flaccid with little control. Horner syndrome if T1 is involved.

C. Periventricular White Matter Injury

1. **Definition and ultrasound findings:** Ischemic necrosis of periventricular white matter, characterized by CNS depression within first week of life and later findings of cysts on ultrasound with or without ventricular enlargement (caused by cerebral atrophy) or noncystic white matter injury visualized by MRI.
2. **Incidence:** More common in preterm infants but also occurs in term infants.
3. **Etiology:** Primarily ischemia-reperfusion injury, hypoxia, acidosis, hypoglycemia, acute hypotension, low cerebral blood flow.
4. **Outcome:** Commonly associated with cerebral palsy with or without sensory and cognitive deficits.

D. Neonatal Seizures (See **Chapter 20**)

E. Neonatal Abstinence Syndrome

1. Onset of symptoms usually occurs within first 24 to 72 hours of life (methadone may delay symptoms until 96 hours or later). Symptoms may last weeks to months. Box 18.1 shows signs and symptoms of opioid withdrawal.
2. Increasing evidence supports benefit of nonpharmacologic management,[32] including rooming in, breastfeeding, skin-to-skin, swaddling, and environmental controls such as decreased disruptions.

F. Peripheral Nerve Injuries

1. **Etiology:** Result from lateral traction on shoulder (vertex deliveries) or head (breech deliveries).
2. **Clinical features** (Table 18.11).
3. **Management:** Evaluate for associated trauma (clavicular and humeral fractures, shoulder dislocation, facial nerve injury, cord injuries). Full recovery is seen in 85% to 95% of cases in first year of life.

XII. UROLOGIC DISORDERS

A. Lower Urinary Tract Obstruction

1. **Definition:** Rare birth defect caused by partial or complete blockage of the urethra. Common causes include posterior urethral valves (PUV), urethral atresia, and triad syndrome (constricted narrowing in midportion of urethra). More common in males.

2. **Diagnosis and Evaluation:** Fetal anatomy ultrasound (18 to 24 weeks) with visualization of markedly distended bladder, often with a thickened wall (greater than 2 mm).[33] A "keyhole" sign representing dilation of the posterior urethral valve proximal to the obstruction may be seen, but is not specific.
   a. Other tests include comprehensive anatomic survey or fetal MRI, echocardiogram, and karyotype to rule out co-existing abnormalities and determine gender. More than 10% of cases are associated with Trisomy 13, 18, or 21.
   b. Vesicocentesis can evaluate renal function by serially assessing urine electrolytes at 24 to 48 hour intervals.
3. **Clinical findings:** Ureterectasis, caliectasis, hydronephrosis, pulmonary hypoplasia, renal dysplasia, oligohydramnios, clubfeet, Potter facies.
4. **Management:** Fetal vesicoamniotic shunting or cystoscopy. Consultation with pediatric urology and nephrology to review postnatal course including dialysis, vesicostomy, and transplantation. Elective termination or expectant management should be offered for fetuses with poor prognostic profiles (Table EC 18.E).

B. Bladder Exstrophy-Epispadias-Cloacal Exstrophy Complex

1. **Definition:** Anomalies involving urinary tract eversion; with genitourinary, musculoskeletal, and occasionally gastrointestinal malformations. See Table EC 18.F for comparison.
2. **Diagnosis:** Fetal anatomy ultrasound showing abnormality of bladder filling, low-set umbilical cord, abdominal mass that increases in size throughout pregnancy, separation of pubic bones and small genitals.
3. **Management:** Reconstructive surgery that aims to establish bladder continence, preserve renal function, repair epispadias and genitalia, and close the pelvic bones.

XIII. RETINOPATHY OF PREMATURITY[34]

A. Definition

Interruption of normal progression of retinal vascularization.

B. Etiology

Exposure of the immature retina to high oxygen concentrations can result in vasoconstriction and obliteration of the retinal capillary network, followed by vasoproliferation. Risk is correlated to degree of prematurity.

C. Diagnosis

Dilated funduscopic examination should be performed in the following patients:

1. All infants born ≤30 weeks gestation
2. Infants born >30 weeks gestation with unstable clinical course, including those requiring cardiorespiratory support
3. Any infant with a birth weight ≤1500 g

D. Timing[35]

1. All infants born ≤27 weeks gestation, initial retinopathy of prematurity (ROP) screening examination performed at 31 weeks postmenstrual age.

TABLE EC 18.E

PROGNOSTIC CRITERIA BASED ON FETAL URINE

Urinary Component	Favorable
Sodium (Na)	Less than 100 mEq/L
Chloride (Cl)	Less than 90 mEq/L
Osmolarity (Osm)	Less than 210 mEq/L
Calcium (Ca)	Less than 2 mmol/L
Beta-2 microglobulin	Less than 2 mg/L

Data from Glick PL, Harrison MR, Golbus MS, et al. Management of the fetus with congenital hydronephrosis II: Prognostic criteria and selection for treatment. *J Pediatr Surg*. 1985;20:376–87.

TABLE EC 18.F

COMPARISON OF BLADDER EXSTROPHY-EPISPADIAS-CLOACAL EXSTROPHY COMPLEX DISORDERS

	Epispadias	Bladder Exstrophy	Cloacal Exstrophy
Severity	Mild, least severe	Intermediate	Most severe
Definition/ symptoms	Defect/opening in the urethra only Males: Urethra is short and split with meatus present on dorsum of penis. Females: Urethra develops too anteriorly with opening located between split clitoris and labia minora.	Defect in the urethra and the bladder. The posterior vesical wall everts through an opening in abdominal wall.	Defect in the urethra, bladder and rectum. Bladder divided in two halves with penis split in two halves in males, or clitoris divided in two halves in females.
Incidence	Males: 1 in 112,000 births. Females: 1 in 400,00 births.	1 in 10,000 to 1 in 50,000 births. Males affected 2–3 times more than females.	1 in 400,000 births.
Associations		Vesicoureteral reflux, urinary incontinence, widening of pubic bones, displacement of umbilicus.	Omphalocele, imperforate anus, spinal abnormalities, (OEIS).

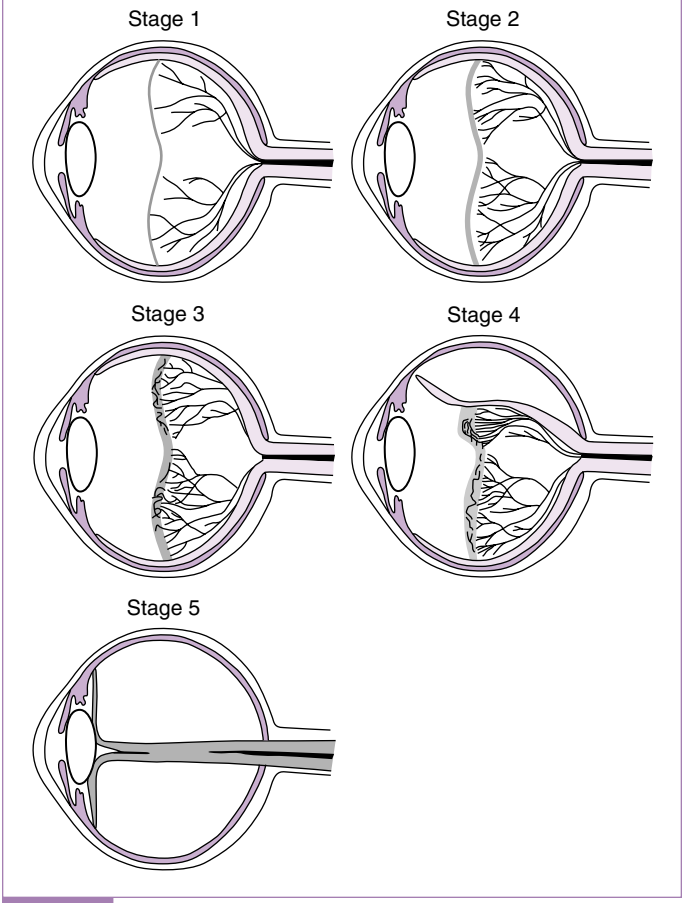


FIGURE 18.7

Retinopathy of prematurity: Stages and plus disease. (From Ann Hellström, Lois EH Smith, Olaf Dammann. Retinopathy of prematurity. *Lancet.* 2013;382(9902):1445–1457, Copyright © 2013 Elsevier Ltd.)

2. All infants born ≥28 weeks gestation, initial ROP screening examination performed at 4 weeks chronologic age.
3. Infants born before 25 weeks gestation, consider earlier screening at 6 weeks chronologic age (even if before 31 weeks postmenstrual age) based on the severity of comorbidities to enable earlier detection and treatment of aggressive posterior ROP (a severe form of rapidly progressive ROP).

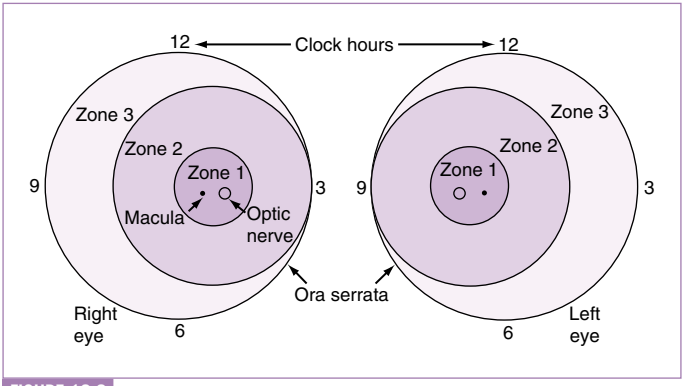


FIGURE 18.8

Zones of the retina. (From American Academy of Pediatrics. Screening examination of premature infants for retinopathy of prematurity, AAP policy statement. *Pediatrics.* 2018(6);142:1–9.)

E. Classification

1. **Stage** (Fig. 18.7)
   a. Stage 1: Demarcation line separates avascular from vascularized retina
   b. Stage 2: Ridge forms along demarcation line
   c. Stage 3: Extraretinal, fibrovascular proliferation tissue forms on ridge
   d. Stage 4: Partial retinal detachment
   e. Stage 5: Total retinal detachment
2. **Zone** (Fig. 18.8)
3. **Plus disease:** Abnormal dilation and tortuosity of posterior retinal blood vessels in two or more quadrants of retina; may be present at any stage
4. **Number of clock hours or 30-degree sectors involved**

F. Management[34-35]

1. **Type 1 ROP:** Peripheral retinal ablation should be considered. Anti-VEGF treatment may be as effective for Zone I disease. Type 1 ROP classified as:
   a. Zone I: Any stage ROP with plus disease
   b. Zone I: Stage 3 ROP without plus disease
   c. Zone II: Stage 2 or 3 ROP with plus disease
2. **Type 2 ROP:** Serial examinations rather than retinal ablation should be considered. Type 2 ROP classified as:
   a. Zone I: Stage 1 or 2 ROP without plus disease
   b. Zone II: Stage 3 ROP without plus disease
3. Follow-up (Table EC 18.G)

XIV. COMMONLY USED MEDICATIONS IN THE NEONATAL INTENSIVE CARE UNIT

See Table 18.12. For neonatal specific drug dosing, refer to Formulary.

TABLE EC 18.G

SUGGESTED SCHEDULE FOR FOLLOW-UP OPHTHALMOLOGIC EXAMINATION IN RETINOPATHY OF PREMATURITY

≤1 Week	1–2 Weeks	2 Weeks	2–3 Weeks
Zone I: stage 1 or 2 ROP Zone II: stage 3 ROP	Zone II: stage 2 ROP	Zone II: stage 1 ROP	Zone III: stage 1 or 2 ROP
Zone I: immature vascularization, no ROP	Posterior zone II: immature vascularization	Zone II: no ROP, immature vascularization	Zone III: regressing ROP
Immature retina extends into posterior zone II near boundary of zone I	Zone I: unequivocally regressing ROP	Zone II: unequivocally regressing ROP	
Suspected presence of aggressive posterior ROP			

NOTE: The presence of plus disease in zone I or II indicates that peripheral ablation rather than observation is appropriate.

ROP, Retinopathy of prematurity.

From American Academy of Pediatrics. Screening examination of premature infants for retinopathy of prematurity, AAP policy statement. *Pediatrics*. 2018;142(6):1–9.

TABLE 18.12

DOSING OF COMMONLY USED ANTIMICROBIALS IN THE NEONATAL INTENSIVE CARE UNIT, BASED ON POSTMENSTRUAL AND POSTNATAL AGE

Drug	Dosing (IV)
Acyclovir	HSV infection: 20 mg/kg/dose
Ampicillin	Typical dosing: 25–50 mg/kg/dose; GBS meningitis: ≤7 postnatal days: 300 mg/kg/day divided Q8H ≥8 postnatal days: 300 mg/kg/day divided Q6H
Cefotaxime	Sepsis/meningitis: 50 mg/kg/dose Gonococcal infections: 25 mg/kg/dose
Ceftazidime	Sepsis/Meningitis: 30–50 mg/kg/dose Consider use of ceftazidime for neonatal sepsis in the absence of cefotaxime due to drug shortages, and in whom ceftriaxone is contraindicated.
Fluconazole[b]	Invasive candidiasis: Loading 12–25 mg/kg/dose; maintenance 6–12 mg/kg/dose
Gentamicin	See chart below See Formulary for recommendations for therapeutic monitoring.
Metronidazole	Loading dose: 15 mg/kg/dose; maintenance dose: See chart below
Oxacillin	25–50 mg/kg/dose; use higher dose for meningitis
Piperacillin/ Tazobactam	100 mg/kg/dose
Vancomycin	Bacteremia: 10 mg/kg/dose; meningitis: 15 mg/kg/dose See Formulary for recommendations for therapeutic monitoring.

Dosing Interval Chart: Ampicillin, Oxacillin

PMA (Weeks)	Postnatal (Days)	Interval (Hours)
≤29[a]	0–28	12
	>28	8
30–36	0–14	12
	>14	8
37–44	0–7	12
	>7	8
≥45	All	6

Dosing Interval Chart: Vancomycin

PMA (Weeks)	Postnatal (Days)	Interval (Hours)
≤29	0–14	18
	>14	12
30–36	0–14	12
	>14	8
37–44	0–7	12
	>7	8
≥45	All	6

Dosing Interval Chart: Metronidazole

PMA (Weeks)	Maintenance Dose (mg/kg)	Interval (Hours)
24–25	7.5	24
26–27	10	24
28–33	7.5	12
34–40	7.5	8
>40	7.5	6

Dosing Interval Chart: Gentamicin

PMA (Weeks)	Postnatal (Days)	Dose (mg/kg)	Interval (Hours)
≤29	0–7	5	48
	8–28	4	36
	≥29	4	24
30–34	0–7	4.5	36
	≥8	4	24
≥35	All	4	24[e]

Dosing Interval Chart: Fluconazole

Gest. Age (Weeks)	Postnatal (Days)	Interval (Hours)
≤29	0–14	48
	>14	24
≥30	0–7	48
	>7	24

Dosing Interval Chart: Acyclovir

PMA (Weeks)	Postnatal (Days)	Interval (Hours)
	All	
<30		8–12
≥30	All	8

TABLE 18.12

DOSING OF COMMONLY USED ANTIMICROBIALS IN THE NEONATAL INTENSIVE CARE UNIT, BASED ON POSTMENSTRUAL AND POSTNATAL AGE

Dosing Interval Chart: Piperacillin/Tazobactam, Ceftazidime

PMA (weeks)	Postnatal (Days)	Interval (Hr)
≤29	0–28	12
	>28	8
30–36	0–14	12
	>14	8
37–44	0–7	12
	>7	8
≥45	All	8

Dosing Interval Chart: Cefotaxime

	Sepsis		Meningitis[c,d]	
GA (Weeks)	Postnatal (Days)	Interval (Hr)	Postnatal (Days)	Interval (Hr)
All weeks	<7	12	0–7	8–12
<32	≥7	8	>7	6–8
≥32	≥7	6		

[a]Or significant asphyxia, PDA, or treatment with indomethacin

[b]Thrush = 6 mg/kg/dose on day 1, then 3 mg/kg/dose orally (PO) Q24 hr, regardless of gestational or postnatal age.

[c]Consider smaller doses and longer intervals for very low–birth weight neonates (less than 2 kg).

[d]Usual dose same for bone and joint, genitourinary, intra-abdominal, lower respiratory tract, or skin and skin structure infections.

[e]Use every 36 hr dosing for patients undergoing therapeutic hypothermia.

See Online NeoFax: http://neofax.micromedexsolutions.com/neofax/neofax.php?strTitle=NeoFax&area=1&subarea=0

GBS, Group B *Streptococcus; GC*, gonococcus; *GA*, gestational age; *IV*, intravenous; *PDA*, patent ductus arteriosus; *PMA*, postmenstrual age.

XV. WEB RESOURCES

- Educational resource: www.nicuniversity.org
- Outcomes calculator: http://www.nichd.nih.gov/about/org/der/branches/ppb/programs/epbo/pages/epbo_case.aspx
- Neonatal dermatology: http://www.adhb.govt.nz/newborn/TeachingResources/Dermatology/Dermatology.htm
- Premature growth chart and calculator: http://peditools.org/fenton2013
- Bilitool: https://bilitool.org
- NeoFax: https://neofax.micromedexsolutions.com/neofax
- Neonatal Sepsis Calculator: https://neonatalsepsiscalculator.kaiserpermanente.org/
- 7th Edition of the Neonatal Resuscitation Program (NRP): https://www.aap.org/en-us/continuing-medical-education/life-support/NRP/Pages/NRP.aspx

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A complete list of references can be found online at www.expertconsult.com.

XVI. ONLINE CONTENT

I. PRENATAL ASSESSMENT OF FETAL HEALTH

A. Fetal Anomaly Screening

1. **Fetal screening:**
   a. Chorionic villus sampling (CVS): Segment of placenta obtained either at 8 to 11 weeks gestation. Detects chromosomal abnormalities and metabolic disorders; however, it cannot detect neural tube defects or measure α-fetoprotein (AFP). Complications include pregnancy loss (0.7% to 2%), maternal infection, increased risk for feto-maternal hemorrhage, and fetal limb and jaw malformations.
   b. Amniocentesis: 20 to 30 mL of amniotic fluid is withdrawn under ultrasound guidance after 16 to 18 weeks gestation. Detects chromosomal abnormalities, metabolic disorders, and neural tube defects. Complications include pregnancy loss (0.06% to 1.0%), leakage of amniotic fluid (1.7%), chorioamnionitis, vertical transmission to infant in mothers with chronic viral infections, and fetal scarring or dimpling of the skin.
   c. Cell free DNA is a noninvasive prenatal screening test available for common trisomies and fetal sex determination. However, there are still limitations to this testing and further diagnostic testing is typically recommended for positive results.[1]
2. **Anatomy ultrasound:** Performed at 18 to 20 weeks gestation.
3. **Maternal AFP:** (Box EC 18.B)

B. Fetal Health

1. **Amniotic fluid volume estimation and amniotic fluid index (AFI):** (Box EC 18.C). AFI is calculated using ultrasound by adding together width of amniotic fluid pockets in four quadrants
2. **Biophysical profile test:** (Table EC 18.H)
3. **Intrapartum Fetal Heart Rate (FHR) Monitoring:**
   a. **Normal baseline FHR:** 120 to 160 beats/min (bpm). Mild bradycardia is 100 to 120 bpm. Severe bradycardia is <90 bpm.
   b. **Normal beat-to-beat variability:** Deviation from baseline of >6 bpm. Absence of variability is <2 bpm from baseline and is a sign of potential fetal distress, particularly when combined with variable or late decelerations.
   c. **Accelerations:** Associated with fetal movements, are benign, and indicate fetal well-being.
   d. **Decelerations:**
      (1) Early decelerations: Begin with onset of contractions. Heart rate reaches nadir at peak of contraction and returns to baseline as contraction ends. Early decelerations occur secondary to changes in vagal tone after brief hypoxic episodes or head compression and are benign.
      (2) Variable decelerations: Represent umbilical cord compression and have no uniform temporal relationship to the onset of a contraction. Variable decelerations are considered severe when

BOX EC 18.B

MATERNAL α-FETOPROTEIN ASSOCIATIONS

Elevated (>2.5 multiples of the median)	Low (<0.75 multiples of the median)
Incorrect gestational dating	Underestimation of gestational age
Neural tube defects	Intrauterine growth retardation
Anencephaly	Trisomy 13
Multiple pregnancy	Trisomy 18
Turner syndrome	Trisomy 21
Omphalocele	
Cystic hygroma	
Epidermolysis bullosa	
Renal agenesis	

Data from Cunningham FG, Leveno KJ, et al. Prenatal diagnosis. In: *Williams Obstetrics*. 25th ed. USA, McGraw-Hill Education; 2018.

BOX EC 18.C

AMNIOTIC FLUID VOLUME ESTIMATION AND AMNIOTIC FLUID INDEX

Oligohydramnios (<500 mL)/(AFI <5)	Polyhydramnios (>2L)/(AFI >25)

• Renal and urologic anomalies:
  • Potter syndrome
  • Lung hypoplasia
• Limb deformities
• Premature rupture of membranes
• Placental insufficiency
	• GI anomalies: Gastroschisis, duodenal atresia, tracheoesophageal fistula, diaphragmatic hernia, esophageal atresia ± tracheoesophageal fistula
	• CNS anomalies: those associated with impaired swallowing (anencephaly, holoprosencephaly), neuromuscular disorders such as myotonic dystrophy, spinomuscular atrophy (SMA, Werdnig-Hoffman disease)
	• Chromosomal trisomies
	• Maternal diabetes
	• Cystic adenomatoid malformation of the lung

AFI, Amniotic fluid index; *CNS*, central nervous system; *GI*, gastrointestinal.
Data from Cunningham FG, Leveno KJ, et al. Amniotic fluid. In: *Williams Obstetrics*. 25th ed. USA, McGraw-Hill Education; 2018.

heart rate drops to <60 bpm for about 60 seconds, with a slow recovery to baseline.

(3) Late decelerations: Occur after peak of contraction, persist after contraction stops, and show a slow return to baseline. Late decelerations result from uteroplacental insufficiency and indicate fetal distress.

C. Estimation of Gestational Age

1. **Last menstrual period (LMP).** Naegele rule gives most accurate determination of gestational age

   Estimation due date = (LMP − 3 months) + 7 days

2. **Ultrasound:** Crown-rump length obtained between 6 and 12 weeks gestation predicts gestational age ± 3 to 4 days. After 12 weeks,

TABLE EC 18.H

THE BIOPHYSICAL PROFILE

Biophysical Variable	Normal (Score = 2)	Abnormal (Score = 0)
Fetal breathing movements	1 or more episodes of ≥20 sec within 30 min	Absent or no episode of ≥20 sec within 30 min
Gross body movements	2 or more discrete body/limb movements within 30 min (episodes of active continuous movement considered as a single movement)	<2 episodes of body/limb movements within 30 min
Fetal tone	1 or more episodes of active extension with return to flexion of fetal limb(s) or trunk (opening and closing of hand considered normal tone)	Slow extension with return to partial flexion, movement of limb in full extension, absent fetal movement, or partially open fetal hand
Reactive fetal heart rate	2 or more episodes of acceleration of ≥5 bpm and of >15 sec associated with fetal movement within 20 min	1 or more episodes of acceleration of fetal heart rate or acceleration of <15 bpm within 20 min
Qualitative amniotic fluid volume	1 or more pockets of fluid measuring ≥2 cm in vertical axis	Either no pockets or largest pocket <2 cm in vertical axis

bpm, Beats per minute.

Adapted from Gearhart et al. Biophysical profile, ultrasound. Emedicine. www.emedicine.com.

the biparietal diameter is accurate within 10 days; beyond 26 weeks, accuracy diminishes to ± 3 weeks.

3. **Postmenstrual age:** Gestational age + chronological age in weeks. Used in perinatal period during hospitalization and until 2 years of age.

D. Expected Birth Weight by Gestational Age (see Table 18.1)

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Chapter 19

Nephrology

Paul M. Gallo, MD, PhD

I. URINALYSIS[1]: TABLE 19.1

A. Common indications include: Infectious workup (urinary tract infection [UTI], pyelonephritis), abdominal trauma, suspected diabetes or renal disease, rhabdomyolysis, edema, failure to thrive.
B. Best if urine specimen is evaluated within 1 hour of voiding, otherwise should be kept at 4°C.
C. Annual screening UAs are not recommended by the American Academy of Pediatrics (AAP) unless patient is at high risk of chronic kidney disease.

II. KIDNEY FUNCTION TESTS

A. Tests of Glomerular Function

1. **Glomerulogenesis is complete at 36 weeks gestation.** Glomerular filtration rate (GFR) increases over the first two years of life related to glomerular maturation.
2. **Normal GFR values**, as measured by inulin clearance (gold standard), are shown in Table 19.2.
3. **Creatinine clearance (CCr):**
   Closely approximates inulin clearance in the normal range of GFR. When GFR is low, CCr overestimates GFR. May be inaccurate in children with obstructive uropathy or problems with bladder emptying secondary to challenges getting complete timed urine collections.

$$\text{CCr (mL/min/1.73 m}^2\text{)} = [U \times (V/P)] \times 1.73/\text{BSA},$$

   where U (mg/dL) = urinary creatinine concentration; V (mL/min)= total urine volume (mL) divided by the duration of the collection (min) (24 hours = 1440 minutes); P (mg/dL) = serum creatinine concentration (may average two levels); and BSA (m^2) = body surface area.
4. **Estimated GFR (eGFR) from plasma creatinine:** Varies related to body size/muscle mass. If body habitus is markedly abnormal or a precise measurement of GFR is needed, consider other methods. Creatinine must be in steady state to estimate GFR; use caution in the setting of acute kidney injury. Three methods to calculate estimated GFR:

TABLE 19.1

URINALYSIS COMPONENTS

Test	Purpose	Normal Findings	Special Notes
Appearance	General impression	Colorless to amber. Cloudy/turbid urine can be normal.	Causes of turbid urine: • Uric acid crystals in acidic urine • Phosphate crystals in alkaline urine • Cellular and infectious material Causes of red/orange urine: Foods, drugs (propofol, chlorpromazine, thioridzine, rifampin), hemoglobinuria, porphyrias
Specific Gravity	Correlates with kidney's ability to concentrate urine; surrogate of osmolality and hydration status	Between 1.003 and 1.030	Isosthenuria: Urine with osmolality equal to plasma (specific gravity of 1.010). May indicate disease affecting ability to concentrate/dilute urine. Falsely elevated by: Glucose, high protein, iodine-based contrast, ketoacids
pH	Evaluate renal tubule hydrogen ion maintenance	pH 4.5–8, average range of 5–6	Influenced by serum pH Alkaline urine may indicate UTI with urea-splitting organisms or certain types of stones
Protein	Evaluate for proteinuria	**Dipstick values:** Negative Trace 1+ (~30 mg/dL) 2+ (~100 mg/dL) 3+ (~300 mg/dL) 4+ (>1000 mg/dL)	Confirm and quantify significant proteinuria with random urine protein/creatinine ratio or 24-hr urine collection Evaluate for postural proteinuria with first morning void Concentrated urine can lead to false positive result
Glucose	Detect glucose in urine	Glucosuria is always abnormal	Glucosuria typically seen when blood glucose >160–180 mg/dL Consider diabetes mellitus, proximal renal tubular disease, pregnancy Dipstick only measures glucose; reduction tests (Clinitest) will detect other sugars for suspected inborn errors of metabolism
Ketones	Detect breakdown of fatty acids	Negative to trace	Suggests diabetes mellitus or starvation-induced catabolism Neonatal ketoacidosis may indicate inborn error of metabolism
Nitrite	Detect gram-negative bacterial metabolism	Negative	Specific (90%–100%), but not sensitive (15%–82%) for UTI False positive from phenazopyridine

Test	Purpose	Normal Findings	Special Notes
Leukocyte Esterase	Detect presence of WBCs	Negative	Indicates pyuria Sensitive (67%–84%), but less specific (64%–92%) for UTI
Hemoglobin	Detects presence of RBCs or hemoglobin	Negative	Indicates hematuria or hemoglobinuria False positive on dipstick: Myoglobin (crush injury, rhabdomyolysis, vigorous exercise, etc.), contamination with blood outside the urinary tract
Bilirubin, Urobilinogen	Evaluate for hyperbilirubinemia	Negative	Positive with indirect hyperbilirubinemia Urobilinogen may be present in low amounts; increased in all cases of hyperbilirubinemia
Red Blood Cells	Differentiate hemoglobinuria from intact RBCs	Centrifuged urine normally contains <5 RBC/hpf	RBC morphology suggest location of bleeding; dysmorphic RBCs suggest a glomerular origin, normal RBCs suggest lower tract bleeding
White Blood Cells	Detect inflammation/infection	Centrifuged urine normally contains <5 WBC/hpf	Consider UTI, sterile pyuria, inflammatory disorders (e.g., Kawasaki)
Epithelial Cells	Index of possible contamination	<5 squamous epithelial cells/hpf	15–20 squamous epithelial cells/hpf suggests contamination, although any amount may indicate contamination
Sediment	Investigate for formed elements: casts, cells, crystals	None	Hyaline casts: may be normal (e.g., dehydration)

RBC, Red blood cell; *UTI*, urinary tract infection; *WBC*, white blood cell

TABLE 19.2

NORMAL VALUES OF GLOMERULAR FILTRATION RATE

Age (Sex)	Mean GFR ± SD (mL/min/1.73 m^2)
1 week (M and F)	41 ± 15
2–8 weeks (M and F)	66 ± 25
>8 weeks (M and F)	96 ± 22
2–12 years (M and F)	133 ± 27
13–21 years (M)	140 ± 30
13–21 years (F)	126 ± 22

F, Female; *M*, male; *SD*, standard deviation.

Adapted from: Hogg RJ, Furth S, Lemley KV, et al. National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease in Children and Adolescents: Evaluation, Classification, and Stratification. *Pediatrics*. 2003;111:1416.

TABLE 19.3

PROPORTIONALITY CONSTANT FOR CALCULATING GLOMERULAR FILTRATION RATE

Age	*k*-Values
Low birth weight during first year of life	0.33
Term AGA during first year of life	0.45
Children and adolescent girls	0.55
Adolescent boys	0.70

AGA, Appropriate for gestational age.

Data from Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. *Pediatr Clin North Am.* 1987;34:571.

a. **Bedside Chronic Kidney Disease in Children (CKiD) cohort**: Only applicable if creatinine measured by enzymatic assay. Recommended for eGFR determination in children aged 1 to 16 years. Estimated GFRs of ≥75 mL/min/1.73 m^2 determined by this equation likely represent normal kidney function; clinical correlation is recommended with GFR estimation.[2]

$$\text{eGFR}(\text{mL}/\text{min}/1.73\ \text{m}^2) = 0.413\times (\text{L}/\text{Pcr}),$$

where *0.413* is the proportionality constant, *L* = height (cm), and *Pcr* = plasma creatinine (mg/dL).

b. **Schwartz equation**: Historical equation for eGFR in children. However, laboratories are increasingly shifting to enzymatic assays to determine creatinine; use of enzymatically determined creatinine (vs Jaffe method) with the Schwartz equation leads to overestimation of GFR and should be considered when applying clinically:

$$\text{eGFR}(\text{mL}/\text{min}/1.73\ \text{m}^2) = \text{kL}/\text{Pcr},$$

where *k* = proportionality constant (Table 19.3); *L* = height (cm); and *Pcr* = plasma creatinine (mg/dL).

c. **Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI):** Used to calculate GFR in those >18 years old. Available at NKDEP website (see Section XII).

5. **Other measurements of GFR:** May be used when more precise determination of GFR is needed (e.g., dosing of chemotherapy). These methods include iothalamate, DTPA, and iohexol. Cystatin C is a low molecular protein that can also be used to estimate GFR and is more accurate than serum creatinine in individuals with conditions that significantly impact muscle mass, the source of creatinine.

B. Tests of Kidney Tubular Function

1. **Proximal tubule and solute handling:**
   a. **Proximal tubule reabsorption:** Proximal tubule is responsible for reabsorption of electrolytes, glucose, and amino acids. Studies to evaluate

proximal tubular function compare urine and blood levels of specific compounds, arriving at a percentage of tubular reabsorption (Tx):

$$Tx = 1 - [(Ux / Px)/(UCr / PCr)] \times 100\,\%,$$

where *Ux* = concentration of compound in urine; *Px* = concentration of compound in plasma; *Ucr* = concentration of creatinine in urine; and *Pcr* = concentration of creatinine in plasma. This formula can be used for amino acids, electrolytes, calcium, and phosphorus. It is commonly used to calculate tubular reabsorption of phosphate (TRP). In a patient with hypophosphatemia and preserved proximal tubular function, the tubular reabsorption of phosphate would be expected to be near 100%.

b. **Fractional excretion of sodium (FENa)[3]:** Commonly used to assess tubular function. Must consider sodium and volume status. May be inaccurate with recent diuretic use.

$$FENa = [(UNa / PNa) / (UCr / PCr)] \times 100\,\%,$$

where *UNa* = concentration of sodium in urine; and *PNa* = concentration of sodium in plasma. FENa is usually <1% in prerenal azotemia or glomerulonephritis, and >1% (usually >3%) in acute tubular necrosis (ATN) or postrenal azotemia. Infants have diminished ability to reabsorb sodium; FENa in volume-depleted infants is <3%.

c. **Fractional excretion of urea (FEurea):** May be useful in certain clinical scenarios, including patients on diuretics. Use FENa equation above, substituting urea for sodium. FEurea is usually <35% in prerenal azotemia and >50% in ATN.[3]

d. **Fractional excretion of bicarbonate ($FHCO_3$)**: May help differentiate the types of renal tubular acidosis (RTA). The majority of bicarb reabsorption occurs in proximal tubule.

$$FeHCO_3 = [(UHCO_3 / PHCO_3) / (UCr / PCr)] \times 100\,\%,$$

Normal $FEHCO_3$ is <5%. Distal RTA is usually <5%. >15% suggests proximal (Type II) RTA.

2. **Distal tubule and pH balance:**

a. **Urine anion gap (UAG):** Used as an indirect measure of ammonium production in the distal nephron.

$$UAG = UNa + UK - UCl,$$

where *UNa* = concentration of sodium in urine; *UK* = concentration of potassium in urine; and *UCl* = concentration of chloride in urine. Positive UAG (usually >20) suggests a distal RTA. Negative UAG (usually <–20) suggests high urinary NH4+ (e.g., secondary to diarrhea).

b. **Urine pH:** A urine acidification defect (distal RTA) should be suspected when random urine pH values are >6 in the presence of moderate systemic metabolic acidosis. Confirm acidification defects by simultaneous venous or arterial pH, plasma bicarbonate concentration, and determination of the pH of fresh urine.

c. **Urine osmolality:** Urine is concentrated distally in the kidney tubules. Urine osmolality, ideally on a first morning urine specimen, may be

TABLE 19.4

AGE-ADJUSTED CALCIUM/CREATININE RATIOS

Age	Ca^{2+}/Cr Ratio (mg/mg) (95th Percentile for Age)
<7 months	0.86
7–18 months	0.60
19 months to 6 years	0.42
Adults	0.22

From Sargent JD, Stukel TA, Kresel J, et al. Normal values for random urinary calcium-to-creatinine ratios in infancy. *J Pediatr.* 1993;123:393.

used to evaluate capacity to concentrate urine. If osmolality is >600 mOsm/L, then tubular dysfunction, including disease states such as diabetes insipidus leading to inappropriate water loss, is unlikely. For more formal testing, see the water deprivation test in Chapter 10.

d. **Urine calcium**: Hypercalciuria may be seen with distal RTA, vitamin D intoxication, hyperparathyroidism, immobilization, excessive calcium intake, use of steroids or loop diuretics, or an idiopathic cause. Diagnosis is as follows:
   (1). 24-hour urine: Calcium >4 mg/kg/24 hr (gold standard)
   (2). Spot urine: Determine calcium/creatinine (Ca/Cr) ratio. Normal urine Ca/Cr ratio does not rule out hypercalciuria. Correlate clinically and follow elevated spot urine Ca/Cr ratio with a 24-hr urine calcium determination if indicated (Table 19.4).[4]

III. CHRONIC HYPERTENSION[5-7]

Note: See Chapter 1 for the management of acute hypertension and Chapter 7 for normal blood pressure (BP) parameters.

A. Definition

Hypertension is defined as the sustained elevation of BP at or above the 95th percentile for those <13 years or ≥130/80 for those ≥13 years. Any BP that is >90th percentile or ≥120/80 should be repeated at a clinic visit; if persistently elevated when confirmed by manual auscultation, the child should return for a repeat measurement for confirmation (see Section III.E).

B. Measurement of Blood Pressure in Children

1. All children ≥3 years should have BP measured annually. Children ≥3 years should have BP measured at **all** visits if at increased risk for hypertension: obesity, taking medications known to increase BP, renal disease, history of aortic arch obstruction/coarctation, diabetes.
2. Children aged <3 years with risk factors should have BP measured at all well-child care visits. Risk factors include history of prematurity <32 weeks gestation or small for gestational age, very low birth weight, congenital heart disease, kidney/urologic disease or family history of

TABLE 19.5

CAUSES OF HYPERTENSION BY AGE GROUP

Age	Most Common	Less Common
Neonates/infants	Renal artery thrombosis after umbilical artery catheterization Coarctation of aorta Renal artery stenosis	Bronchopulmonary dysplasia Medications Patent ductus arteriosus Intraventricular hemorrhage
1–10 years	Renal parenchymal disease Coarctation of aorta	Renal artery stenosis Hypercalcemia Neurofibromatosis Neurogenic tumors Pheochromocytoma Mineralocorticoid excess Hyperthyroidism Transient hypertension Immobilization-induced Sleep apnea Essential hypertension Medications
11 years to adolescence	Renal parenchymal disease Essential hypertension	All diagnoses listed in this table

Modified from Sinaiko A. Hypertension in children. *N Engl J Med.* 1996;335:26.

kidney disease, recurrent UTIs, malignancy, solid organ or bone marrow transplant, taking medications known to increase BP, systemic illness associated with hypertension, and evidence of increased intracranial pressure.

3. BP should be measured in a seated position in an upper extremity after 5 minutes of rest with feet/back/arm supported and mid-cuff at heart level; auscultation is preferred. Appropriate cuff size has a bladder width at least 40% of upper arm circumference at midway point. Bladder length should cover 80% to 100% of arm circumference. Cuffs that are too small may result in falsely elevated BPs. Choose a larger-sized cuff if there is a choice between two.

C. Etiologies of Hypertension in Neonates, Infants, and Children (Table 19.5)

Drugs causing hypertension include glucocorticoids, calcineurin inhibitors, sympathomimetics, oral contraceptives, stimulants (methylphenidate), ephedrine, erythropoietin, NSAIDs, caffeine, tobacco, ethanol, cocaine, amphetamines.

D. Evaluation of Chronic Hypertension

1. Rule out factitious causes of hypertension (improper cuff size or measurement technique [e.g., manual vs. oscillometric]), non-pathologic causes of hypertension (e.g., fever, pain, anxiety, muscle spasm), and iatrogenic mechanisms (e.g., medications, excessive fluid administration).

2. **History:** Headache, blurred vision, dyspnea on exertion, edema, obstructive sleep apnea symptoms (including poor sleep quality or duration), endocrine symptoms (diaphoresis, flushing, constipation, weakness, etc.), history of neonatal intensive care unit stay, rule out pregnancy, history of UTIs, history of medications and supplements, illicit drug use, or any family history of kidney dysfunction or hypertension.
3. **Physical examination:** Four-extremity pulses and BPs, endocrine disease stigmata, edema, hypertrophied tonsils, skin lesions, abdominal mass, or abdominal bruit.
4. **Clinical evaluation of confirmed hypertension:**
   a. Laboratory studies:
      (1) All patients: Urinalysis (UA), serum electrolytes, creatinine, blood urea nitrogen (BUN), lipid profile
      (2) Obese patients: Hgb A1c, AST/ALT, fasting lipid panel
      (3) Consider on basis of history and exam: Fasting serum glucose, thyroid stimulating hormone, drug screen, polysomnography, complete blood count
   b. Clinical practice guidelines recommend 24-hour ambulatory blood pressure monitoring (ABPM) be conducted in all children with persistently elevated blood pressure to confirm the diagnosis of hypertension. Other at-risk populations (e.g., coarctation of the aorta status–post repair, CKD, history of hypertension) should also have this monitoring done yearly regardless of clinic blood pressure.
   c. Imaging:
      (1) Renal ultrasound in patients <6 years old or those with abnormal UA or renal function.
      (2) Echocardiography to evaluate for left ventricular hypertrophy if pharmacologic treatment considered.
      (3) Consider renovascular imaging if renal artery stenosis is suspected.
   d. Patients ≥6 years of age do not require extensive evaluation for secondary causes if they have a strong family history of hypertension (HTN), are overweight, and do not have any evidence of secondary causes on history and physical exam.

E. Classification and Treatment of Hypertension (Table 19.6)

Target: SBP and DBP to <90th percentile and <130/80 mmHg in adolescents ≥13 years old. Consider target 50th percentile in those with CKD.

1. **Nonpharmacologic:** Aerobic exercise, sodium restriction, smoking cessation, and weight loss indicated in all patients with hypertension. Reevaluate BP after lifestyle interventions, and begin pharmacologic therapy if hypertension persists.
2. **Pharmacologic:** Indications include secondary hypertension, symptomatic hypertension, stage 2 hypertension without a clearly modifiable factor (e.g., obesity), diabetes mellitus, and persistent hypertension despite nonpharmacologic measures.

TABLE 19.6

CLASSIFICATION OF HYPERTENSION IN CHILDREN AND ADOLESCENTS AND MANAGEMENT RECOMMENDATIONS

	Ages 1–13 Years	Ages ≥13 Years	Frequency of BP Measurement	Pharmacologic Therapy (in Addition to Lifestyle Modifications)
Normal BP	<90th percentile	<120/<80	Annually (or sooner if at increased risk; see Section III.B)	None
Elevated BP	90th to <95th percentile *OR* 120/80 to <95th percentile, whichever is lower	120/<80 to 129/<80	Recheck in 6 months; if persistent over 2 additional visits, conduct ABPM and diagnostic evaluation	None, unless compelling indications: CKD, DM
Stage 1 Hypertension	95th to 95th percentile plus 12 mmHg *OR* 130/80 to 139/89, whichever is lower	130/80 to 139/89	Recheck in 1–2 weeks; if persistently elevated over 2 additional visits, conduct ABPM and diagnostic evaluation	Initiate therapy, especially if symptomatic, end-organ damage is present, CKD, DM, persistent hypertension despite nonpharmacologic measures
Stage 2 Hypertension	≥95th percentile plus 12 mmHg *OR* ≥140/90, whichever is lower	≥140/90	Evaluate and refer within 1 week, or immediately if the patient is symptomatic	Initiate therapy

All blood pressures expressed in mmHg.

ABPM, Ambulatory blood pressure monitoring; *CKD*, chronic kidney disease; *DBP*, diastolic blood pressure; *DM*, diabetes mellitus; *SBP*, systolic blood pressure.

Modified from Flynn JT, Kaelber DC, Baker-Smith CM, et al., and AAP Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3):e20171904.

3. **Treatment monitoring:** Repeat echocardiogram every 6 to 12 months in those with cardiac end organ damage or those at high risk. Repeated 24-hour ABPM can be used to assess treatment effectiveness as needed.

F. Antihypertensive Drugs for Outpatient Management of Primary Hypertension in Children 1 to 17 Years of Age

Clinical guidelines recommend angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, thiazide diuretics, or long-acting calcium channel blockers as first-line medications for management of chronic hypertension in children.[6] Medication choice may be impacted by underlying comorbidities, contraindications, and side effects. Providers should familiarize themselves with existing guidelines, medication contraindications, and side effects. A list of medications and common side effects is found in Table 19.7.

TABLE 19.7

ANTIHYPERTENSIVE DRUGS FOR OUTPATIENT MANAGEMENT OF HYPERTENSION IN CHILDREN 1–17 YEARS OF AGE

Class	Drug	Comments
Angiotensin-converting enzyme (ACE) inhibitor	Benazepril Captopril Enalapril Fosinopril Lisinopril Ramipril Quinapril	Blocks conversion of angiotensin I to angiotensin II Decreases proteinuria while preserving renal function **Contraindicated**: Pregnancy, compromised renal perfusion (e.g., renal artery stenosis) Check serum potassium and creatinine periodically to monitor for hyperkalemia and uremia Monitor for cough and angioedema
Angiotensin-II receptor blocker (ARB)	Candesartan Irbesartan Losartan Olmesartan Valsartan	**Contraindicated**: Pregnancy Check serum potassium and creatinine periodically to monitor for hyperkalemia and uremia
α- and β-Blockers	Labetalol Carvedilol	Cause decreased peripheral resistance and decreased heart rate **Contraindications**: Asthma, heart failure, insulin-dependent diabetes Heart rate is dose-limiting May impair athletic performance
β-Blocker	Atenolol Esmolol Metoprolol Propranolol	Decreases heart rate, cardiac output, and renin release Noncardioselective agents (e.g., propranolol) are contraindicated in asthma and heart failure Metoprolol and atenolol are β_1 selective Heart rate is dose-limiting May impair athletic performance Should not be used in insulin-dependent diabetics
Calcium channel blocker	Amlodipine Felodipine Isradipine Extended-release nifedipine	Acts on vascular smooth muscles Renal perfusion/function is minimally affected; generally few side effects Amlodipine and isradipine can be compounded into suspensions May cause tachycardia

Class	Drug	Comments
Central α-agonist	Clonidine	Stimulates brainstem α_2 receptors and decreases peripheral adrenergic drive May cause dry mouth and/or sedation (↓ opiate withdrawal) Transdermal preparation also available Sudden cessation of therapy can lead to severe rebound hypertension
Loop diuretics	Furosemide Bumetanide	Side effects are hyponatremia, hypokalemia, and ototoxicity
Thiazide diuretics	Hydrochlorothiazide Chlorthalidone Chlorothiazide	Side effects are hypokalemia, hypercalcemia, hyperuricemia, and hyperlipidemia
Potassium-sparing diuretics	Spironolactone Triamterene Amiloride	Useful as add-on therapy in patients being treated with drugs from other drug classes Potassium-sparing diuretics are modest antihypertensives. They may cause severe hyperkalemia, especially if given with ACE inhibitor or ARB
Peripheral α-antagonist	Doxazosin Prazosin Terazosin	May cause hypotension and syncope, especially after first dose
Vasodilator	Hydralazine	Directly acts on vascular smooth muscle and is very potent Tachycardia, sodium retention, and water retention are common side effects
	Minoxidil	Used in combination with diuretics or β-blockers Minoxidil is usually reserved for patients with hypertension resistant to multiple drugs

Modified from Flynn JT, Kaelber DC, Baker-Smith CM, et al., and AAP Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3):e20171904.

IV. URINARY TRACT INFECTIONS[8-13]

A. History

Highly dependent on patient age. Inquire about fever, dysuria, frequency, urgency, and back/abdominal pain. Obtain voiding history (stool, urine), stream characteristics in toilet-trained children, sexual activity, sexual abuse, circumcision status, prolonged/bubble baths or swimming, evaluation of growth curve, recent antibiotic use, and family history of vesicoureteral reflux (VUR), recurrent UTIs, or chronic kidney disease.

B. Physical Examination

Vital signs, abdominal examination for tenderness, flank masses, bowel distention, evidence of impaction, meatal stenosis or circumcision in males, vulvovaginitis or labial adhesions in females, neurologic examination of lower extremities, perineal sensation and reflexes, and rectal and sacral examination (for anteriorly placed anus).

C. Risk Factors

2011 AAP guidelines,[8] reaffirmed in 2016,[9] for children 2 to 24 months provide resources to help clinicians stratify the risk of UTI in the absence of another source of infection in a febrile child.

1. Females are at higher risk for UTI than males.
2. Uncircumcised males are at higher risk than circumcised males.
3. Other risk factors include non-black race, fever ≥39°C, and fever >1 to 2 days.

D. Methods of Urine Collection

1. **If a child is 2 months to 2 years old, has a fever, and appears sufficiently ill to warrant immediate antibiotics**, obtain UA and urine culture by transurethral catheterization. **Suprapubic percutaneous aspiration** may be useful in critically ill children, is generally very safe, and is similar to bladder catheterization in sensitivity and specificity.
2. **If a child is 2 months to 2 years old, has a fever, and does not appear ill enough to warrant immediate antibiotics**, obtain urine by catheterization or the most convenient method available. **Bag or absorbent pad** may be helpful when UTI is unlikely (to rule out infection), but both have very high false positive rates (>75% of cultures positive) and should not be sent for culture.[8] If UA does not suggest UTI, it is reasonable to avoid antimicrobial therapy. If UA does suggest UTI, urine culture should be obtained by catheterization.
3. **If a child is >2 years old and toilet trained**, may provide midstream clean-catch urine specimen.

E. Diagnosis

To establish the diagnosis of UTI, both UA results suggestive of infection and positive urine culture are recommended.

1. Nitrite test:
   a. Detects products of reduction of dietary nitrates by urinary gram-negative bacterial species (especially *Escherichia coli*, *Klebsiella*, and *Proteus*).
   b. Sensitivity 15% to 82% and specificity 90% to 100% for UTI.[8]
   c. Special circumstances: False-negative (low sensitivity) results commonly occur with insufficient time (<4 hours) for conversion of urinary nitrates to nitrites (age-dependent voiding frequency) and inability of bacteria to reduce nitrates to nitrites (many gram-positive organisms such as *Enterococcus*, *Mycobacterium* spp., and fungi).
2. Leukocyte esterase test:
   a. Detects esterase released from leukocyte lysis.
   b. Sensitivity 67% to 84% and specificity 64% to 92% for UTI.[8]
3. Pyuria is defined at a threshold of ≥5 WBCs/hpf. Absence of pyuria is rare if a true UTI is present.
4. Urine culture:
   a. Transurethral catheterization or suprapubic aspiration: >50,000 colony-forming units (CFU) per mL diagnostic of UTI. Some sources suggest >10,000 CFU/mL in the presence of fever, symptoms, and pyuria may also be diagnostic.[10]

b. Clean catch: >100,000 CFU/mL necessary to diagnose a UTI.
c. Bagged specimen: Should not be used to collect urine culture.
d. Catheter-associated (indwelling urethral or suprapubic): No specific data for pediatric patients. Adult Infectious Diseases Society of America guidelines define it as presence of symptoms and signs compatible with UTI and >1000 CFU/mL of one or more bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose catheter has been removed within previous 48 hours.[11]

F. Classification

Pyelonephritis (upper UTI), rather than cystitis (lower UTI), is suggested by fever ≥38.5°C (especially if lasting >48 hours after initiating appropriate antibiotics), systemic symptoms, costovertebral angle tenderness, elevated CRP, leukocytosis.

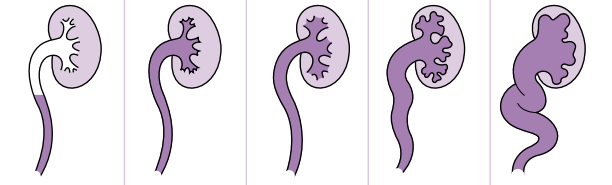
G. Imaging

1. **Renal and bladder ultrasound (RBUS):** Evaluates for anatomic abnormalities and abscesses. Indications include children 2 to 24 months with first UTI, recurrent or atypical UTIs, or if no response to treatment within 48 hours. If there is clinical improvement <48 hours and follow up is reliable, should be done after full recovery. If there is no response to treatment or follow up is uncertain, then RBUS during illness is indicated.
2. **Voiding cystourethrography (VCUG):** Evaluates bladder anatomy, emptying, and looks for signs of vesicoureteral reflux (VUR). Should not be obtained routinely after first febrile UTI. Indications include children 2 to 24 months with abnormal RBUS findings (hydronephrosis, scarring, or other findings suggestive of either high-grade VUR or obstructive uropathy), complicated or recurrent pyelonephritis.[8] Consider if family history of VUR. Optimal time is 2 to 6 weeks after infection.

H. Treatment of Culture-Positive Urinary Tract Infection

For empiric therapy, see Chapter 17.

1. **Organisms:**
   a. *E. coli* is the most common cause of pediatric UTI.
   b. Other common pathogens: *Klebsiella, Proteus* spp., *Staphylococcus saprophyticus,* and *Staphylococcus aureus.*
   c. Neonatal UTI: Group B streptococci and other bloodborne pathogens.
   d. *Enterococcus* and *Pseudomonas* are more prevalent in abnormal hosts (e.g., recurrent UTI, abnormal anatomy, neurogenic bladder, hospitalized patients, or those with frequent bladder catheterizations). Consider blood cultures if urine grows uncommon organism or *Staphylococcus.*
2. **Treatment considerations and duration:**
   a. Route: Parenteral antibiotics for children who are toxic, dehydrated, or unable to tolerate oral medication due to vomiting or noncompliance.



Grade I	Grade II	Grade III	Grade IV	Grade V
Ureter only	Ureter, pelvis, calyces; no dilatation, normal calyceal fornices	Mild or moderate dilatation and/or tortuosity of ureter; mild or moderate dilatation of the pelvis, but no or slight blunting of the fornices	Moderate dilatation and/or tortuosity of the ureter; mild dilatation of renal pelvis and calyces; complete obliteration of sharp angle of fornices, but maintenance of papillary impressions in majority of calyces	Gross dilatation and tortuosity of ureter; gross dilatation of renal pelvis and calyces; papillary impressions are no longer visible in majority of calyces

FIGURE 19.1

International classification of vesicoureteral reflux. (Modified from Rushton H. Urinary tract infections in children: epidemiology, evaluation, and management. *Pediatr Clin North Am.* 1997;44:5 and International Reflux Committee. Medical vs. surgical treatment of primary vesicoureteral reflux: report of the International Reflux Study Committee. *Pediatrics.* 1981;67:392.)

   b. Duration: 3 to 5 days for uncomplicated cases[12]; 7 to 14 days for toxic children and those with pyelonephritis.
3. **Inadequate response to therapy:** Consider renal abscess or urinary obstruction; RBUS and repeat urine culture is indicated. Repeat cultures should also be considered in patients with recurrent UTIs to rule out persistent bacteriuria.
4. **Management of VUR:**
   a. Classification of VUR: Fig. 19.1
   b. Antibiotic prophylaxis: Evidence suggests that prophylactic trimethoprim-sulfamethoxazole reduces the risk of UTI recurrence by 50%, but with no significant difference in renal scarring. Some experts suggest that recent studies are insufficiently powered to detect a difference in the relatively rare outcomes of renal

scarring, and thus recommend shifting guideline recommendations from "no prophylaxis" to "selective prophylaxis" in certain groups of patients.[13]

c. Surgical intervention: Monitor persistence/grade of VUR annually, often in consultation with a pediatric urologist. Spontaneous resolution may occur, although less likely with higher grade. Higher-grade VUR that persists as the child grows may ultimately require surgical intervention.

5. **Asymptomatic bacteriuria:** Defined as bacteria in urine on microscopy and Gram stain in an afebrile, asymptomatic patient without pyuria. Antibiotics not necessary if voiding habits and urinary tract are normal.
6. **Referral to pediatric urology:** Consider in children with abnormal voiding patterns based on history or imaging, neurogenic bladder, abnormal anatomy, recurrent UTI, or poor response to appropriate antibiotics.

V. PROTEINURIA[14–16]

A. Definitions

1. **Orthostatic proteinuria:** Excretion of significant amounts of protein while in the upright position. A benign condition and common cause of proteinuria in children and adolescents.
2. **Fixed proteinuria:** Proteinuria found on first morning urine void over several consecutive days. Suggestive of kidney disease.
3. **Microalbuminuria:** Presence of albumin in urine below detectable range of dipsticks. In adults, defined as 30 to 300 mg/g creatinine. Most often used in screening for kidney disease secondary to diabetes.
4. **Significant proteinuria:** Urine protein to urine creatinine (UPr:UCr) ratio 0.2 to 2.0 mg/mg or 4 to 40 mg/m^2/hr in a 24-hour collection.
5. **Nephrotic-range proteinuria:** UPr:UCr ratio >2 mg/mg or >40 mg/m^2/hr in a 24-hour collection. In adults, 24-hour urine protein excretion of 3000 mg/24 hours.
6. **Nephrotic syndrome:** Nephrotic-range proteinuria, hypoalbuminemia, edema, and hyperlipidemia (cholesterol >200 mg/dL).

B. Methods of Detection

1. **Urinalysis** (see Table 19.1): Proteinuria on a urine dipstick should be verified by a urine protein/creatinine ratio in an appropriately collected first morning urine specimen. Urine samples collected immediately upon rising in the morning help distinguish the contribution of benign orthostatic proteinuria to the proteinuria detected on dipstick or randomly timed spot urine collection.
2. **First morning urine protein/creatinine ratio:**
   a. Approximates 24-hour urine collections well.
   b. Appropriate collection is essential for accurate results. A child must empty the bladder before going to bed. If the child gets up during the night, the bladder should be emptied before returning to bed. When the child wakes up in the morning, the urine sample should be provided immediately.

BOX 19.1

CAUSES OF PROTEINURIA

Transient proteinuria: Caused by fever, exercise, dehydration, cold exposure, seizure, stress

Orthostatic proteinuria

Glomerular diseases with isolated proteinuria: Idiopathic (minimal change disease) nephrotic syndrome, focal segmental glomerulosclerosis, mesangial proliferative glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis, amyloidosis, diabetic nephropathy, sickle cell nephropathy

Glomerular diseases with proteinuria as a prominent feature: Acute postinfectious glomerulonephritis, immunoglobulin A nephropathy

Tubular disease: Cystinosis, Wilson disease, acute tubular necrosis, tubulointerstitial nephritis, polycystic kidney disease, renal dysplasia, toxic tubular injury (medications, heavy metals)

Adapted from Kliegman RM, Stanton BF, St. Geme JW, et al. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Saunders; 2015.

c. Normal ratios:
   (1) <2 years old: <0.5 mg/mg
   (2) >2 years old: <0.2 mg/mg
d. Abnormal ratios (mg/mg): Significant proteinuria detected on a first morning protein/creatinine ratio should prompt verification of appropriate collection. Repeat specimen should be analyzed within 1 to 2 weeks, or sooner based on clinical scenario (e.g., edema, hypertension, or symptom of concern would prompt a more expedited workup).

3. **24-hour urine protein:** May have a contribution from benign orthostatic proteinuria, which cannot be ruled out without a fractional urine collection. Protein level >4 mg/m^2/hr is considered significant.

C. Etiologies (Box 19.1)

See Section VI.E for discussion of nephrotic syndrome.

D. Evaluation[15]

Further evaluation is necessary if proteinuria is significant/symptomatic and not secondary to orthostatic proteinuria (Box 19.2).

E. Nephrotic Syndrome[16]

1. **Epidemiology:** Idiopathic nephrotic syndrome of childhood is the most common form, representing approximately 90% of cases in children between the ages of 1 and 10 years. *Minimal change disease* is the most common renal pathology found among children with idiopathic nephrotic syndrome in this age group. Nephrotic syndrome may be a manifestation of a primary kidney disease, a systemic disorder resulting in glomerular injury, or rarely medication.
2. **Clinical manifestations**: Hypoalbuminemia and decrease in oncotic pressure results in generalized edema. Initial swelling commonly occurs on the face (especially periorbital), as well as in the pretibial area. Eye swelling is often mistaken for allergic reactions or seasonal allergies (Box 19.3).

BOX 19.2

BASIC EVALUATION OF SIGNIFICANT (NEPHROTIC AND NONNEPHROTIC) PROTEINURIA

Complete metabolic panel with phosphorus
C3 and C4
ESR, CRP
Antinuclear antibody, anti–double stranded DNA antibody
Hepatitis B, C, and HIV in high-risk populations
Antineutrophil antibodies (c- and p-ANCA)
Lipid panel
Renal and bladder ultrasonography
Referral to nephrologist

BOX 19.3

FACTORS SUGGESTING DIAGNOSIS OTHER THAN IDIOPATHIC MINIMAL CHANGE NEPHROTIC SYNDROME

Age <1 year or >10 years
Family history of kidney disease
Extrarenal disease (arthritis, rash, anemia)
Chronic disease of another organ or systemic disease
Symptoms due to intravascular volume expansion (hypertension, pulmonary edema)
Kidney failure
Active urine sediment (red blood cell casts)

TABLE 19.8

ETIOLOGIES OF NEPHROTIC SYNDROME

Primary Causes (90%)	Secondary Causes (10%)
Minimal change nephrotic syndrome (MCNS): 85% of idiopathic causes in children	Infections (HIV, hepatitis B, hepatitis C)
Focal segmental glomerulosclerosis (FSGS)	Systemic lupus erythematosus
Membranous nephropathy	Diabetes mellitus
IgA nephropathy	Drugs
Genetic disorders involving the slit diaphragm	Malignancy (leukemias, lymphomas)

3. **Etiologies:** See Table 19.8.
4. **Investigations at first presentation:** UA and microscopy (microhematuria present in 30% and is not prognostic); urine P/Cr ratio; serum albumin, total protein, cholesterol, creatinine; infectious workup (consider tuberculosis, HIV, hepatitis B, hepatitis C, as indicated).
5. **Management of idiopathic nephrotic syndrome of childhood:** Empirical corticosteroid treatment without kidney biopsy is recommended for children without atypical features. Hospitalization recommended for children with overwhelming edema or infection.

a. Steroid-responsive: Approximately 95% of patients with minimal change disease (MCD) and 20% with focal segmental glomerulosclerosis (FSGS) achieve remission within 4 to 8 weeks of starting prednisone. Response to corticosteroids is the best prognostic indicator, including the likelihood of underlying MCD.
   (1) Although duration of therapy varies, one common regimen includes prednisone 60 mg/m^2 daily or 2 mg/kg/day (maximum dose 60 mg/day) for 6 weeks, followed by 40 mg/m^2 or 1.5 mg/kg on alternate days for 6 weeks.[16]
   (2) Relapses of idiopathic nephrotic syndrome are treated with a shorter duration of corticosteroids, which also vary according to the center and the consensus body. Commonly, prednisone 60 mg/m^2 or 2 mg/kg/day (maximum dose 60 mg/day) until urine protein is negative for 3 consecutive days, followed by 40 mg/m^2 or 1.5 mg/kg on alternate days for 4 weeks.
b. Frequently relapsing: Defined as 2 or more relapses within 6 months of initial response, or 4 or more relapses in any 12-month period.
c. Steroid-dependent: Defined as 2 consecutive relapses during tapering or within 14 days of cessation of steroids. Some patients can be managed with low-dose steroids, given daily or on alternate days, but many will relapse. Second-line treatments for frequently relapsing and steroid-dependent nephrotic syndrome: Cyclophosphamide, mycophenolate mofetil (MMF), calcineurin inhibitors, levamisole, or rituximab.
d. Steroid-resistant: Lack of remission or partial remission after 8 weeks of corticosteroids. Second-line agents, including calcineurin inhibitors or MMF, are often introduced once steroid resistance is confirmed.
e. Indications for renal biopsy: Macroscopic hematuria, age <12 months or >12 years, systemic or syndromic findings, persistent creatinine elevation >1 to 2 weeks, low complement levels, and persistent proteinuria after 4 to 8 weeks of adequate steroid treatment.[17]

6. **Complications:**
   a. AKI; thromboembolic disease; potentially life-threatening infection. See Chapter 16 for vaccine recommendations.
   b. Chronic systemic steroids: Cushingoid skin changes, cataracts, accelerated atherosclerosis, osteoporosis, gastric ulcer, mood swings, insomnia, insulin resistance, immunosuppression.

VI. HEMATURIA[18]

A. Definition

1. **Microscopic hematuria:** >5 RBCs/hpf on centrifuged urine. Not visible to the naked eye.
2. **Macroscopic (gross) hematuria:** Visible blood in urine.
3. **Acute nephritic syndrome:** Classically tea or cola-colored urine, facial or body edema, hypertension, and oliguria.

B. Etiologies: See Table 19.9.

TABLE 19.9

CAUSES OF HEMATURIA IN CHILDREN

Kidney-related disease	Isolated glomerular disease	IgA nephropathy, Alport syndrome, thin glomerular basement membrane nephropathy, postinfectious/poststreptococcal glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, antiglomerular basement membrane disease
	Multisystem disease involving glomerulus	Systemic lupus erythematosus nephritis, Henoch-Schönlein purpura nephritis, granulomatosis with polyangiitis, polyarteritis nodosa, Goodpasture syndrome, hemolytic-uremic syndrome, sickle cell glomerulopathy, HIV nephropathy
	Tubulointerstitial disease	Pyelonephritis, interstitial nephritis, papillary necrosis, acute tubular necrosis
	Vascular	Arterial or venous thrombosis, malformations (aneurysms, hemangiomas), nutcracker syndrome, hemoglobinopathy (sickle cell trait/disease)
	Anatomical	Hydronephrosis, cystic kidney disease, polycystic kidney disease, multicystic dysplasia, tumor, trauma
Urinary tract disease		Inflammation (cystitis, urethritis) Urolithiasis Trauma Coagulopathy Arteriovenous malformations (AVMs) Bladder tumor Factitious

Data from Kliegman RM, Stanton BF, St. Geme JW, et al. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2015.

C. Evaluation (Fig. 19.2)

Differentiate glomerular and extraglomerular hematuria: Examine urine sediment, looking for RBC casts and protein.

1. Glomerular hematuria
   a. Usually hypertensive; dysuria usually absent; edema, fever, pharyngitis, rash, and arthralgia may suggest glomerular disease.
   b. Laboratory: Dysmorphic RBCs and casts on UA, complete blood cell count (CBC) with differential and smear, serum electrolytes with calcium, BUN/creatinine, serum protein/albumin, and other testing driven by history and exam, including ANA, hepatitis B and C serologies, HIV, audiology screen, if indicated.
   c. Consider other studies to determine underlying diagnosis: C3/C4, antineutrophil antibody (c- and p-antineutrophil cytoplasmic antibodies), anti–double-stranded DNA
2. Extraglomerular hematuria
   a. Rule out infection: Urine culture, gonorrhea, chlamydia
   b. Rule out trauma: History, consider imaging of abdomen/pelvis
   c. Investigate other potential causes: Urine Ca/Cr ratio or 24-hour urine for kidney stone risk analysis, sickle cell screen, renal/bladder ultrasound. Consider serum electrolytes with calcium, coagulation studies.

D. Management (Fig. 19.3)

VII. ACUTE KIDNEY INJURY[19,20]

A. Definition

Sudden decline in kidney function; clinically represented by rising creatinine, with or without changes in urine output.

B. Etiology (Table 19.10)

Causes are generally subdivided into three categories:

1. **Prerenal:** Impaired perfusion of kidneys, the most common cause of acute kidney injury (AKI) in children. Volume depletion is a common cause of prerenal AKI.
2. **Renal:**
   a. Parenchymal disease due to vascular or glomerular lesions.
   b. Acute tubular necrosis: Diagnosis of exclusion when no evidence of renal parenchymal disease is present and prerenal and postrenal causes have been eliminated, if possible.
3. **Postrenal:** Obstruction of the urinary tract, commonly due to inherited anatomic abnormalities in children.

C. Clinical Presentation

Pallor, decreased urine output, systemic and pulmonary edema, hypertension, vomiting, and lethargy. The hallmark of early kidney failure is often oliguria.

1. **Oliguria:** Urine output <0.5 mL/kg/hr (for at least 6 hours). May reflect intrinsic or obstructive kidney disease. Always interpret urine output in the context of physical exam, clinical scenario, and fluid delivery.

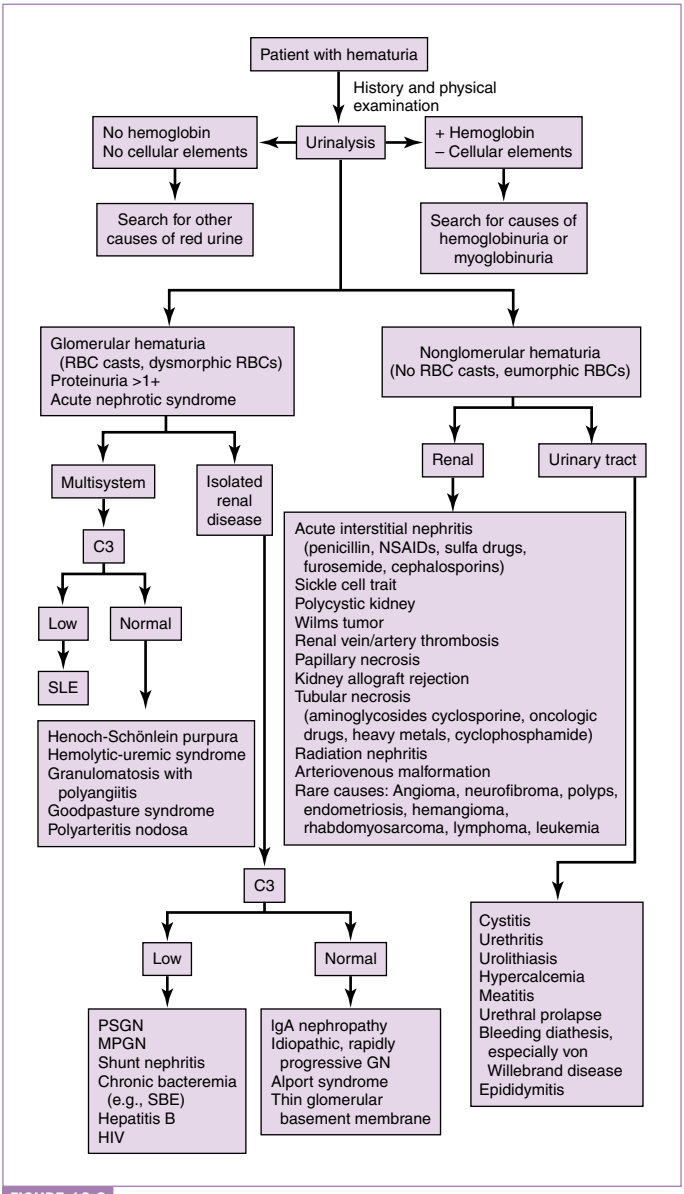


FIGURE 19.2

Diagnostic strategy for hematuria. *GN*, Glomerulonephritis; *HIV*, human immunodeficiency virus; *MPGN*, membranoproliferative glomerulonephritis; *NSAIDs*, nonsteroidal antiinflammatory drugs; *PSGN*, poststreptococcal glomerulonephritis; *RBC*, red blood cell; *SBE*, subacute bacterial endocarditis; *SLE*, systemic lupus erythematosus.

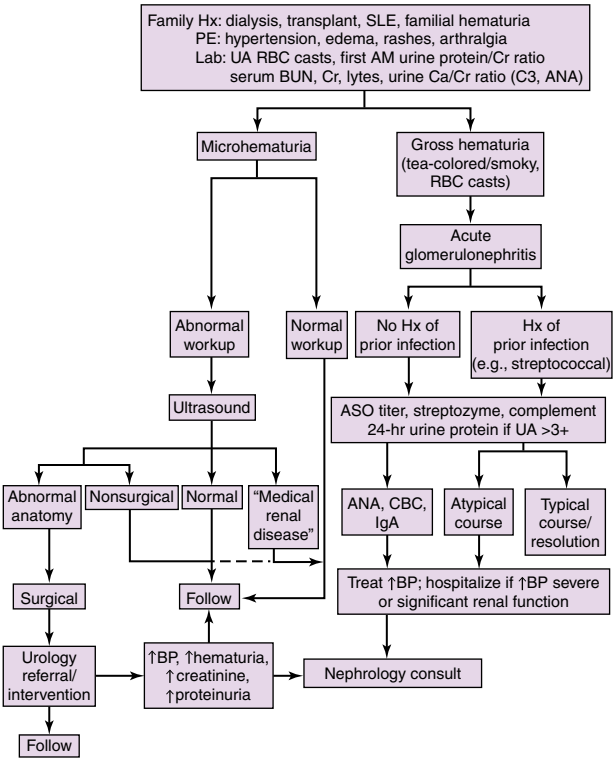


FIGURE 19.3

Management algorithm for hematuria. (Data from Hay WM, Levin MJ, Deterding RR, Azbug MJ, Sondheimer JM. *CURRENT Diagnosis & Treatment Pediatrics*. 21st ed. www.accessmedicine.com, Fig. 24.1.)

For example, low urine output may be appropriate (physiologic response to water depletion in a prerenal state) and "normal" urine output may be inappropriate in a volume-depleted patient (potentially representing kidney tubular damage or another pathologic state). Laboratory differentiation of oliguria is found in Table 19.11.

2. **Blood urea nitrogen/creatinine (BUN/Cr) ratio (both in mg/dL):** Interpret ratios with caution in small children with low serum creatinine.
   a. 10 to 20 (normal ratio): Suggests intrinsic renal disease in the setting of oliguria.

TABLE 19.10

ETIOLOGIES OF ACUTE KIDNEY INJURY

PRERENAL	**Decreased True Intravascular Volume:** Hemorrhage, volume depletion, sepsis, burns **Decreased Effective Intravascular Volume:** Congestive heart failure, hepatorenal syndrome **Altered Golmerular Hemodynamics:** NSAIDs, ACE inhibitors (when renal perfusion is already low)
INTRINSIC RENAL	**Acute Tubular Necrosis:** Hypoxic/ischemic insults Drug-induced—aminoglycosides, amphotericin B, acyclovir, chemotherapeutic agents (ifosfamide, cisplatin) Toxin-mediated—endogenous toxins (myoglobin, hemoglobin); exogenous toxins (ethylene glycol, methanol) **Interstitial Nephritis:** Drug-induced—β-lactams, NSAIDs (may be associated with high-grade proteinuria), sulfonamides, PPIs Idiopathic **Uric acid nephropathy:** Tumor lysis syndrome **Glomerulonephritis:** In most severe degree, presents as rapidly progressive glomerulonephritis (RPGN) **Vascular Lesions:** Renal artery thrombosis, renal vein thrombosis, cortical necrosis, hemolytic uremic syndrome **Hypoplasia/Dysplasia:** Idiopathic or exposure to nephrotoxic drugs in utero
POSTRENAL	Obstruction in a Solitary Kidney Bilateral Ureteral Obstruction Urethral Obstruction Bladder Dysfunction

ACE, Angiotensin-converting enzyme; *NSAIDs*, nonsteroidal antiinflammatory drugs; *PPIs*, proton pump inhibitors.
Data from Andreoli SP. Acute kidney injury in children. *Pediatr Nephrol*. 2009;24:253–263.

TABLE 19.11

LABORATORY DIFFERENTIATION OF OLIGURIA

Test	Prerenal	Renal
FENa	≤1%	>3%
BUN/Cr ratio	>20:1	<10:1
Urine specific gravity	>1.015	<1.010

BUN, Blood urea nitrogen; *Cr*, creatinine; *FENa*, fractional excretion of sodium.

b. >20: Suggests volume depletion, prerenal azotemia, or gastrointestinal bleeding.
c. <5: Suggests liver disease, starvation, or inborn error of metabolism.

D. Acute Tubular Necrosis

Clinically defined by three phases:

1. **Oliguric phase:** Period of severe oliguria that may last days. If oliguria or anuria persists for longer than 3 to 6 weeks, kidney recovery from ATN is less likely.
2. **High urine output phase:** Begins with increased urine output and progresses to passage of large volumes of isosthenuric urine containing sodium levels of 80 to 150 mEq/L.
3. **Recovery phase:** Signs and symptoms usually resolve rapidly, but polyuria may persist for days to weeks.

E. Treatment Considerations

1. Careful monitoring of volume status (daily weights, strict input/output). Consider placement of indwelling catheter to monitor urine output.
2. Prerenal and postrenal factors should be addressed or excluded.
3. Intravascular volume resuscitation and maintenance with appropriate fluids in consultation with a pediatric nephrologist.
4. Monitor metabolic/electrolyte abnormalities, discontinue unnecessary nephrotoxic medications and follow drug levels closely when available, adjust dosing of medications based on creatinine clearance (see Chapter 31), monitor blood pressure closely, and maintain appropriate nutrition (low phosphorus, low potassium).
5. See Section IX for indications for acute dialysis

F. Complications

1. Dependent on clinical severity.
2. Usually includes fluid overload (hypertension, congestive heart failure [CHF], or pulmonary edema), electrolyte disturbances (hyperkalemia), metabolic acidosis, hyperphosphatemia, and uremia.

G. Radiographic Imaging Considerations in AKI/CKD

1. To prevent radiographic contrast-induced nephropathy, select radiographic studies that do not require administration of a radiographic iodinated contrast media (RICM) if possible, particularly in high-risk populations, such as patients with AKI or CKD.[21]
2. If RICM is required, use of low or iso-osmolality contrast media is preferred.[21]
3. Hydration has been found to be effective in preventing or minimizing contrast-induced nephropathy in some studies of high-risk populations. Intravenous hydration 6 hours prior to and 6 to 12 hours after contrast administration has been studied.[21]
4. Use of N-acetylcysteine is controversial in preventing contrast-induced nephropathy.[21]
5. Gadolinium and nephrogenic systemic fibrosis: The triad of gadolinium use, a pro-inflammatory state, and renal impairment (GFR <30 mL/min per 1.73 m^2, peritoneal or hemodialysis) is associated with nephrogenic

systemic fibrosis. Gadolinium is contraindicated in patients with GFR <30 mL/min per 1.73 m^2, and caution should be used at GFR levels between 30 and 60 mL/min per 1.73 m^2.[22]

VIII. CHRONIC KIDNEY DISEASE[23]

A. Definition

Kidney damage for >3 months, as defined by structural or functional abnormalities, with or without decreased GFR. Classified as:

Stage I: Kidney injury with normal or increased GFR
Stage II: GFR 60 to 89 mL/min/1.73 m^2
Stage III: GFR 30 to 59 mL/min/1.73 m^2
Stage IV: GFR 15 to 29 mL/min/1.73 m^2
Stage V: GFR <15 mL/min/1.73 m^2 or dialysis

B. Etiology

1. Children <5 years: Most commonly due to congenital abnormalities (e.g., kidney hypoplasia/dysplasia, urologic malformations).
2. Older children: More commonly acquired glomerular diseases (e.g., glomerulonephritis, FSGS) or hereditary disorders (e.g., Alport syndrome).

C. Clinical Manifestations (Table 19.12)

D. General Management

1. **Nutrition:** Growth should be monitored closely; supplemental nutrition should be considered if not reaching caloric goals, which are higher in children with CKD. Potassium and sodium restriction may be required in advanced CKD. Growth hormone therapy may be considered in consultation with pediatric nephrology/endocrinology.
2. **Anemia:** Evaluate with CBC and iron studies. Iron deficiency is common and should be treated with oral (preferred) or IV iron. Consider erythropoietin-stimulating agents in consultation with pediatric nephrology.
3. **CKD–mineral and bone disorder:** Characterized by phosphate retention, decreased free calcium, and decreased 1,25 hydroxyvitamin D. Serum calcium, phosphate, alkaline phosphatase, vitamin D, and parathyroid hormone should be regularly monitored. Control phosphate with phosphate binders, supplement with calcium and vitamin D, as indicated.
4. **Cardiovascular:** Regularly monitor blood pressure and lipid panel. Treating hypertension slows the progression of CKD.

IX. DIALYSIS

A. Indications for Acute Dialysis

When metabolic or fluid derangements are not controlled by aggressive medical management alone. Should be initiated in consultation with a nephrologist. Generally accepted criteria include the following:

1. **Acidosis:** Intractable metabolic acidosis.

TABLE 19.12

CLINICAL MANIFESTATIONS OF CHRONIC KIDNEY DISEASE

Manifestation	Mechanisms
Edema	Accumulation of Na+ and water Decreased oncotic pressure Reduced cardiac output Mineralocorticoid excess
Uremia	Decline in GFR
Acidosis	Urinary bicarbonate wasting Decreased excretion of NH_4 and acid
Sodium wasting	Solute diuresis, tubular damage Aldosterone resistance
Sodium retention	Nephrotic syndrome CHF Reduced GFR
Urinary concentrating defect	Solute diuresis, tubular damage ADH resistance
Hyperkalemia	Decline in GFR, acidosis Aldosterone resistance
Renal osteodystrophy	Impaired production of 1,25(OH) vitamin D Decreased intestinal calcium absorption Impaired phosphorus excretion Secondary hyperparathyroidism
Growth retardation	Protein-calorie deficiency Renal osteodystrophy Acidosis Anemia Inhibitors of insulin-like growth factors
Anemia	Decreased erythropoietin production Low-grade hemolysis Bleeding, iron deficiency Decreased erythrocyte survival Inadequate folic acid intake Inhibitors of erythropoiesis
Bleeding tendency	Thrombocytopenia Defective platelet function
Infection	Defective granulocyte function Glomerular loss of immunoglobulin/opsonins
Neurologic complaints	Uremic factors
Gastrointestinal ulceration	Gastric acid hypersecretion/gastritis Reflux Decreased motility
Hypertension	Sodium and water overload Excessive renin production
Hypertriglyceridemia	Diminished plasma lipoprotein lipase activity
Pericarditis and cardiomyopathy	Unknown
Glucose intolerance	Tissue insulin resistance

ADH, Antidiuretic hormone; *CHF*, congestive heart failure; *GFR*, glomerular filtration rate; *NH_4*, ammonium.
Adapted from Brenner BM. *Brenner and Rector's The Kidney.* 10th ed. Philadelphia: Elsevier; 2015.

2. **Electrolyte abnormalities:** Hyperkalemia >6.5 mEq/L despite restriction of delivery and medical management; calcium and phosphorus imbalance (e.g., hypocalcemia with tetany, seizures in the presence of a very high serum phosphate level); derangements implicated in neurologic abnormalities.
3. **Ingestion or accumulation of dialyzable toxins or poisons:** Lithium, ammonia, alcohol, barbiturates, ethylene glycol, isopropanol, methanol, salicylates, theophylline. Consult poison control experts when available.
4. **Volume overload:** Evidence of pulmonary edema or hypertension.
5. **Uremia:** BUN >150 mg/dL (lower if rising rapidly), uremic pericardial effusion, neurologic symptoms.

B. Techniques

1. **Peritoneal dialysis (PD):** Requires catheter to access peritoneal cavity, as well as adequate peritoneal perfusion. May be used acutely or chronically. Contraindications: Abdominal wall defects (omphalocele, gastroschisis, bladder exstrophy, diaphragmatic hernia), severe inflammatory bowel disease, or infectious source in the abdomen.[24]
2. **Intermittent hemodialysis (HD):** Requires placement of special vascular access catheters. May be method of choice for certain toxins (e.g., ammonia, uric acid, poisons) or when there are contraindications to peritoneal dialysis.
3. **Continuous arteriovenous hemofiltration/hemodialysis (CAVH/D) and continuous venovenous hemofiltration/hemodialysis (CVVH/D):** Requires special vascular access catheter. Lower efficiency of solute removal compared with intermittent hemodialysis, but higher efficiency is not necessary because of the continuous nature of this form of dialysis. Sustained nature of dialysis allows for more gradual removal of volume/solutes, which is ideal for patients with hemodynamic or respiratory instability.

C. Complications

1. **PD catheter leaks:** Confirm leakage of PD fluid with glucose dipstick. Discontinue PD for 7 to 10 days or lower dialysate volume.
2. **PD associated peritonitis (PDAP):** Acute clouding of dialysate, abdominal pain/distention, vomiting. Culture peritoneal fluid and start empiric intraperitoneal antibiotics in consultation with nephrology. Refer to published Consensus Guidelines for treatment recommendations.[25]
3. **Intradialytic hypotension in HD:** Causes include rapid fluid removal, pre-dialysis antihypertensive medication, bradykinin release, hypotonic dialysate. Reduce or pause ultrafiltration.

X. TUBULAR DISORDERS

A. Renal Tubular Acidosis (Table 19.13)[26]

1. A group of transport defects resulting in abnormal urine acidification; due to defects in reabsorption of bicarbonate (HCO_3^-), excretion of hydrogen ions (H^+), or both.

TABLE 19.13

RENAL TUBULAR ACIDOSIS BIOCHEMICAL AND CLINICAL CHARACTERISTICS

	Type 1 (Distal)	Type 2 (Proximal)	Type 4 (Hypoaldosteronism)
Mechanism	Impaired distal acidification	Impaired bicarbonate absorption	Decreased aldosterone secretion or aldosterone effect
Etiology	Hereditary Sickle cell disease Toxins/drugs Cirrhosis Obstructive uropathy Connective tissue disorder	Hereditary Metabolic disease Fanconi syndrome Prematurity Toxins/heavy metals Amyloidosis PNH	Absolute mineralocorticoid deficiency Adrenal failure CAH DM Pseudohypoaldosteronism Interstitial nephritis
Minimal urine pH	>5.5	<5.5 (urine pH can be >5.5 with a bicarbonate load)	<5.5
Fractional excretion of bicarbonate ($FeHCO_3$)	↓ (<5%)	↑ (>15%)	↓ (<5%)
Plasma K^+ concentration	Normal or ↓	Usually ↓	↑
Urine anion gap	Positive	Positive or negative	Positive
Nephrocalcinosis/ nephrolithiasis	Common	Rare	Rare
Treatment	1–3 mEq/kg/day of HCO_3 (5–10 mEq/kg/day if bicarb wasting)	5–20 mEq/kg/day of HCO_3	1–5 mEq/kg/day of HCO_3 May add fludrocortisone and potassium binders

CAH, Congenital adrenal hyperplasia; *DM*, diabetes mellitus; *PNH*, paroxysmal nocturnal hemoglobinuria.
Adapted from Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Goldstein LS. *Pediatric Nephrology*. Baltimore: Springer-Verlag Berlin Heidelberg; 2016.

2. Results in a persistent normal anion gap hyperchloremic metabolic acidosis.
3. RTA syndromes have a normal GFR and often do not progress to kidney failure.
4. Clinical presentation may be characterized by failure to thrive, polyuria, constipation, vomiting, and dehydration.
5. **Fractional excretion of bicarbonate ($FeHCO_3$) should be checked after a HCO_3 load.** Can help differentiate the types of RTA. See Section II.B for equation.
6. **Urine anion gap (UAG) is also useful**; however, it should not be used when a patient is volume depleted or has an anion-gap metabolic acidosis. See Section II.B for equation.

B. Fanconi Syndrome

1. Generalized dysfunction of the proximal tubule resulting not only in bicarbonate loss but also in variable wasting of phosphate, glucose, and amino acids.
2. May be hereditary, as in cystinosis and galactosemia, or acquired through toxin injury and other immunologic factors.
3. Clinically characterized by rickets and impaired growth.

C. Nephrogenic Diabetes Insipidus

1. **Water conservation is dependent on antidiuretic hormone (ADH) and its effects on the distal renal tubules.** Polyuria (urine output >5 mL/kg/hr or >2 L/day), a hallmark of nephrogenic diabetes insipidus (NDI), is due to diminished or lack of response of the ADH receptor in the distal renal tubules. Hereditary defects of ADH receptor or acquired insults (e.g., interstitial nephritis, sickle cell disease, lithium toxicity, CKD) may underlie NDI.
2. **Must be differentiated from other causes of polyuria:** Central diabetes insipidus (ADH deficiency that may be idiopathic or acquired through infection or pituitary trauma; see Chapter 10), diabetes mellitus, psychogenic polydipsia, cerebral salt wasting.

XI. NEPHROLITHIASIS[27-30]

A. Risk Factors

Male sex; history of UTI (especially those <5 years); congenital and structural urologic abnormalities (urinary stasis), neurogenic bladder, hypercalciuria, hyperoxaluria/oxalosis, hypocitraturia, other metabolic abnormalities; family history of stones, renal failure, consanguinity.

B. Presentation

1. Microscopic hematuria (90%), flank/abdominal pain (50% to 75%), gross hematuria (30% to 55%), and concomitant UTI in up to 20%.
2. Have higher likelihood than adults of having asymptomatic stones, especially younger children.

C. Diagnostic Imaging

1. Ultrasonography is an effective and preferred modality, particularly at centers with expertise, given benefit of avoiding radiation exposure (75% sensitive for renal stones).[29]
2. Noncontrast CT may be preferred to improve diagnostic sensitivity (e.g., with radiolucent stones such as uric acid stones, ureteral stones, lack of ultrasonographic expertise).

D. Management

1. **Pain control, urine culture, hydration.** Some centers initiate α-blockers to facilitate stone passage, although evidence of benefit in children is equivocal.[30-32]

2. **Antibiotics:** Should be considered in treatment of all stones, especially if fever and/or pyuria present, because of the high association with UTI.
3. **Urologic intervention** (e.g., extracorporeal shock wave lithotripsy, ureteroscopy, percutaneous nephrolithotomy): Consider with unremitting pain, urinary obstruction, increasing stone size, size ≥7 mm, or cystine/struvite stone, especially in the setting of AKI or at-risk patients (e.g., solitary kidney, anatomic anomalies).[32]
4. **Strain urine to collect stone; analyze stone composition to aid in prevention of future stones.**

E. Workup

1. Up to 75% of children with a kidney stone will have a metabolic abnormality (e.g., hypercalciuria, hyperoxaluria, hyperuricosuria, cystinuria).
2. Workup should include analysis of the stone (if possible); UA; basic metabolic panel; and serum calcium, phosphate, magnesium, and uric acid levels. If evidence of elevated calcium or phosphate, obtain parathyroid hormone (PTH) level and consider checking 25- and 1,25(OH) vitamin D levels.
3. After symptoms have resolved, a 24-hour urine collection should be obtained. Risk factors for stone formation should be analyzed: urine volume, osmolarity, sodium, calcium, urate, oxalate, citrate, and cystine. This test is also referred to as a "stone risk analysis."

F. Prevention

1. **All children with history of stones should increase fluid intake** (e.g., at least 2 L/day in those aged >10 years old).
2. **Targeted interventions of any identified metabolic abnormalities** (e.g., low-sodium diet in those with hypercalciuria). Pharmacologic interventions are also available in certain scenarios (e.g., citrate supplementation).
3. **Dietary Modifications:** Long–term adherence (5 years) to normal calcium, low–sodium diet may decrease recurrence of stones in people with idiopathic hypercalciuria with recurrent nephrolithiasis.[33]

XII. WEB RESOURCES

A. International Pediatric Nephrology Association: www.ipna-online.org

B. National Kidney Disease Education Program: https://www.niddk.nih.gov/health-information/communication-programs/nkdep

C. National Kidney Foundation: www.kidney.org

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A complete list of references can be found online at www.expertconsult.com.

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Chapter 20

Neurology

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See additional content on Expert Consult

I. NEUROLOGIC EXAMINATION

A. Mental Status

Alertness, orientation (person, place, time, situation), language, cognition

1. **Infants:** Observe "cuteness" and ability to dynamically engage caretakers.
2. **Toddlers:** Bring toys. Observe and engage in play.
3. **School age:** Ask children to draw or describe school or friends.

B. Cranial Nerves (Table EC 20.A)

1. For a quick assessment of cranial nerves for all patients, observe:
   a. (II) Visual response to objects in each visual quadrant.
   b. (III, IV, VI) Conjugate gaze at full lateral and vertical positions, nystagmus.
   c. (VII) Symmetry and expressiveness of face at rest and with emotive activation.
   d. (VIII) Finger rub, or response to and localization of sound for infants.
   e. (IX, X, XII) Quality of phonation and articulation; ask about feeding, chewing, swallowing.

C. Motor

1. **Muscle bulk:** Atrophy is a red flag.
2. **Tone:** Spasticity, rigidity, hypotonia.
   a. Infants: Observe infant undressed to assess resting posture (varies with age). Active tone: traction response, axillary stability (slip-through), posture in horizontal suspension. Passive tone (resistance of movements of the joints): flap hands/feet, scarf sign.
   b. Red flags: Scissoring, toe-walking, inability to supinate hand, clasped thumb or grasp.
3. **Strength:**
   a. Observe ease of normal functions: rising from floor, standing broad jump, running, climbing onto chair or exam table. Note presence of accommodations child is making in order to execute movements (e.g., shoulder shrug or trunk tilt to raise arm).
   b. For conventional rating scale, see Box 20.1.
4. **Involuntary movements:** Fasciculations, tics, dystonia, chorea, athetosis, tremor.

D. Sensory

1. Primarily important if any concern for spinal cord defect or peripheral nerve injury.

TABLE EC 20.A

CRANIAL NERVES

Function	Cranial Nerve and Test
Smell	**I. Olfactory.**
Vision	**II. Optic.** Visual acuity and fundus (*Infants:* Fix and follow, red reflex; *Older children:* Snellen chart, fundoscopic exam).
Pupillary reflex	**II. Optic.** Detection of light and/or visual stimulus. **III. Oculomotor.** Control of pupil size in response to light, accommodation.
Eye movements and eyelids	**III. Oculomotor.** Eyelid elevation, adduction, elevation. Palsy—"down and out," ptosis. **IV. Trochlear.** Eye depression and intorsion. Palsy—head tilt. **VI. Abducens.** Lateral gaze. Note: Nystagmus can be physiologic or pathologic (intoxication, lesions in vestibular system, brainstem, or cerebellum).
Sensation	**V. Trigeminal.** Facial sensation, corneal reflex.
Mastication	**V. Trigeminal.** Clench teeth.
Facial movement	**VII. Facial.** Observation of emotional expressions and facial symmetry, eyebrow elevation, eye closure, smile, puffing out cheeks.
Hearing	**VIII. Vestibulocochlear.** Localize sound, finger rub, audiologic testing.
Vestibular.	**VIII. Vestibulocochlear.** Sense of balance, horizontal nystagmus, reading with passive head movement, Romberg, tandem gait.
Oropharynx	**IX. Glossopharyngeal.** Palate elevation, gag reflex. **X. Vagus.** Soft palate elevation, muscles of pharynx and larynx. Unilateral palsy—soft, hoarse voice; bilateral—respiratory distress.
Head control	**XI. Accessory.** Lateral head turn, shoulder shrug.
Tongue	**XII. Hypoglossal.** Tongue protrusion, push tongue against inner cheek.

BOX 20.1

STRENGTH RATING SCALE

0/5: No movement (i.e., no palpable tension at tendon)
1/5: Flicker of movement
2/5: Movement in a gravity-neutral plane
3/5: Movement against gravity but not resistance
4/5: Subnormal strength against resistance (requires accommodation to execute movement)
5/5: Normal strength against resistance (motion is smooth, comfortably executed, without any accommodations)

2. Focus initial investigation along three axes for meaningful lesion localization:
   a. Distal deficit with preserved (or less impaired) proximal sensation suggests polyneuropathy.
      (1) Pain/temperature deficit: small fiber polyneuropathy/anterior spinal cord.
      (2) Position/vibration deficit: large fiber polyneuropathy/posterior spinal cord.
   b. Lower body more affected than upper body suggests spinal cord injuries.
      (1) See Fig. 20.1 for dermatomes.
      (2) Ask about continence.
   c. If difference between left and right, concern for unilateral brain or spinal cord lesion.

E. Reflexes

1. **Tendon Reflexes:** Gradation (Box 20.2) and localization (Table EC 20.B). Helpful in localizing abnormalities including upper versus lower motor neuron pathology, especially in presence of weakness or asymmetry (Table EC 20.C). Compare right to left, upper to lower extremities, and distal to proximal reflexes. Generalized high or low reflexes of little significance in setting of normal strength and coordination.
2. **Primitive reflexes:** Expected during specific time windows (Table 20.1).

F. Coordination and Gait

1. **Evaluate coordination while watching age-appropriate activities.**
2. **Tests for cerebellar function:** Rapid alternating movements, finger-to-nose, heel-to-shin, walking, running.

II. HEADACHES[1–11]

A. Classification of Headaches

1. **Primary headaches:** Migraines, tension-type, cluster, trigeminal autonomic cephalgias (TACs), other primary headache disorders.
2. **Secondary headaches:** Trauma, infection, substance use or withdrawal, vascular disorder, neurologic disorder, increased intracranial pressure (ICP).
3. **Differential diagnosis:** Acute (Box 20.3) and chronic (Box 20.4)

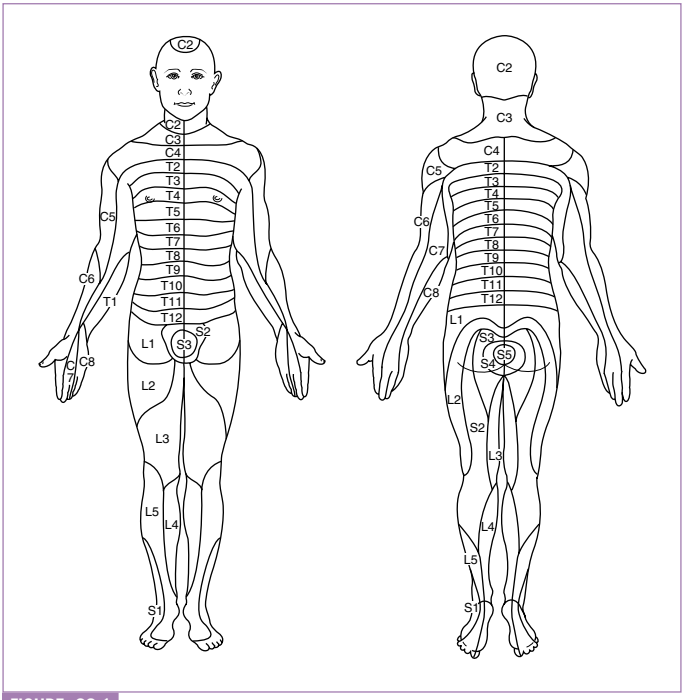

FIGURE. 20.1

Dermatomes. (From Athreya BH, Silverman BK. *Pediatric Physical Diagnosis*. Norwalk, CT: Appleton-Century-Crofts; 1985:238–239.)

BOX 20.2

REFLEX RATING SCALE

0: None
1+: Diminished (require use of clasped hands/gritting teeth to engage reflex)
2+: Normal
3+: Increased (reflexes cross neighboring joint or cross to other side)
4+: Hyperactive with clonus

B. Evaluation of Headaches

Obtain history (Box 20.5) and physical exam (Table EC 20.D); evaluate for red flags (Box 20.6). If red flags present, obtain appropriate imaging (computed tomography [CT] for hemorrhage, magnetic resonance imaging/angiography (MRI/MRA) for vascular abnormalities). Perform lumbar puncture (LP) if concern for subarachnoid hemorrhage (not detected on CT), infection, or increased ICP (Box 20.7). *If no red flags present and normal neurologic exam, imaging and LP not recommended.*

TABLE EC 20.B

MUSCLE STRETCH REFLEXES

Reflex	Site
Biceps	C5, C6
Brachioradialis	C5, C6
Triceps	C7, C8
Knee	L(2,3)4
Ankle	L5–S2

C, Cervical spinal root; *L*, lumbar spinal root.

TABLE EC 20.C

UPPER AND LOWER MOTOR NEURON FINDINGS

On Examination	Upper	Lower
Power	Decreased	Decreased
Tendon reflexes	Increased	Decreased
Tone	Increased (*Infants:* decreased)	Normal or decreased
Plantar response	Upgoing	Downgoing
Fasciculations	Absent	Present
Muscle wasting	Absent	Present

TABLE 20.1

PRIMITIVE REFLEXES[49]

Reflex	Appears	Extinguishes
Palmar grasp	28 WGA	2–3 months
Rooting	32 WGA	1 month
Moro	28 WGA	5–6 months
Tonic neck	35 WGA	6–7 months
Parachute	7–8 months	Remains for life

WGA, Weeks gestational age.

BOX 20.3

DIFFERENTIAL DIAGNOSIS OF ACUTE HEADACHE

Evaluation of the first acute headache should exclude pathologic causes listed here before more common etiologies are considered.

1. Increased ICP: Trauma, hemorrhage, tumor, hydrocephalus, idiopathic intracranial hypertension, abscess, arachnoid cyst, cerebral edema
2. Decreased ICP: Ventriculoperitoneal shunt placement, lumbar puncture, cerebrospinal fluid leak
3. Meningeal inflammation: Meningitis, leukemia/lymphoma, subarachnoid or subdural hemorrhage
4. Vascular: Vasculitis, arteriovenous malformation, hypertension, cerebrovascular accident
5. Bone, soft tissue: Referred pain from scalp, eyes, ears, sinuses, nose, teeth, pharynx, cervical spine, temporomandibular joint
6. Infection: Systemic, encephalitis, sinusitis
7. Medication/intoxicant exposure (e.g., stimulants, steroids, drugs of abuse)
8. First primary headache

ICP, Intracranial pressure.

BOX 20.4

DIFFERENTIAL DIAGNOSIS OF RECURRENT OR CHRONIC HEADACHES

1. Migraine (with or without aura)
2. Tension
3. Analgesic rebound
4. Caffeine withdrawal
5. Sleep deprivation or chronic hypoxia (e.g., sleep apnea)
6. Tumor
7. Psychogenic: Conversion disorder, malingering, depression, acute stress, mood disorder
8. Cluster headache
9. New daily persistent headache

BOX 20.5

IMPORTANT HISTORICAL INFORMATION IN EVALUATING HEADACHE

1. When did the headaches begin?
2. How did the headache begin? Associated trauma, social stressors (school, home)?
3. What is the frequency and duration of the headaches?
   a. Headache pattern (intermittent, progressive, chronic, etc.)
   b. Time of day
4. Where is the pain, what is it like, and does it radiate? Focal occipital pain is concerning for secondary headaches.
5. Associated symptoms? What do you do during the headache?
   a. Aura or prodrome
   b. Constitutional symptoms (weight changes), vision changes, or any other neurologic symptoms (weakness, tingling, photophobia, phonophobia)
   c. Triggers and alleviating/exacerbating factor
6. Other history (e.g., health problems, medications, family history of migraine)
7. How do the headaches affect your ability to function? Ask about school absences.

C. Migraine Headache

1. Migraines can be throbbing, pulsatile, or pressure-like in children. Usually bifrontal in children and unilateral in adolescents and adults. There are many potential triggers (e.g., stress, caffeine, menses, sleep disruption). See Box 20.8 for diagnostic criteria.
2. **Classification**[1]: With versus without aura. An aura is any neurologic symptom that occurs prior to onset of a migraine (e.g., visual aberrations, paresthesias, numbness, dysphasia).
3. **Precursors to migraines and close associations:** Cyclic vomiting, abdominal migraines, paroxysmal vertigo of childhood, paroxysmal torticollis of infancy, and motion sickness.
4. **Treatment**: Combination of acute and prophylactic treatment.
   a. **Acute symptomatic**: Avoid medication overuse (no more than 2 to 3 days/week); can lead to rebound headaches. Optimal acute therapy can prevent progression to chronic migraines.
   b. Outpatient setting:
      (1) Dark, quiet room and sleep.
      (2) Acetaminophen and/or nonsteroidal antiinflammatory drugs (NSAIDs) (e.g., naproxen, ibuprofen, ketorolac).
      (3) Caffeine (e.g., coffee, tea, soda).
      (4) Triptans: Not typically used in emergency room or inpatient setting (only effective at migraine onset). Limit use to twice per week.

TABLE EC 20.D

PHYSICAL AND NEUROLOGIC EXAMINATION OF THE CHILD WHO HAS HEADACHES

Feature	Significance
Growth parameters	Chronic illness may affect linear growth Hypothalamic-pituitary dysfunction may disturb growth
Head circumference	Increased ICP before fusion of the sutures may accelerate head growth
Skin	Evidence of trauma or a neurocutaneous disorder
Blood pressure	Hypertension
Neurologic exam	Signs of increased ICP Focal abnormality on neurological exam. Key areas: Fundoscopic exam (for optic nerve edema), extraocular movements, asymmetric reflexes, asymmetric strength/weakness/motor exam, coordination (cerebellar signs), abnormal gait.
Cranial bruits	May reflect an intracranial arteriovenous malformation
Fundoscopy exam	Papilledema may reflect elevated ICP or pseudotumor cerebri

ICP, Intracranial pressure.

BOX 20.6

RED FLAGS IN HEADACHE EVALUATION

1. Progressively worsening headaches
2. "Thunderclap" headache (<5 min from onset to maximal intensity)
3. Altered mental status
4. New onset focal neurological symptoms
5. Optic nerve edema
6. Nuchal rigidity
7. Seizures
8. Visual symptoms not typical of migraines (e.g., colorful, hallucinatory, short duration), diplopia, decreased visual acuity, visual field deficits
9. Concurrent fever (especially if accompanied by other red flags)
10. Headache worse with supine position or Valsalva (cough, straining)
11. Association with persistent emesis
12. Immunocompromised or on anticoagulation
13. Signs of endocrine pathology (e.g., short stature, obesity, polyuria, sluggishness, constipation, virilization)

BOX 20.7

LUMBAR PUNCTURE[7,47]

1. See Chapter 4 for indications, contraindications, and procedure.
2. Standard tests: Cell counts + differential, Gram stain, CSF culture, protein, glucose. Consider viral studies (e.g., herpes simplex virus, enterovirus, etc.).
3. Manometer for OP if concern for increased intracranial pressure. Performed in a lateral decubitus position. OP of <28 cm H_2O generally considered normal; however, interpret results in concert with other clinical and examination findings.
4. There is inconsistent evidence regarding correction factors for CSF white blood cell counts in the setting of blood-contaminated CSF from a traumatic lumbar puncture.
5. Xanthochromia: Yellow or pink discoloration of CSF due to breakdown of hemoglobin. Suspect subarachnoid hemorrhage.

CSF, Cerebrospinal fluid; *OP*, opening pressure.

(5) Antidopaminergics have antiemetic properties, though effective even if nausea is not a predominant factor. Prochlorperazine shown to be superior to metoclopramide.[48] Sometimes more effective than NSAIDs in emergency department setting.

c. Emergency department (ED)/inpatient setting:
   (1) Often helpful to combine medications and administer intravenous (IV) "migraine cocktail" (see Fig. 20.2 for example ED algorithm).
   (2) Steroids (e.g., methylprednisolone) may be useful in intractable cases, although evidence is lacking.
   (3) Dihydroergotamine.

BOX 20.8

DIAGNOSTIC CRITERIA FOR PEDIATRIC MIGRAINE WITHOUT AURA[1-3]

At least five attacks fulfilling the following criteria:

1. Headache 2–72 hr in children younger than 18 years (untreated or unsuccessfully treated)
2. At least two of the following characteristics:
   a. Unilateral or bilateral
   b. Pulsating quality
   c. Moderate to severe in intensity
   d. Aggravated by or causing avoidance of routine physical activities
3. At least one of the following occur during the headache:
   a. Nausea and/or vomiting
   b. Photophobia and phonophobia (which may be inferred from behavior)
4. Not better accounted for by another diagnosis

d. **Preventative treatment:**
   (1) Lifestyle modification is mainstay. Adequate sleep,[9] meals, hydration, regular exercise. Avoid triggers, stress, caffeine withdrawal.
   (2) **Alternative/complementary therapies:**
      (a) Cognitive-behavioral therapy
      (b) Biofeedback
      (c) Physical therapy
      (d) Acupuncture
   (3) Consider prophylactic medications (Table EC 20.E) if migraines occurring more than once per week, affecting quality of life, frequent ED visits, complicated migraines, or migraines not responsive to abortive medications. Conflicting evidence regarding efficacy. Recent randomized controlled trial demonstrated that preventative medication was no more effective than placebo. New biologic (calcitonin gene-related peptide or CGRP)[10,11] approved in adults in 2018; there are no published studies yet in pediatric population.

III. SEIZURES[12–25]

A. Differential Diagnosis of Recurrent Events That Mimic Epilepsy in Childhood (Table 20.2)

B. Seizures: First and Recurrent

1. **Definition:** Paroxysmal, transient, synchronized discharge of cortical neurons resulting in alteration of function (motor, sensory, cognitive).
2. **Causes of seizures**
   a. Diffuse brain dysfunction: Fever, metabolic compromise, toxins or drugs, hypertension.
   b. Focal brain dysfunction: Stroke, neoplasm, focal cortical dysgenesis, trauma.

TABLE EC 20.E

PREVENTIVE THERAPIES FOR MIGRAINE[A]

Medications	Adverse Effects	Consider in Patients With the Following Comorbidities
VITAMINS		
Riboflavin, magnesium, CoQ10	Low side effect profile, limited data of efficacy in children	Poor nutritional intake
ANTIHISTAMINES		
Cyproheptadine (Periactin)	Sedation, increased appetite, hepatitis	Seasonal allergies, poor appetite, insomnia
β-BLOCKERS		
Propranolol (Inderal)	Hypotension, bronchospasm, masks hypoglycemia, bradyarrhythmia	Hypertension
ANTIDEPRESSANTS		
Amitriptyline (Elavil)	Black box: suicidal thoughts. Other: sedation, constipation, weight gain	Depression, insomnia, underweight
Nortriptyline (Pamelor)	Black box: suicidal thoughts. Other: constipation	Depression
ANTISEIZURE MEDICATIONS		
Topiramate (Topamax)	Cognitive changes, weight loss, sensory changes, paresthesia, kidney stones	Obesity, epilepsy
Divalproex sodium (Depakote)	Black box: hepatotoxicity. Other: dizziness, drowsiness, weight gain, gastrointestinal upset, teratogenicity	Bipolar disorder, epilepsy, underweight

[a]See Formulary for specific dosing.
CoQ10, Coenzyme Q10.

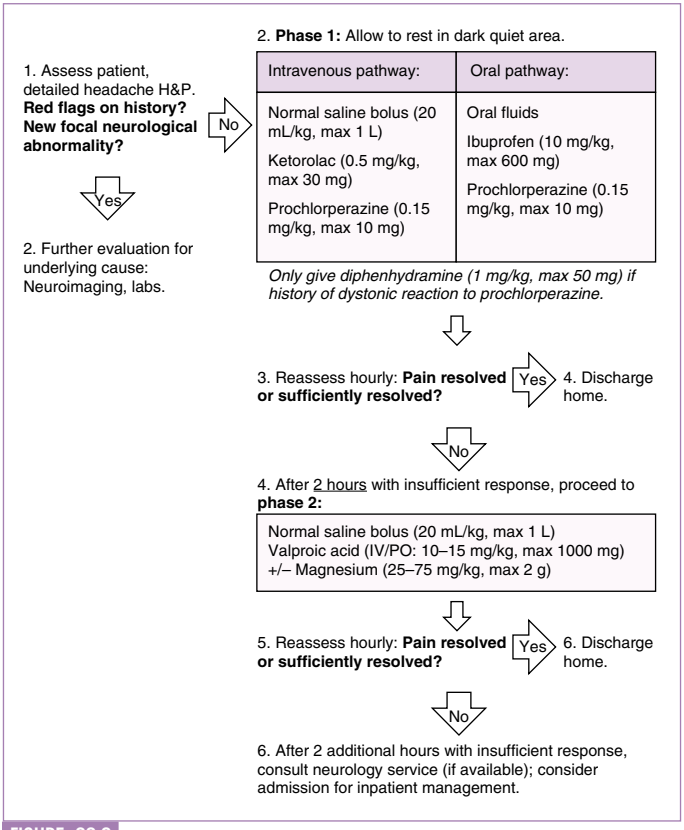

FIGURE. 20.2

ED management pathway of migraine headaches[8] at Johns Hopkins Children's Center.

3. **Febrile seizures**[12,13]
   a. Simple febrile seizure: Primary generalized seizure associated with fever in a child 6 to 60 months of age that is nonfocal, lasts for <15 minutes, and does not recur in a 24-hour period.
      (1) Management: Identify the source of fever. No further workup (neuroimaging or electroencephalogram [EEG]) or antiseizure drugs are necessary for a simple febrile seizure in a well-appearing fully immunized child with a normal neurologic examination and no meningeal signs.
      (2) Indications for LP: Meningeal signs, incomplete or unknown *Haemophilus influenzae* or *Streptococcus pneumoniae* immunization status, or if pretreated with antibiotics (which can mask signs and symptoms of meningitis).

TABLE 20.2

DIFFERENTIAL DIAGNOSIS OF RECURRENT EVENTS THAT MIMIC EPILEPSY IN CHILDHOOD[20,50]

Event	Differentiation from Epilepsy
SYNCOPE AND ANOXIC EVENTS	
Breath-holding spells (18 months–3 years)	Loss of consciousness and generalized convulsions, always provoked by an event that makes child upset.
Vasovagal syncope	Triggers: Postural change, heat, emotion. Preceded by dizziness and vision loss. Slow collapse to floor, may have brief confusion after event.
Cardiogenic syncope	Triggers: Exercise, strong emotion. Abnormal ECG/Holter monitor finding. No consistent convulsive movements.
Cough syncope	Prolonged cough spasm during sleep in asthmatic, leading to loss of consciousness, often with urinary incontinence.
BEHAVIORAL, PSYCHOLOGICAL, AND PSYCHIATRIC DISORDERS	
Psychogenic nonepileptic seizure (PNES)	Also known as pseudoseizures. No EEG changes except movement artifact during event. Thrashing, proximal truncal movements. Eye closure with resistance to opening. Guards face with hand drop. Brief/absent postictal period. Often exacerbated by psychological stressor.
SLEEP-RELATED CONDITIONS	
Narcolepsy	Excessive daytime sleepiness, cataplexy (sudden atonia triggered by emotion), sleep paralysis, sudden onset REM on EEG.
PAROXYSMAL MOVEMENT DISORDERS	
Tics	Involuntary, nonrhythmic, repetitive movements not associated with impaired consciousness. Strong urge to perform movement but suppressible.
Stereotypies (mannerisms)	Repetitive movements or vocalizations (e.g., rocking, head banging).
Paroxysmal dyskinesias	Dystonia, choreoathetosis in response to specific triggers (e.g., startle). Often familial.
MIGRAINE-ASSOCIATED DISORDERS	
Migraine	Headache or visual changes that may precede attack. Autonomic or sensory changes can mimic focal seizure. Family history of migraines. EEG with regional area of slowing during attack.
Paroxysmal vertigo (toddler)	Episode of vertigo, vomiting, staggering, and falling in a child. May become anxious, no loss of awareness.
MISCELLANEOUS EVENTS	
Sandifer syndrome	GER in infancy. Paroxysmal dystonic posturing (back arching) associated with meals.
Myoclonus	Involuntary muscle jerking or twitch

ECG, Electrocardiography; *EEG,* electroencephalography; *GER,* gastroesophageal reflux; *REM,* rapid eye movement.

b. Complex febrile seizure: Seizure associated with a fever that is focal, lasts for >15 minutes, or recurs within a 24-hour period. Management: Identify the source of fever. Consider EEG, neuroimaging. Consider prescribing rectal diazepam for home emergency use. Slightly increased risk of developing epilepsy at later age.

4. **Evaluation of unprovoked seizures**
   a. Rule out provocative factors: Obtain vitals. Consider checking glucose, electrolytes, blood urea nitrogen, creatinine, complete blood cell count, toxicology screen.
   b. EEG is recommended in all children with first unprovoked seizure to evaluate for an epilepsy syndrome, however it does not need to be emergently obtained.[14] Interictal EEGs may be normal, particularly in children with focal seizures. Repeat EEGs, prolonged EEG monitoring with video as clinically indicated.
   c. Imaging: High resolution MRI can assist with identification of underlying brain malformation, although is not routinely indicated when evaluating a first-time seizure. CT scan is not recommended.
5. **Epilepsy:** Recurrent, unprovoked seizures *or* diagnosis of genetic syndrome characterized by recurrent seizures. Assess seizure type, epilepsy classification (Table EC 20.F),[15–17] and severity of disorder. See Table 20.3 for selected epilepsy syndromes of childhood.
6. **Breakthrough seizures:** Assess for missed medications or significant weight gain, lack of sleep, stress, drugs/alcohol, physical exertion, illness, dehydration, flickering lights, menses, and drug interactions that can lower seizure threshold (tricyclic antidepressants, certain antibiotics, over-the-counter cold preparations, diphenhydramine, herbal supplements). Obtain drug levels (see Table 20.4 for therapeutic drug levels).
7. **Status epilepticus**[22]: Traditionally defined as continuous seizure activity lasting approximately > 5 minutes or two discrete seizures without return of consciousness between them. See Chapter 1 for management.
8. **Treatment**[19,20,23–25]
   a. First seizure, nonfocal, and with return to baseline: No antiseizure drug indicated. Overall recurrence approximately 50% in 2 to 5 years. Epileptiform abnormalities on EEG indicate a higher chance of recurrence.
   b. Educate parents and patient regarding seizure safety.[20] Review seizure first aid, including supervision during bathing or swimming. Be aware of driver's license laws in the state. Advocate teacher and school awareness.
   c. Pharmacotherapy (see Table 20.4): Initiate if known etiology of seizure (diagnosis of epilepsy syndrome), recurrent unprovoked seizure (risk of recurrent seizure >80% after second unprovoked seizure). Choose therapy according to seizure type. Consider rectal diazepam if seizures are prolonged or hemodynamic instability.
   d. Ketogenic diet[25]:
      (1) High-fat, low-carbohydrate therapy typically used for intractable seizures.
      (2) Should be managed by trained providers.
      (3) Urine/serum ketones can be monitored to assess compliance.
      (4) Side effects include transient GI upset and hyperlipidemia, chronic metabolic acidosis, kidney stones, fractures.

TABLE EC 20.F

INTERNATIONAL CLASSIFICATION OF SEIZURES AND EPILEPSY SYNDROMES[11,13,14]

Seizure type nomenclature	Classification of epilepsies
I. FOCAL ONSET 1. Aware (previously termed simple partial) a. With motor onset b. With nonmotor onset 2. Impaired awareness (previously termed complex partial) a. With motor onset b. With nonmotor onset **II. GENERALIZED ONSET** 1. Motor a. Tonic-clonic b. Other motor 2. Nonmotor (Absence) **III. UNKNOWN ONSET** 1. Motor a. Tonic-clonic b. Other motor 2. Nonmotor 3. Unclassified	1. Seizure types (see left column) a. Focal, generalized, or unknown b. Takes into account etiologies 2. Epilepsy type (predisposition to seizures) a. Focal, generalized, combined generalized and focal, unknown b. Takes into account seizure types, co-morbidities, and etiologies 3. Epilepsy syndrome (e.g., genetic syndrome known to cause epilepsy); takes into account seizure types, epilepsy types, and etiologies

TABLE 20.3

SELECTED EPILEPSY SYNDROMES[16,18–20]

Syndrome	Etiology	Evaluation	Treatment	Comments
Neonatal seizures (broad category encompassing a spectrum from benign to morbid syndromes)	Brain malformation, hypoxic-ischemic encephalopathy, intracranial hemorrhage, inborn errors of metabolism, CNS infection, cerebral infarction, hypoglycemia, hypocalcemia, hypomagnesemia. Consider benign neonatal seizures ("fifth day fits").	Screen for electrolyte and metabolic abnormalities, pyridoxine deficiency, and sepsis. Obtain LP, head ultrasound, CT or MRI, EEG.	Treat underlying abnormality, consider pyridoxine ± EEG, phenobarbital (± additional agents). No treatment needed for benign neonatal seizures.	Occur within first 28 days of life; may be myoclonic, tonic, clonic, or subtle. Presents as blinking, chewing, bicycling, or apnea. Distinguished from jitteriness by vital sign changes and inability to provoke or suppress movements.
Early infantile epileptic encephalopathy (Ohtahara syndrome) and early myoclonic encephalopathy	Structural malformations, metabolic disorders (glycine encephalopathy, pyridoxine dependent epilepsy, mitochondrial mutations), genetic mutations.	EEG with burst suppression pattern.	Trial of pyridoxine. Antiseizure medications, ketogenic diet. Seizures are difficult to control. If due to metabolic disorder, treat appropriately.	Tonic and myoclonic seizures with onset in neonatal period. Can progress to infantile spasms and/or Lennox Gastaut. Poor neurodevelopmental outcome.
Infantile spasms	Often early insult (HIE, postnatal hemorrhage), structural, genetic (tuberous sclerosis, Down syndrome), or metabolic abnormalities.	EEG with interictal hypsarrhythmia, MRI.	High dose steroids (oral prednisone) or ACTH; vigabatrin (particularly for tuberous sclerosis). Ketogenic diet.	Onset after age 2 months, peak onset 4–6 months. Highly variable appearance (flexor, extensor, mixed) often upon awakening and in clusters. Overall poor long-term outcomes, especially if known etiology. Early recognition and treatment can improve this.
Lennox-Gastaut syndrome	Multifactorial etiology. Often progression from other epileptic encephalopathy.	EEG with slow spike-wave discharges and intermittent runs of multiple spikes or fast activity.	Clobazam, felbamate, lamotrigine, rufinamide, topiramate, valproic acid. Ketogenic diet. Cannabidiol approved.	Multiple seizure types, cognitive impairment, and characteristic EEG findings. Significant secondary morbidity associated with atonic seizures.

Childhood absence seizures	Suspected to be genetic.	EEG with sudden generalized 3–4 Hz spike-and-wave discharges. Hyperventilation precipitates seizure.	Ethosuximide, lamotrigine, valproic acid.	Onset 4–10 years. Staring spells with diminished awareness, +/– automatisms (eye blinking, mouth movements). Often resolves by adolescence, with good neurologic outcome.
Childhood epilepsy with centro-temporal spikes (BECTS, benign rolandic epilepsy)	Suspected to be genetic.	EEG with spike wave discharges in centro-temporal region, increased with sleep.	Treatment is not always necessary. If frequent or distressing, may use levetiracetam or oxcarbazepine.	Onset 4–11 years. Seizures often nocturnal and upon awakening, with paresthesia of mouth or tongue, motor phenomena of ipsilateral face occasionally with generalization. Seizure remission by 14–16 years of age.
Dravet syndrome	Most cases caused by SCN1A mutation.	Genetic testing, EEG with polyspike-wave bursts.	Clobazam, levetiracetam, stiripentol, valproate. Cannabidiol approved.	Seizures starting in infancy or early childhood, often associated with heat. Developmental regression, prolonged (often myoclonic) seizures.
Juvenile myoclonic epilepsy	Suspected to be genetic.	Clinical history, sleep-deprived EEG (reveals generalized spike-and-wave discharges with normal background activity).	Lamotrigine, levetiracetam, valproate, zonisamide.	Adolescent onset often with absence seizures. Develop myoclonus upon awakening and GTCs. Triggers: sleep deprivation, excessive alcohol intake, photic stimulation. Full remission rare, majority require lifelong antiseizure medications.
Panayiotopoulos syndrome (early onset childhood occipital epilepsy)	Unknown	EEG with shifting multifocal spikes (often occipital spikes).	Often not treated. Occasionally intermittent benzodiazepines, levetiracetam, oxcarbazepine.	Onset 3–6 years. Characteristic autonomic component (e.g., vomiting, pallor, hypersalivation, thermoregulatory or cardiorespiratory irregularities). Resolves 2–3 years after onset.

BECTS, Benign epilepsy with centrotemporal spikes; *CNS,* central nervous system; *CT,* computed tomography; *EEG,* electroencephalography; *GTC,* generalized tonic–clonic; *HIE,* hypoxic-ischemic encephalopathy; *LP,* lumbar puncture; *MRI,* magnetic resonance imaging.

TABLE 20.4

COMMONLY USED ANTISEIZURE MEDICATIONS[21,24]

Antiseizure drug (Trade Name)	Standard Therapeutic Levels[a]	IV Preparation Available?	Side Effects
Brivaracetam (Briviact)	–	–	Somnolence/sedation, dizziness, fatigue, nausea/vomiting.
Cannabidiol (Epidiolex)	–	–	Hepatotoxicity, somnolence, decreased appetite, diarrhea, fatigue, insomnia, infections. Can interact with other antiseizure drugs (clobazam).
Carbamazepine (Tegretol/ Carbatrol)	4–12 mg/L	–	Black box: TEN/SJS in patients with HLA-B*1502 allele, aplastic anemia, agranulocytosis. Other: sedation, ataxia, diplopia, hyponatremia, hepatotoxicity, may worsen generalized seizures.
Clobazam (Onfi)	30–300 mCg/L	–	Sedation, dizziness.
Clonazepam (Klonopin)	20–70 mCg/L	–	Sedation, drooling, dependence.
Diazepam (Diastat, Valium)	–	Yes, 1:1 conversion	Sedation, dry mouth, respiratory depression.
Eslicarbazepine acetate (Aptiom)	10–35 mg/L	–	Hyponatremia, dizziness, somnolence, vomiting, headache, diplopia, vertigo, ataxia, tremor.
Ethosuximide (Zarontin)	40–100 mg/L	–	GI upset.
Felbamate (Felbatol)	30–60 mg/L	–	Black box: aplastic anemia (rare), liver failure. Other: sleep disturbances, weight loss.
Gabapentin (Neurontin)	2–20 mg/L	–	Weight gain, leg edema, dizziness.
Lacosamide (Vimpat)	5–10 mg/L	Yes, 1:1 conversion	Sedation, reduced benefit with sodium channel drugs, increased PR interval.
Lamotrigine (Lamictal)	2.5–15 mg/L	–	Black box: SJS/TEN (risk greater in pediatric patients, increased risk in combination with valproate). OCPs significantly decrease level. Other: fatigue, ataxia, diarrhea.
Levetiracetam (Keppra)	12–46 mg/L	Yes, 1:1 conversion	Abnormal behavior, irritability, rare psychosis.
Oxcarbazepine (Trileptal)	3–35 mg/L (10–hydroxy-carbazepine level)	–	Hyponatremia, weight gain, dizziness.
Perampanel (Fycompa)	–	–	Black box: psychiatric/behavioral reactions (hostility). Other: dizziness, headache.
Phenobarbital (Luminal)	10–40 mg/L	Yes, 1:1 conversion	Somnolence, syncope, erythroderma.

Phenytoin (Dilantin)	10–20 mg/L	Yes, 1:1 conversion	Ataxia, hirsutism, gingival hyperplasia, teratogenicity, morbilliform rash, purple-glove syndrome with infusion.
Pregabalin (Lyrica)	2–5 mg/L	–	Peripheral edema, weight gain, constipation, dizziness, ataxia, sedation.
Rufinamide (Banzel)	5–30 mg/L	–	Shortened QT interval, nausea, dizziness, sedation, headache. Interacts with other antiseizure drugs.
Tiagabine (Gabitril)	20–200 mCg/L	–	Can worsen generalized seizures.
Topiramate (Topamax)	5–20 mg/L	–	Cognitive side effects, weight loss, renal stones, metabolic acidosis, glaucoma.
Valproic acid (Depakote, Depakene)	50–100 mg/L	Yes, 1:1 conversion (Use total PO daily dose divided q6h, see Formulary)	Black box: hepatotoxicity. Other: weight gain, alopecia, pancreatitis, PCOS, teratogenicity.
Vigabatrin (Sabril)	0.8–36 mg/L	–	Black box: permanent visual field defects. Other: rash, weight gain, irritability, dizziness, sedation.
Zonisamide (Zonegran)	10–40 mg/L	–	Renal stones, weight loss. Rare: SJS, aplastic anemia.

[a]Draw level immediately before an oral dose for ideal sampling time.

GI, Gastrointestinal; *HLA*, human leukocyte antigen; *IV*, intravenous; *MHD*, 10-monohydroxy metabolite; *OCP*, oral contraceptive pill; *PCOS*, polycystic ovarian syndrome; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

(5) Factor in carbohydrate content of formulations when prescribing medications to child on ketogenic diet.
(6) Avoid dextrose-containing IV fluids.

e. Surgical therapies considered for children with identified seizure focus located in noneloquent cortex and/or failed antiseizure drug therapies.
(1) Device implantation: Vagus nerve stimulation, deep brain stimulation, responsive neurostimulation (NeuroPace).
(2) Resections: Hemispherectomy, focal resection (e.g., temporal lobectomy), corpus callosotomy.

IV. HYDROCEPHALUS[26–28]

A. Etiology

Communicating (due to abnormal cerebrospinal fluid [CSF] reabsorption) versus noncommunicating (due to obstruction of CSF flow) and congenital versus acquired (postinfectious, posthemorrhagic, due to mass lesions).

B. Diagnosis

1. **Clinical signs:** apneas, bradycardias, macrocephaly, increasing head circumference (HC), bulging/tense fontanelle, splayed sutures, headaches, blurry/spotty vision, decreased level of consciousness, "setting-sun" eye sign due to upward gaze paresis, vomiting, Cushing triad (hypertension, bradycardia, irregular respirations), papilledema, CN palsies (III, IV, VI).
2. **In infants, obtain serial measurements of HC.** Obtain neuroimaging if significant increase in HC percentile or if patient is symptomatic.
3. **Imaging:** Ultrafast MRI preferred to CT where available (see Chapter 26).

C. Treatment

1. **Medical:**
   a. Emergently manage acute increase of ICP (see Chapter 1).
   b. Slowly progressive hydrocephalus: Acetazolamide and furosemide may provide temporary relief by decreasing the rate of CSF production.
2. **Surgical:** CSF shunting versus endoscopic third ventriculostomy (ETV).
   a. Ventriculoperitoneal shunts used most commonly.
   b. Patients with shunt dysfunction often present with signs of increased ICP. Causes include infection, obstruction (clogging or kinking), disconnection, migration of proximal or distal tips, valve programming.
   c. Evaluation of shunt integrity: See Chapter 26 for discussion of imaging. Consult pediatric neurosurgery (if available).

V. ATAXIA[29,30]

A. Impaired Coordination of Movement and Balance; Broad-Based Gait

B. Differential Diagnosis of Acute Ataxia (**Box 20.9**)

C. Evaluation (**Box 20.10**)

BOX 20.9

DIFFERENTIAL DIAGNOSIS OF ACUTE ATAXIA

1. Ingestion (e.g., antiseizure drugs, antipsychotics, sedatives, hypnotics) or intoxication (e.g., alcohol, hydrocarbon fumes, heavy metals)
2. Postinfectious: cerebellitis (e.g., viral causes), acute disseminated encephalomyelitis
3. Head trauma: cerebellar contusion or hemorrhage, posterior fossa hematoma, vertebrobasilar dissection, postconcussion syndrome
4. Basilar migraine
5. Benign paroxysmal vertigo
6. Intracranial mass lesion: tumor, vascular malformation
7. Opsoclonus–myoclonus ataxia syndrome: Chaotic eye movements combined with ataxia and myoclonus. Postinfectious or paraneoplastic (neuroblastoma/neural crest tumors) etiology.
8. Hydrocephalus
9. Infection: labyrinthitis, abscess
10. Seizure: ictal or postictal
11. Vascular events: cerebellar hemorrhage or stroke
12. Guillain-Barré syndrome or Miller-Fisher variant (ataxia, ophthalmoplegia, and areflexia). Warning: If bulbar signs present, patient may lose ability to protect airway.
13. Rare inherited paroxysmal ataxias
14. Inborn errors of metabolism
15. Multiple sclerosis
16. Somatic symptom disorder

BOX 20.10

CONSIDERATIONS FOR INITIAL EVALUATION OF ACUTE ATAXIA

1. Complete blood cell count, electrolytes, and urine and serum toxicology
2. Imaging (CT or MRI)
3. Lumbar puncture
4. EEG
5. If neuroblastoma is suspected (opsoclonus–myoclonus ataxia syndrome), obtain urine vanillylmandelic acid and homovanillic acid, and CT of chest and abdomen.

CT, Computed tomography; *EEG,* electroencephalogram; *MRI,* magnetic resonance imaging.

VI. STROKE[31–33]

A. Pediatric Stroke

50% ischemic, 50% hemorrhagic. Presents similarly to stroke mimics, but less common and frequently missed (Box 20.11). Neonatal stroke frequently presents with nonfocal symptoms: seizures, altered level of consciousness, feeding difficulties. Important to consider stroke on differential of acute neurologic changes.

BOX 20.11

STROKE MIMICS PRESENTING WITH ACUTE-ONSET FOCAL NEUROLOGIC DEFICIT

1. Migraine
2. Seizure +/– postictal (Todd) paralysis
3. Functional disorders
4. Mass lesion
5. Infection
6. Drug toxicity (e.g., methotrexate)
7. PRES
8. Metabolic abnormality

PRES, Posterior reversible encephalopathy syndrome.

B. Etiologies Vary by Age (Table EC 20.G)[31]

Patients with increased risk of recurrent stroke: history of cardiac disease and cardiac surgery, cerebral arteriopathy, sickle cell disease, thrombophilias.

C. Management

1. **Stroke team activation** (where available) or **urgent neurology consultation,** along with transfer to a tertiary care center with expertise in childhood stroke.
2. **Supportive care and neurologic monitoring.** Maintain normoglycemia, maintain normothermia (avoid fevers). Monitor for signs of increased ICP.
3. **Optimize cerebral perfusion pressure:** Ensure adequate fluid volume and maintenance of median blood pressure (BP) for age, allow permissive hypertension.
4. **Reperfusion therapies:** Not routinely recommended in children due to lack of evidence, but an active area of research. Thrombolytic therapy with IV tissue plasminogen activator (tPA) or mechanical thrombectomy may be considered under appropriate circumstances in centers with extensive pediatric stroke experience (American Heart Association guidelines).
5. **Children with sickle cell disease:** Consult a hematologist. Hydration and emergent exchange transfusion to reduce sickle hemoglobin to <30% (see Chapter 14).

VII. ENCEPHALOPATHY/ALTERED MENTAL STATUS[34–37]

A. Definitions

1. **Encephalopathy:** Diffuse neuronal dysfunction manifesting as acute or chronic altered mental status.

TABLE EC 20.G

RISK FACTORS AND INITIAL INVESTIGATIONS FOR CHILDHOOD STROKE[31]

	Perinatal Stroke (Occurring from 20 Weeks Gestational Age to 28 Days Old)	Childhood Arterial Ischemic Stroke	Cerebral Venous Thrombosis
Risk factors	Not fully understood. Combination of maternal and fetal factors, both ante- and peripartum.	Cardiac (congenital or acquired heart diseases, surgeries) Cerebral arteriopathy (Moya Moya, arterial dissection, VZV-associated vasculopathy, CNS vasculitis, arterial dissection) Hypercoagulable state (genetic anticoagulant deficiencies, rheumatologic conditions, malignancies) Hematologic disorders (sickle cell disease, iron deficiency anemia, thrombocytosis, malignancies) Infections (meningitis, varicella) Drugs (asparaginase, estrogen, cocaine, methamphetamines) Inflammatory/autoimmune (SLE, RA, systemic vasculitis)	Inherited thrombophilia (genetic anticoagulant deficiencies) Drugs (asparaginase, estrogen) Infections (sinusitis, otitis media, mastoiditis, oropharyngeal infections, varicella) Inflammatory/autoimmune (SLE, IBD) Dehydration Nephrotic syndrome Malignancies Sickle cell disease Trauma
Initial workup	Diagnosis by neuroimaging: MRI more sensitive than CT, obtain DWI, FLAIR, SWI, GRE, and MRA sequences Thrombophilia work-up may not change management. Consider echocardiogram. Manage symptomatology.	Diagnosis by neuroimaging: MRI more sensitive than CT, obtain DWI, FLAIR, SWI, GRE, and MRA sequences Consider echocardiogram, ECG Laboratory studies based on suspected etiology (start with CBC, PT/INR, PTT, ESR, CRP, electrolytes, antithrombin III activity, lupus anticoagulant, toxicology screen) Consider CSF studies (may include VZV DNA PCR)	Diagnosis by neuroimaging: MRI more sensitive than CT, obtain MRV Laboratory studies (CBC, electrolytes, BUN, creatinine, glucose, PT, PTT, ESR, antithrombin III activity, pregnancy test)

CBC, Complete blood count; *CNS,* central nervous system; *CRP,* c-reactive protein; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *DWI,* diffusion-weighted imaging; *FLAIR,* fluid-attenuated inversion recovery; *GRE,* gradient echo; *IBD,* inflammatory bowel disease; *MRA/MRV,* magnetic resonance angiography/venography; *MRI,* magnetic resonance imaging; *PT/INR,* prothrombin time/international normalized ration; *RA,* rheumatoid arthritis; *SLE,* systemic lupus erythematosus; *SWI,* susceptibility-weighted imaging; *VZV,* varicella zoster virus.

BOX 20.12

DIFFERENTIAL DIAGNOSIS OF ENCEPHALOPATHY

1. Infectious and parainfectious: meningitis, encephalitis, ADEM
2. Autoimmune: NMDAR, VGKC-complex, Hashimoto thyroiditis–associated
3. Trauma
4. Seizure-related: status epilepticus, postictal, epileptic encephalopathy
5. Toxins: medications, drugs, heavy metals, carbon monoxide
6. Metabolic: uremia, hyperammonemia, hyper- or hypoglycemia, lactic acidosis
7. Hypertension, PRES
8. Hypoxic-ischemic: neonatal, drowning, cardiorespiratory arrest, vascular
9. Intracranial hemorrhage
10. Malignancy
11. Genetic: leukoencephalopathy, mitochondrial, ADANE

ADANE, Autosomal-dominant acute necrotizing encephalitis; *ADEM,* acute disseminated encephalomyelitis; *NMDAR,* N-methyl-D-aspartate receptor; *PRES,* posterior reversible encephalopathy syndrome; *VGKC,* voltage-gated potassium channel.

2. **Encephalitis:** Inflammation of brain parenchyma due to infection or inflammatory response.

B. Selected Causes of Encephalopathy (Box 20.12)

C. Diagnosis

Targeted based on clinical scenario and associated symptoms. See Chapter 1 for emergency management of acute altered level of consciousness. Further workup based on suspected etiology. May require serum and/or cerebrospinal fluid (CSF) studies for infectious/inflammatory/metabolic markers, EEG, neuroimaging (e.g., MRI or PET).

D. Treatment

Dependent on etiology. See Chapter 1 for emergency management of acute altered level of consciousness. See Chapter 17 for treatment of meningitis.

VIII. NEUROMUSCULAR DISORDERS[38–45]

A. Spinal Muscular Atrophy[38,39]

1. **Etiology:** Motor neuron degeneration caused by autosomal recessive mutations in *SMN1* gene with resulting insufficient levels of SMN protein. Severity correlates inversely with copy number of *SMN2.*
2. **Clinical features:** Varying degrees of symmetric and progressive, proximal more than distal, muscle weakness with preserved cognition. Patients with severe forms do not survive past early childhood without treatment due to respiratory failure.
3. **Treatment:** Evaluation of weak/hypotonic infant for possible spinal muscular atrophy (SMA) is urgent, as effective treatment (nusinersen [Spinraza]) is possible, but magnitude of benefit decreases with time.

B. Duchenne or Becker Muscular Dystrophy[40]

1. **Etiology:** X-linked mutation in Duchenne muscular dystrophy *(DMD)* gene, encoding dystrophin, causes disruption of muscular cytoskeleton. Mostly affects males. Duchenne form is more severe and caused by complete disruption of dystrophin; partial disruption causes milder Becker muscular dystrophy (BMD).
2. **Clinical features:** Delayed motor milestones. Progressive proximal symmetric muscle weakness starting in early childhood leading to wheelchair use for mobility by age 13. Elevated serum CK levels.
3. **Treatment**: Corticosteroids (prednisone or deflazacort [Emflaza]) are mainstays.[41] Requires multidisciplinary management: At high risk for cardiomyopathy and respiratory and orthopedic complications. Novel disease-modifying agent, eteplirsen (Exondys 51), limited to patients with specific *DMD* mutations.

C. Myasthenia Gravis[42]

1. **Etiology**: Autoantibodies binding the acetylcholine receptor impair neuromuscular junction function. Subtypes include transient neonatal myasthenia (due to transplacental transfer of maternal antibodies from mother with myasthenia), congenital myasthenic syndrome (genetic defects of neuromuscular junction proteins), and juvenile (classic autoimmune in children).
2. **Clinical features:** A key feature is fatigable, variable weakness. Often concentrates in orbital muscles (double vision, ptosis, ophthalmoparesis), or bulbar weakness (slurred/nasal voice, difficulty chewing, swallowing, talking). Can also manifest with generalized weakness of limbs and trunk. Triggers include illness, fever, heat, and some medications. Bulbar weakness can worsen with illness and compromised airway. A good bedside test of bulbar muscle fatigue is the "slurp test."[43] Ask patient to imbibe four ounces of water through a straw quickly—if consumption slows after 1 or 2 ounces, at risk of bulbar decompensation; if marked slowing or times especially prolonged, at risk for respiratory failure.
3. **Treatment**: Refer to/consult specialist for management.
   a. Myasthenic crisis/rapid onset of symptoms: plasmapheresis, IVIG, and IV neostigmine. Evaluate the need to secure definitive airway.
   b. Chronic management:
      (1) Oral pyridostigmine
      (2) Prednisone (caution about paradoxical worsening with any large initial dose)
      (3) Immunosuppressive medications (e.g., mycophenolate, rituximab)
      (4) Thymectomy may be helpful

D. Acute Guillain-Barré Syndrome[44,45]

1. **Etiology:** Presumed immune attack against peripheral nerve myelin. In some cases, triggered by illness, notably *Campylobacter jejuni* infection.

2. **Clinical features and diagnosis:** Rapid decline with nadir less than two weeks after onset; respiratory status can be compromised. Back pain often prominent in children. Often with autonomic instability. Elevated spinal fluid protein without cellular infiltrate ("albumocytologic dissociation"). Nerve conduction studies can be helpful.
3. **Treatment:** Patients should be hospitalized at presentation to monitor for respiratory stability. Acute phase treatment with IVIG, plasmapheresis helpful if initiated early. Supportive care.
4. **Variants of Guillain-Barré syndrome (GBS)**
   a. Acute: Miller Fisher syndrome (ataxia, ophthalmoplegia, and areflexia), acute motor axonal neuropathy (AMAN)
   b. Chronic: Chronic inflammatory demyelinating polyneuropathy (CIDP) is a similar but slower progressive autoimmune disorder that often requires chronic immunosuppressive therapy.

E. Infantile Botulism[46]

1. **Etiology:** Affects infants <1 year of age, most commonly <6 months, due to colonization of colon by *Clostridium botulinum* bacteria (infants are susceptible due to immaturity of gut flora). Botulinum toxin released into bloodstream, irreversibly cleaves protein complex necessary for acetylcholine vesicle release into neuromuscular junction.
2. **Clinical features and diagnosis:** Subacute onset weakness of skeletal muscles diffusely, concentrating in eye, face, and bulbar muscles early. Weak pupil constriction responses common and specific when present. Presenting symptom often constipation for days to weeks before onset of weakness, poor feeding, and weak cry. At high risk for respiratory failure due to respiratory and bulbar muscle weakness. Tachycardia is common. Confirmation of diagnosis by toxin assay of stool (not culture) performed by state lab or CDC; may use minimal amount of sterile, nonbacteriostatic water colonic enema for specimen collection. Electromyography and nerve conduction studies can help confirm diagnosis.
3. **Treatment:** Assess and stabilize airway: approximately 50% of infants require intubation/advanced airway. Treat with one-time dose of human botulism immune globulin (BabyBIG or BIG-IV), available through Infant Botulism Treatment and Prevention Program (http://www.infantbotulism.org/). Prompt treatment is key; do not wait for confirmatory testing. With appropriate treatment, prognosis for full recovery is excellent. See Chapter 16 for recommended interval before measles or varicella vaccination after botulism immune globulin administration.

IX. WEB RESOURCES

- American Academy of Neurology Practice Guidelines: www.aan.com/Guidelines
- American Migraine Foundation: www.americanmigrainefoundation.org
- Child Neurology Foundation: www.childneurologyfoundation.org
- Child Neurology Society: www.childneurologysociety.org

- Epilepsy Diagnosis (with videos): www.epilepsydiagnosis.org
- Epilepsy Foundation: www.epilepsy.com
- Headache resource (from Children's Mercy Kansas): www.headachereliefguide.com
- International League Against Epilepsy: www.ilae.org
- Muscular Dystrophy Association: www.mda.org

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A complete list of references can be found online at www.expertconsult.com.

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Chapter 21

Nutrition and Growth

Jaime La Charite, MD, MPH

I. ASSESSMENT OF GROWTH

A. Types of Growth Charts

1. Child <24 months: World Health Organization (WHO) international growth charts[1]
2. Child ≥2 years: Centers for Disease Control and Prevention (CDC) growth charts[2]
3. Growth charts for premature infants
   a. Corrected age = infant's chronologic age – number of weeks of prematurity (using 40 weeks as full-term gestation) and should be used up to 3 years.[3,4]
   b. Chronologic age should be used if child's growth "catches up" before 3 years.[5]
   c. Oslen, Bertino, and Fenton growth charts can be used to assess growth in premature infants up to 41 weeks (Oslen) to 50 weeks (Fenton).[6] After 4 to 8 weeks post-term, the WHO growth chart can be used.[7]
   d. The choice of growth chart has some variability across practice sites and preferences.[8]
4. Special populations[9,10]
   a. WHO or CDC growth charts are recommended in all cases due to limited reference data for condition-specific growth charts.
   b. Condition-specific growth charts can show families how a specific condition can alter growth potential.
   c. Growth charts have been created for Down syndrome, Prader-Willi syndrome, Williams syndrome, Cornelia de Lange syndrome, Turner syndrome, and Marfan syndrome.

B. Interpretation of Growth Charts[11,12]

1. Stunting/short stature: Length or height <5th percentile
2. Underweight:
   a. Children <2 years: Weight for length/height <5th percentile
   b. Children ≥2 years: Body mass index (BMI) for age <5th percentile or BMI <18.5 kg/m^2
3. Healthy weight: BMI for age 5th percentile to <85th percentile or BMI 18.5 to 24.9 kg/m^2
4. Overweight:
   a. Children <2 years: Weight for length/height >95th percentile

   b. Children ≥2 years: BMI for age ≥ 85th to <95th percentile or BMI 25 to 29.9 kg/m^2
5. Obese:
   a. Children <2 years: No consensus definition exists
   b. Children ≥2 years: BMI for age ≥95th percentile or BMI ≥30 kg/m^2

C. General Guidelines Regarding Appropriate Growth[13,14]

1. Term infants usually lose approximately 5% to 10% of their birth weight, but regain the weight within 2 weeks.
2. Infants should gain 20 to 30 g/day from birth to 3 months, 15 to 22 g/day from 3 to 9 months, and 6 to 11 g/day from 9 to 12 months.
3. Term infants double their birth weight in 4 to 5 months and triple it by 1 year of age.
4. Height doubles from birth to age 3 to 4 years of age.
5. The average size of a 4-year-old is 40 in. and 35 lb.
6. From age 3 to 10 years of age, children grow an average of 2.5 inches per year.

II. MANAGEMENT OF OVERWEIGHT AND OBESE CHILDREN

A. AAP Recommendations for the Prevention of Obesity[15-17]

1. Exclusive breastfeeding until 6 months of age and then breastfeeding maintenance until at least 12 months.
2. Daily breakfast and family meal times.
3. Limit sugary beverages, fast food, energy-dense foods, and encourage fruits and vegetables.
4. Develop a family media plan with limits and technology-free zones. For infants less than 18 months, no media other than video chatting. If media used with toddlers 18-24 months, parents should watch and engage with children during use. For children 2 to 5 years, a max of one hour of high-quality programming a day with co-viewing when possible.
5. Recommend 60 minutes of moderate-to-vigorous exercise per day.

B. Prevention and Management of Obesity in the Primary Care Setting (Table 21.1)

C. Conditions Associated with Obesity[15]

1. Endocrine:
   a. Polycystic ovarian syndrome
   b. Precocious puberty
   c. Pre-diabetes/Type 2 diabetes
2. Gastrointestinal:
   a. Cholelithiasis
   b. Gastroesophageal reflux
   c. Nonalcoholic fatty liver disease
3. Neurologic: Pseudotumor cerebri
4. Orthopedic:
   a. Blount disease
   b. Slipped capital femoral epiphysis (SCFE)

5. Behavioral health:
   a. Anxiety
   b. Binge eating disorder
   c. Depression

TABLE 21.1

MANAGEMENT AND MONITORING STRATEGIES FOR CHILDREN BASED ON BODY MASS INDEX[50-52]

BMI	Initial Management	Monitoring—Follow up
Normal BMI	• Praise child and family • Screen for genetic dyslipidemia with nonfasting lipid profile between ages 9–11 and 18–21 • Maintain weight velocity	Next well child visit
Normal BMI that is increasing percentiles (crossing two percentile lines is a risk factor for obesity)	• Screen for genetic dyslipidemia as above • Patient education	Next well child visit
Overweight BMI	• Patient education • If health risk factors, obtain fasting glucose, hemoglobin A1c or oral glucose tolerance test, lipid profile, ALT, and AST	2–4 weeks
Obese BMI	• Patient education • Obtain fasting glucose, hemoglobin A1c or oral glucose tolerance test, lipid profile, ALT, and AST • Some specialist clinics screen for vitamin D deficiency and insulin resistance (i.e., measure fasting insulin), but their clinical utility and cost effectiveness is unclear • No guidelines on which age to start laboratory screening, but some experts start at 2 years of age • Consider other labs (e.g., thyroid studies, cortisol) based on clinical picture	2–4 weeks

Further follow-up and management for those who are overweight or obese:

(a) At each follow-up, record weight, measure blood pressure, and use an empathetic and empowering counseling style (e.g., motivational interviewing).

(b) Establish goals: Positive behavior change, weight maintenance, or decrease in BMI velocity. Children aged 2 to 5 years who have obesity should not lose more than 1 pound/month; older children and adolescents with obesity should not lose more than an average of 2 pounds/week.

(c) If no improvement after 3 to 6 months, refer to structured weight management program. If no improvement after 3 to 6 months, the next step is a comprehensive, multidisciplinary approach. If no improvement, refer for evaluation at a tertiary care center for medication management and weight reduction surgery.

ALT, Alanine aminotransferase; *AST*, aspartate aminotransferase; *BMI*, body mass index.

III. MALNUTRITION IN INFANTS AND CHILDREN

A. Defining Malnutrition[16]

NOTE: Also called growth failure or under-nutrition; previously called failure to thrive.

1. Condition of under-nutrition generally identified in the first 3 years of life
2. Can be described by the following growth scenarios:
   a. Primary indicators when single data point available
      (1) Weight for length/height z-score
      (2) BMI for age z-score
      (3) Length/height for age z-score
      (4) Wasting or mid-upper arm circumference (MUAC)
      (5) Presence of nutritional edema
   b. Primary indicators when two or more data points available
      (1) Weight gain velocity (<2 years old)
      (2) Degree of weight loss (2 to 20 years of age)
      (3) Deceleration in weight for length/height z-score
      (4) Inadequate nutrient intake

B. Classifying the Degree to Which a Patient Is Malnourished (Table 21.2)[17]

1. Acute (duration <3 months)
2. Chronic or stunting (duration >3 months); suggested by height/length for age

C. Resources for Determining Z-scores[18]

1. PediTools (peditools.org)
2. Standardized height and weight calculator (https://www.quesgen.com/BMIPedsCalc.php).

TABLE 21.2

DEFINITIONS FOR CATEGORY OF MALNUTRITION[40]

	Mild	Moderate	Severe
Weight for height and BMI	−1 to −1.9 z-score	−2 to −2.9 z-score	−3 or greater z-score
Mid-upper arm circumference z-score[a]	≥ −1 to −1.9	≥ to −2.9	≥ −3
Weight gain velocity (<2 years)	Less than 75% of the norm for expected weight gain	Less than 50% of the norm for expected weight gain	Less than 25% of the norm for expected weight gain
Weight loss (2–20 years)	5% usual body weight	7.5% usual body weight	10% usual body weight
Deceleration in weight for length/height z-score	Decline of 1 z-score	Decline of 2 z-scores	Decline of 3 z-scores
Inadequate nutritional intake	51%–75% estimated energy/protein need	26%–50% estimated energy/protein need	<26% estimated energy/protein need

[a]See Section IIIC for how to calculate z-score.

BMI, Body mass index.

Adapted from Becker P, Carney LN, Corkins MR, et al. Primary indicators when 2 or more data points available. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: indicators recommended for the identification and documentation of pediatric malnutrition. *Nutr Clin Pract.* 2015;30(10):147–161. Tables 3 and 4.

3. CDC website (cdc.gov/growthcharts/zscore.htm)
4. WHO website (who.int/childgrowth/standards/chart_catalogue)

D. Differential Diagnosis of Malnutrition[19]

1. Secondary to disease/injury
2. Decreased intake (e.g., fluid restriction, cardiac failure, anorexia nervosa, food insecurity)
3. Increased requirement/hyper-metabolism (e.g., burns)
4. Excessive loss (e.g., chronic diarrhea, burn, proteinuria)
5. Malabsorption (e.g., Crohn's disease, cystic fibrosis)

E. Physical Exam Findings Consistent with Malnutrition[23-25]

1. Fat loss (e.g., orbital, buccal, triceps, ribs)
2. Muscle wasting (e.g., temporalis, pectoralis, deltoid, latissimus dorsi, quadriceps)
3. Edema
4. Functional limitations (e.g., hand grip strength)
5. Macronutrient deficiencies
   a. Iron
      (1) Exam findings: Koilonychias, pale conjunctiva and nail beds
      (2) Risk factors: Low birth weight, feeding problems, poor growth, exclusive breast feeding >6 months
   b. Vitamin C
      (1) Exam findings: Perifollicular hemorrhage, scorbutic tongue, bleeding gum, bruising
      (2) Risk factors: Limited diet, infant on cow's milk, dialysis, malabsorption
   c. Vitamin A
      (1) Exam findings: Bitot spot, follicular hyperkeratosis
      (2) Risk factors: Limited diet, fat malabsorption, alcoholism, cystic fibrosis, short bowel
   d. Vitamin B6
      (1) Exam findings: Seborrheic dermatitis, angular palpebritis, hypertrophied papillae
      (2) Risk factors: Dialysis, sickle cell disease, malabsorption; diuretic, anticonvulsant, contraceptive, and isoniazid use
   e. Zinc
      (1) Exam findings: Dermatitis, vesico-bullous lesions, diaper rash
      (2) Risk factors: Prematurity, parenteral nutrition (PN), cholestasis, diarrhea, high phytate intake, celiac or Crohn's disease, AIDS, liver or renal disease, alcoholism, trauma, burn, sleeve gastrectomy, diuretic and valproate use

F. Diagnostic Evaluation of Malnutrition[26-29]

1. There is no consensus on work-up algorithm.
2. Routine labs and imaging are often low yield and generally not recommended; work-up should be guided by clinical suspicion.
3. If warranted, reasonable initial testing could include complete blood count, complete metabolic panel, urinalysis, and erythrocyte sedimentation rate.

4. If the child's length has decelerated and is below 50%, can screen for hypothyroidism and growth hormone deficiency.
5. If recurrent or severe upper respiratory or opportunistic infections, consider testing for human immunodeficiency and tuberculosis and measuring immunoglobulin and complement levels.
6. Based on clinical suspicion, can consider celiac screening, sweat chloride testing, echocardiogram, hepatitis serology, stool studies.
7. Consider hospitalization for observed feeding if the child fails outpatient management, suspicion for abuse/neglect or traumatic injury, severe psychological caregiver impairment, serious malnutrition, or at risk for re-feeding.

G. Red Flags That Suggest a Medical Cause of Malnutrition[20]

1. Developmental delay or dysmorphic features
2. Cardiac findings (e.g., murmur, edema, jugular venous distension)
3. Failure to gain weight despite adequate calories
4. Organomegaly or lymphadenopathy
5. Recurrent or severe respiratory, mucocutaneous, or urinary infections
6. Recurrent vomiting, diarrhea, or dehydration

H. Approach to the Management of Malnourished Patients[21,22] (Box 21.1)

1. Address the etiology of malnutrition.
2. Approximately 20% to 30% more energy may be required to achieve catch-up growth in children. This should continue until the previous growth percentiles are regained.
3. Catch-up linear growth may lag several months behind weight.
4. See Box 21.1 for instructions on the calculation of catch-up growth requirements.

BOX 21.1

DETERMINING CATCH-UP GROWTH REQUIREMENTS

1. Plot the child's height and weight on the appropriate growth charts.
2. Determine recommended calories required for age [recommended dietary allowances (RDA)].
3. Determine the ideal weight (50th percentile) for child's height.
4. Multiply the RDA calories by ideal body weight for height (kg).
5. Divide this value by the child's actual weight (kg). For example, for a 12-month-old boy whose weight is 7 kg and length is 72 cm, RDA for age would be 98 kcal/kg/day, and ideal body weight for height is 9 kg (50th percentile weight for height); thus his catch-up growth requirement would be as follows:

$$98 \text{ kcal/kg/day} \times (9 \text{ kg}/7 \text{ kg}) = 126 \text{ kcal/kg/day}$$

Adapted from Nestle Health Science. Calorie and protein requirements. Pediatric nutrition helpful hints: Specialized nutrition for your most vulnerable patients. Available at https://www.nestlehealthscience.us/asset-library/documents/resources/pediatric%20helpful%20hints.pdf; and Corrales KM, Utter SL. Failure to thrive. In: Samour PQ, Helm KK, Lang CE, eds. *Handbook of Pediatric Nutrition*. 2nd ed. Aspen Publishers; 1999:406.

5. Screen for food insecurity and offer social work and community resources.
6. Pharmacotherapy (e.g., cyproheptadine, megestrol) may be helpful for patients with significant underlying diseases (e.g., cancer, cystic fibrosis).

IV. RE-FEEDING SYNDROME

A. Patients at Risk of Developing Re-Feeding Syndrome[23]

1. Chronic malnutrition (e.g., prolonged fasting ≥5 days, malignancy)
2. Renal/endocrine (e.g., chronic diuretic use, diabetic hyperglycemic hyperosmolar syndrome)
3. Gastrointestinal loss (e.g., inflammatory bowel disease, chronic pancreatitis, short bowel)
4. Infectious (e.g., AIDS, tuberculosis)
5. Cardiac (e.g., congenital heart disease)
6. Pulmonary (e.g., cystic fibrosis)
7. Psychiatric (e.g., anorexia nervosa, chronic alcohol use)
8. Social (e.g., child abuse/neglect, homelessness, food insecurity)

B. Management of Re-Feeding Syndrome[24]

1. Maintain continuous cardiorespiratory monitoring or check vital signs every 4 hours, depending on level of concern.
2. Ensure strict intake and output monitoring with calorie count and daily weights.
3. Obtain at least daily basic metabolic panel with phosphorous and magnesium. Obtain more frequently if electrolyte replacement needed, or if there are concerning trends.
4. Measure pre-albumin, albumin, zinc.
5. Consider giving thiamine 100 to 300 mg PO daily (or 50 to 100 mg IV) × 3 days before feeding. There is some debate whether this is required.
6. Give a multivitamin daily.
7. Feeding should not proceed without appropriate supplementation.
8. Recommendations vary, but start at 1/4 to 1/2 of estimated caloric needs depending on degree of risk.
9. Dietary advancement over 3 to 7 days with caloric increases of 10% to 25% per day until recommended caloric goals achieved.
10. Enteral feeding is preferred over parenteral feeding.

V. NUTRITIONAL NEEDS OF HEALTHY CHILDREN

A. Dietary Allowances for Carbohydrates and Protein (Table 21.3)

B. Fat Requirements (Table 21.4)

C. Vitamin Requirements (Tables 21.5 and 21.6)

1. Vitamin D[25,26]
   a. Breast-fed and partially breast-fed infants should be supplemented with 400 international units (IU) per day beginning in the first few days of life until 12 months.

TABLE 21.3

RECOMMENDED DIETARY ALLOWANCES, CALORIE, AND PROTEIN REQUIREMENTS[a]

Category	Age (years)	kcal/kg	Protein g/kg
Infants	0–0.5	108	2.2
	0.5–1	98	1.6
Children	1–3	102	1.2
	4–6	90	1.1
	7–10	70	1.0
Males	11–14	55	1.0
	15–18	45	0.9
	19–24	40	0.8
Females	11–14	47	1.0
	15–18	40	0.8
	19–24	38	0.8

[a]This RDA was determined and by definition meets the needs of 97% of healthy children. This is a quick reference to estimate calorie and protein needs, but further estimation may be required, using various other energy and protein need equations and factors, typically used by a registered dietitian

Data from Nestle Health Science. Calorie and protein requirements. Pediatric nutrition helpful hints. Specialized nutrition for your most vulnerable patients. Available at https://www.nestlehealthscience.us/asset-library/documents/resources/pediatric%20helpful%20hints.pdf; and Recommended Dietary Allowances. 10th ed. National Academy of Sciences, National Academy Press; 1989:33–36.

TABLE 21.4

FAT REQUIREMENTS: ADEQUATE INTAKE[a]

Age	Total Fat (g/day)	Linoleic Acid (g/day)	α-Linolenic Acid (g/day)
0–6 months	31	4.4 (n-6 PUFA)	0.5 (n-3 PUFA)
7–12 months	30	4.6 (n-6 PUFA)	0.5 (n-3 PUFA)
1–3 years	[b]	7	0.7
4–8 years	[b]	10	0.9
9–13 years, boys	[b]	12	1.2
9–13 years, girls	[b]	10	1.0
14–18 years, boys	[b]	16	1.6
14–18 years, girls	[b]	11	1.1
Pregnancy	[b]	13	1.4
Lactation	[b]	13	1.3

[a]If sufficient scientific evidence is not available to establish a recommended dietary allowance (RDA), an adequate intake (AI) is usually developed. For healthy breast-fed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all healthy individuals in the group, but a lack of data or uncertainty in the data prevents from being able to specify with confidence the percentage of individuals covered by this intake.

[b]No AI, estimated average requirement (EAR), or RDA established.

PUFA, Polyunsaturated fatty acid.

From Otten JJ, Hellwig JP, Meyers LD, eds. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements.* Washington, DC: National Academies Press; 2006.

b. Formula-fed infants should be supplemented until the infant is taking 34 oz of formula per day.
c. For preterm infants tolerating full enteral feeds and weighing >1500-2000 g, supplement with 400 IU/day. Supplement with 200-400 IU/day for infants <1500g.
d. Supplement children and adolescents with 600 IU/day if the child is ingesting <1000 mL (34 oz) per day of vitamin D fortified milk or not taking that amount through fortified foods.

TABLE 21.5

DIETARY REFERENCE INTAKES: RECOMMENDED INTAKES FOR INDIVIDUALS—VITAMINS

Life Stage	Vit. A[a] (IU)	Vit. C (mg/day)	Vit. D[b,c] (IU)	Vit. E[d] (IU)	Vit. K (mCg/day)	Thiamin (mg/day)	Riboflavin (mg/day)	Niacin[e] (mg/day)	Vit. B_6 (mg/day)	Folate[f] (mCg/day)	Vit. B_{12} (mCg/day)	Pantothenic Acid (mg/day)	Biotin (mCg/day)	Choline[g] (mg/day)
INFANTS														
0–6 months	**1333**	40*	400*	4*	2.0*	0.2*	0.3*	2*	0.1*	65*	0.4*	1.7*	5*	125*
7–12 months	**1666**	50*	400*	5*	2.5*	0.3*	0.4*	4*	0.3*	80*	0.5*	1.8*	6*	150*
CHILDREN														
1–3 years	**1000**	**15**	600*	**6**	**30***	**0.5**	**0.5**	**6**	**0.5**	**150**	**0.9**	2*	8*	200*
4–8 years	**1333**	**25**	600*	**7**	**55***	**0.6**	**0.6**	**8**	**0.6**	**200**	**1.2**	3*	12*	25*
MALES														
9–13 years	**2000**	**45**	600*	**11**	**60***	**0.9**	**0.9**	**12**	**1.0**	**300**	**1.8**	**4***	20*	375*
14–18 years	**3000**	**75**	600*	**15**	**75***	**1.2**	**1.3**	**16**	**1.3**	**400**	**2.4**	**5***	25*	550*
19–30 years	**3000**	**90**	600*	**15**	**120***	**1.2**	**1.3**	**16**	**1.3**	**400**	**2.4**	**5***	30*	550*
FEMALES														
9–13 years	**2000**	**45**	600*	**11**	**60***	**0.9**	**0.9**	**12**	**1.0**	**300**	**1.8**	4*	20*	375*
14–18 years	**2333**	**65**	600*	**15**	**75***	**1.0**	**1.0**	**14**	**1.2**	**400**	**2.4**	5*	25*	400*
19–30 years	**2333**	**75**	600*	**15**	**90***	**1.1**	**1.1**	**14**	**1.3**	**400**	**2.4**	5*	30*	425*

Continued

TABLE 21.5

DIETARY REFERENCE INTAKES: RECOMMENDED INTAKES FOR INDIVIDUALS—VITAMINS—Cont'd

Life Stage	Vit. A[a] (IU)	Vit. C (mg/day)	Vit. D[b,c] (IU)	Vit. E[d] (IU)	Vit. K (mCg/day)	Thiamin (mg/day)	Riboflavin (mg/day)	Niacin[e] (mg/day)	Vit. B_6 (mg/day)	Folate[f] (mCg/day)	Vit. B_{12} (mCg/day)	Pantothenic Acid (mg/day)	Biotin (mCg/day)	Choline[g] (mg/day)
PREGNANCY														
<18 years	**2500**	**80**	600*	**15**	75*	**1.4**	**1.4**	**18**	**1.9**	**600**	**2.6**	6*	30*	450*
19–30 years	**2567**	**85**	600*	**15**	90*	**1.4**	**1.4**	**18**	**1.9**	**600**	**2.6**	6*	30*	450*
LACTATION														
<18 years	**4000**	**115**	600*	**19**	75*	**1.4**	**1.6**	**17**	**2.0**	**500**	**2.8**	7*	35*	550*
19–30 years	**4333**	**120**	600*	**19**	90*	**1.4**	**1.6**	**17**	**2.0**	**500**	**2.8**	7*	35*	550*

[a]One international unit (IU) = 0.3 mCg retinol equivalent.

[b]One mCg cholecalciferol = 40 IU vitamin D.

[c]In the absence of adequate exposure to sunlight.

[d]One IU = 1 mg vitamin E.

[e]As niacin equivalents (NE). 1 mg of niacin = 60 mg of tryptophan; 0 to 6 months = preformed niacin (not NE).

[f]As dietary folate equivalents (DFE). 1 DFE = 1 mCg food folate = 0.6 mCg of folic acid from fortified food or as a supplement consumed with food = 0.5 mCg of a supplement taken on an empty stomach.

[g]Although AIs have been set for choline, there are few data to assess whether a dietary supply of choline is required at all life stages, and it may be that the choline requirement can be met by endogenous synthesis at some of these stages.

NOTE: This table presents recommended dietary allowances (RDAs) in **bold type** and adequate intakes (AIs) in regular type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97% to 98%) individuals in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover needs of all individuals in the group, but lack of data or uncertainty in the data prevent from being able to specify with confidence the percentage of individuals covered by this intake.

Modified from Otten JJ, Hellwig JP, Meyers LD, eds. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: National Academies Press; 2006; www.nap.edu.

TABLE 21.6

VITAMIN D LABATORY INTERPRETATION

25-Hydroxy Vitamin D	Value (ng/mL)
Severe deficiency	<10
Deficiency	<10–20
Insufficiency	>20–<30
Optimal level	≥ 30[a]

[a]Cut-off values are not yet well-defined. Controversy exists regarding the optimal 25-hydroxy vitamin D level. Some experts recommend a level of 20 to 30 ng/mL as being sufficient. These are the Johns Hopkins Hospital Pediatrics guidelines used for dosing.

NOTE: 1,25-dihydroxy vitamin D is the physiologically active form, but 25-hydroxy vitamin D is the value to monitor for vitamin D deficiency as it approximates body stores of vitamin D.

e. At risk children (e.g., cystic fibrosis) and those with laboratory confirmed vitamin D insufficiency/deficiency should also be supplemented.
f. See Table 21.6 for interpreting vitamin D levels.

2. Folate[27,28]
   a. All women capable of becoming pregnant should consume 400 mCg from supplements or diet.
   b. This should continue as women enter prenatal care.
   c. If a woman had a prior pregnancy with a neutral tube defect and is planning another pregnancy, she should consume 4 mg of folic acid daily (requires a prescription) at least 4 weeks before becoming pregnant and continue through the first 12 weeks of pregnancy.

D. Mineral Requirements (Table 21.7)

1. Iron[29]
   a. Breast-fed term infants should receive 1 mg/kg/day of an oral iron supplement beginning at 4 months of age, preferably from iron-fortified cereal or, alternatively, elemental iron.
   b. Breast-fed preterm infants should receive 2 mg/kg/day by 1 month of age, which should continue until the infant is weaned to iron-fortified formula or begins eating complementary foods.
   c. Formula-fed term infants receive adequate iron from fortified formula.
   d. Formula-fed preterm infants need 2 mg/kg/day, which is the amount supplied by iron-fortified formulas.
2. Fluoride[30]
   a. Consider fluoride supplementation for those patients who use bottled water or home filtration systems. Some home water treatment systems can reduce fluoride levels.
   b. For infants and children at high risk for the development of caries, fluoride supplementation ranging from 0.25-1 mg/day is recommended according to the American Dental Association's schedule.
   c. Fluoridated toothpaste is recommended for all children starting at tooth eruption, using a smear (grain-of-rice-sized) until age 3 and then a pea-sized amount after that time.

TABLE 21.7

DIETARY REFERENCE INTAKES: RECOMMENDED INTAKES—ELEMENTS

Life Stage	Calcium (mg/day)	Chromium (mCg/day)	Copper (mCg/day)	Fluoride (mg/day)	Iodine (mCg/day)	Iron (mg/day)	Magnesium (mg/day)	Manganese (mg/day)	Molybdenum (mCg/day)	Phosphorus (mg/day)	Selenium (mCg/day)	Zinc (mg/day)
INFANTS												
0–6 months	200*	0.2*	200*	0.01*	110*	0.27*	30*	0.003*	2*	100*	15*	2*
7–12 months	260*	5.5*	220*	0.5*	130*	**11**	75*	0.6*	3*	275*	20*	**3**
CHILDREN												
1–3 years	**700**	11*	**340**	0.7*	**90**	**7**	**80**	1.2*	**17**	**460**	**20**	**3**
4–8 years	**1000**	15*	**440**	1.0*	**90**	**10**	**130**	1.5*	**22**	**500**	**30**	**5**
MALES												
9–13 years	**1300**	25*	**700**	2*	**120**	**8**	**240**	1.9*	**34**	**1250**	**40**	**8**
14–18 years	**1300**	35*	**890**	3*	**150**	**11**	**410**	2.2*	**43**	**1250**	**55**	**11**
19–30 years	**1000**	35*	**900**	4*	**150**	**8**	**400**	2.3*	**45**	**700**	**55**	**11**
FEMALES												
9–13 years	**1300**	21*	**700**	2*	**120**	**8**	**240**	1.6*	**34**	**1250**	**40**	**8**
14–18 years	**1300**	24*	**890**	3*	**150**	**15**	**360**	1.6*	**43**	**1250**	**55**	**9**
19–30 years	**1000**	25*	**900**	3*	**150**	**18**	**310**	1.8*	**45**	**700**	**55**	**8**
PREGNANCY												
<18 years	**1300**	29*	**1000**	3*	**220**	**27**	**400**	2.0*	**50**	**1250**	**60**	**13**
19–30 years	**1000**	30*	**1000**	3*	**220**	**27**	**350**	2.0*	**50**	**700**	**60**	**11**
LACTATION												
<18 years	**1300**	44*	**1300**	3*	**290**	**10**	**360**	2.6*	**50**	**1250**	**70**	**14**
19–30 years	**1000**	45*	**1300**	3*	**290**	**9**	**310**	2.6*	**50**	**700**	**70**	**12**

NOTE: This table presents recommended dietary allowances (RDAs) in **bold type** and adequate intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97% to 98%) individuals in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover needs of all individuals in the group, but lack of data or uncertainty in the data prevent from being able to specify with confidence the percentage of individuals covered by this intake.

Modified from Otten JJ, Hellwig JP, Meyers LD, eds. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: National Academies Press; 2006. Includes updates from Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press; 2011.

TABLE 21.8

FIBER REQUIREMENTS: ADEQUATE INTAKE[a]

Age	Total Fiber (g/day)
0–12 months	Not determined
1–3 years	19
4–8 years	25
9–13 years, boys	31
9–13 years, girls	26
14–18 years, boys	38
14–18 years, girls	26
Pregnancy	28
Lactation	29

[a]Adequate intake (AI). If sufficient scientific evidence unavailable to establish recommended dietary allowance (RDA), an AI is usually developed. For healthy breast-fed infants, the AI is the mean intake. AI for other life stage and gender groups is believed to cover the needs of all healthy individuals in the group, but a lack of data or uncertainty in the data prevents from being able to specify with confidence the percentage of individuals covered by this intake.
g, Grams.
Modified from Otten JJ, Hellwig JP, Meyers LD, eds. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: National Academies Press; 2006.

E. Fiber Requirements (Table 21.8)

VI. BREASTFEEDING AND THE USE OF HUMAN MILK

A. Benefits of Breast Milk[31]

1. Decreased risk of infections (e.g., otitis media, respiratory), necrotizing enterocolitis, inflammatory bowel, sudden infant death syndrome (SIDS).
2. Decreased incidence of atopic conditions, obesity, and diabetes.

B. Contraindications to Breastfeeding[32,33] (Box 21.2)

1. Tobacco smoking is not contraindicated but is strongly discouraged because of an association with increased risks of SIDS, respiratory disease, and infections in exposed infants.
2. Alcohol should be limited to the occasional intake of 2 oz of liquor, 8 oz of wine, or two beers for the average 60 kg woman >2 hours prior to the onset of nursing.
3. Methadone and buprenorphine are not contraindications, if the mother is in a stable maintenance program and not using street drugs.

C. Use of Milk Bank Donor Human Milk[34]

1. Most commonly used in low birth weight infants (<1.5 kg).
2. Can be considered in infants with intestinal disease with documented intolerance to specialized infant formulas.

D. Safe Handling of Breast Milk[35]

1. Freshly expressed or pumped milk can be stored at room temperature for up to 4 hours, in the refrigerator for up to 4 days, in the freezer for approximately 6 months (up to 12 months), and in an insulated cooler bag with frozen packs up to 24 hours while traveling.
2. Once breast milk is thawed to room temperature or warmed, it should be used within 2 hours.

BOX 21.2
CONTRAINDICATIONS TO BREASTFEEDING[39]

Infant galactosemia
Maternal human T-cell lymphotropic virus I/II infection
Maternal untreated brucellosis
Maternal HIV (developed countries)
Maternal active, untreated tuberculosis (may give expressed BM)
Maternal active HSV lesions on breast (may give expressed BM)
Maternal varicella infection 5 days before through 2 days after delivery (may give expressed BM)
Maternal use of diagnostic or therapeutic radioactive isotopes, antimetabolites, or chemotherapeutic agents
Illicit street drugs such as cannabis, cocaine, phencyclidine, etc.

BM, Breast milk; *HIV*, human immunodeficiency virus; *HSV*, herpes simplex virus.
Modified from American Academy of Pediatrics, Section on Breastfeeding. Policy Statement—Breastfeeding and the Use of Human Milk. *Pediatrics*. 2012;129:e827–e841.

3. If the baby did not finish the bottle, the leftover breast milk should only be used within 2 hours of the baby finishing the feed.

E. Breastfeeding Challenges

See Section IX.C.

VII. ENTERAL NUTRITION

A. Feeding the Healthy Infant

1. Recommended formula amount by age[36]
   a. 1st days of life: 1 to 2 ounces every 2 to 3 hours
   b. 1st month: 2 to 4 ounces every 3 to 4 hours
   c. 2nd month: 5 to 6 ounces every 4 to 5 hours
   d. 3rd to 5th month: 6 to 7 ounces every 4 to 5 hours
   e. 6th to 8th month: 24 to 32 ounces in 24 hours
   f. 8th to 10th month: 16 to 32 ounces in 24 hours
   g. 10th to 12th month: 12 to 24 ounces in 24 hours
2. Properties of formula options for healthy infants and toddlers (Table 21.9)
3. Appropriate preparation and fortification of formulas (Table 21.10)
4. Methods to further increase calories, protein, carbohydrate, fat, or a combination (Table 21.11)

B. Available Formulas for Patients with Specific Clinical Conditions or for Those Requiring Special Diets (Tables 21.12 and 21.13)

C. Use of Enteral Tube Feeds[37]

1. Insufficient oral intake (e.g., anorexia nervosa, food aversion, malabsorption, increased needs)
2. As a primary therapy (e.g., metabolic or inflammatory bowel disease, fasting intolerance)
3. Oral motor dysfunction (e.g., prematurity, neuromuscular and neurologic disease)

TABLE 21.9

PROPERTIES OF FEEDING OPTIONS FOR HEALTHY INFANTS AND CHILDREN[54-58]

	Examples	Calories (kcal/oz)	Carbohydrate Source	Protein Source	Unique Properties	Indications
Human Milk		20	Lactose	Human milk	See Section VI.A	Preferred for most infants
Cow's Milk–based Formulas	Enfamil Infant, Similac Advance, Similac Sensitive, Gerber Good Start Gentle	20	Lactose	Cow's milk		Typical term infant
Toddler/Child	Boost Kids Essential, Carnation Instant Breakfast Essential, Compleat Pediatric, Nutren Junior, Pediasure Enteral, Pediasure	20–45	Lactose	Cow's milk	Milk-based Contain added iron, vitamin C, E, and zinc, DHA/AA, calcium	Age 1 year to 10–13 years

AA, Amino acids; *DHA*, docosahexaenoic acid; *kcal*, kilocalorie; *oz*, ounce.

Data from O'Connor, N. Infant formula. *Am Fam Phys*. 2009; 79(7):565–570, Table 21.9; and Comparison of breast milk and available infant formulas, available at https://www.aafp.org/afp/2009/0401/p565.html), Table 1. Additional sources listed in references.

TABLE 21.10

PREPARATION OF INFANT FORMULAS FOR MOST FULL-TERM STANDARD AND SOY FORMULAS[a]

Formula Type	Desired Caloric Concentration (kcal/oz)	Amount of Formula 13 oz = 1 can	Water (oz)	Approximate Final Volume (oz)
Liquid concentrates (40 kcal/oz)	20	13 oz	13 oz	26 oz
	22	13 oz	11 oz	24 oz
	24	13 oz	9 oz	22 oz
	26	13 oz	7 oz	20 oz
	27	13 oz	6 oz (3/4 cup)	19 oz
	30	13 oz	4.3 oz	17.3 oz
Powder (approx 44 kcal/scoop)[b]	20	1 scoop	2 oz	2 oz
	22	3 scoop	5.5 oz	6 oz
	24	3 scoops	5 oz	5.5 oz
	26	6 scoops	9 oz	10 oz
	27	6 scoops	8.5 oz	10 oz
	30	6 scoops	7.5 oz	9 oz

[a]Does not apply to Enfacare, Neocate Infant, Alfamino Infant, or NeoSure. Of note, Enfamil A.R. and Similac for Spit-Up is not recommended to be concentrated greater than 24 kcal/oz. Use a packed measure for Nutramigen and Pregestimil; all others unpacked powder.

[b]Slight variations in brands, range 40 to 45 kcal/scoop.

kcal, kilocalorie; *oz*, ounce.

Modified from University of Michigan Hospitals & Health Centers: Powdered and liquid concentrate recipe chart, available at https://www.med.umich.edu/1libr/pa/FormulaAdjustmentstandard.pdf

TABLE 21.11

COMMON CALORIC MODULARS[a]

Component	Calories
PROTEIN	
Beneprotein (powder)	25 kcal/scoop (6 g protein)
ProSource protein powder	30 kcal/scoop (6 g protein)
Complete Amino Acid Mix (powder)	3.28 kcal/g (0.82 g protein) 2.9 g/teaspoon (9.5 kcal, 2.38 g protein)
Abbott Liquid Protein Fortifier	0.67 kcal/mL (0.167 g protein/mL)
CARBOHYDRATE	
SolCarb	3.75 kcal/g; 23 kcal/tbsp
Polycal	3.84 kcal/g; 28 kcal/tbsp; 20 kcal/scoop
FAT	
MCT oil[b]	7.7 kcal/mL
Vegetable oil	8.3 kcal/mL
Microlipid (emulsified LCT)	4.5 kcal/mL
Liquigen (emulsified MCT)[b]	4.5 kcal/mL
FAT AND CARBOHYDRATE	
Duocal (powder)	42 kcal/tbsp; 25 kcal/scoop (59% carb, 41% fat, 35% fat as MCT)

[a]Use these caloric supplements when you want to increase protein, carbohydrate or fat; or when you have reached the maximum concentration tolerated and wish to further increase caloric density.

[b]Medium-chain triglyceride (MCT) oil is unnecessary unless there is fat malabsorption.

Carb, Carbohydrate; *g*, grams; *kcal*, kilocalorie; *LCT*, long chain–triglyceride; *MCT*, medium chain–triglyceride; *mL*, milliliter; *tbsp*, tablespoon.

TABLE 21.12

FORMULA PROPERTIES AND INDICATIONS FOR SPECIFIC CONDITIONS[59-67]

	Examples	Calories (kcal/oz)	Carbohydrate Source	Protein Source	Unique Properties	Indications
Human Milk Fortifiers					Contain protein, carbohydrates, fat, vitamins, and minerals	Preterm infants, especially <1500 g who are receiving human milk
Preterm Formulas	Enfamil Premature, Similac Special Care Advance	24	Lactose	Cow's milk	Higher protein, calcium, magnesium, phosphorous, and vitamin A and D Contain taurine	Generally use until infant weighs 1800–2000 g or until 34 weeks corrected gestational age
Enriched or Transitional Formula	Enfamil Enfacare, Similac Neosure	22	Lactose	Cow's milk	Higher protein, calcium, magnesium, and phosphorous	Transition from pre-term to enriched as described above until age 6–12 months
Cow's Milk-based Formulas	Enfamil Infant, Similac Advance, Similac Sensitive	20	Lactose	Cow's milk		Typical term infant
Soy	America's Store Brand Soy, Enfamil ProSobee, Gerber Good Start Soy, Similac Soy Isomil, Similac for Diarrhea	20	Corn-based	Soy	Contain higher protein concentration and supplemental amino acids	Galactosemia, congenital lactase deficiency, strict vegan families Should NOT be used for preterm infants (increased risk of poor growth, osteopenia of prematurity). Avoided in infants with milk protein intolerance given association with soy allergy.

Continued

TABLE 21.12

FORMULA PROPERTIES AND INDICATIONS FOR SPECIFIC CONDITIONS—Cont'd

	Examples	Calories (kcal/oz)	Carbohydrate Source	Protein Source	Unique Properties	Indications
Hydrolyzed Casein	Alimentum, Nutramigen, Pregestimil	20	Corn or sucrose	Casein	Easier to digest Hypoallergenic	IgE-mediated milk protein allergy Fat malabsorption
Partially Hydrolyzed Whey	Gerber Good Start Gentle, Gerber Good Start Soothe, Similac Pro-Total Comfort	20	Corn or sucrose	Hydrolyzed whey + casein or 100% whey	Reduced lactose content	May reduce risk of developing allergic diseases (especially eczema), improve gastric emptying, decrease colic, but data limited and may differ between products
Amino Acid	Neocate Infant and Junior, Elecare Infant and Junior, Alfamino Infant and Junior, PurAmino Infant and Junior	20	Corn or sucrose	Amino acids	Easier to digest, nonallergenic	Milk protein allergy Severe malabsorption

g, Grams; *kcal*, kilocalorie; *oz*, ounce.

Data from O'Connor, N. Infant formula. *Am Fam Phys*. 2009; 79(7):565–570; Comparison of breast milk and available infant formulas, available at https://www.aafp.org/afp/2009/0401/p565.html). Additional sources listed in references.

TABLE 21.13

ADDITIONAL FORMULAS FOR SPECIAL CLINICAL CIRCUMSTANCES

A. INFANTS	
Severe carbohydrate intolerance	MJ3232A Ross Carbohydrate Free (RCF)
Requiring lower calcium and phosphorus	Similac PM 60/40
B. TODDLERS AND YOUNG CHILDREN AGED 1–10 YEARS	
Vegetarian, lactose intolerance, or milk protein intolerance	Bright Beginnings Soy Pediatric Drink
Protein allergy/intolerance and/or fat malabsorption	PediaSure Peptide (and Peptide 1.5) Pepdite Junior Peptamen Junior (with and without Prebio) Vivonex Pediatric EleCare Junior Neocate Junior Neocate Splash Alfamino Junior PurAmino Junior
Fat malabsorption, intestinal lymphatic obstruction, chylothorax	Monogen Enfaport
Increased caloric needs	Boost Kids Essentials Carnation Instant Breakfast Essentials Nutren Junior (also with fiber) PediaSure (also with fiber)
Requiring clear liquid diet	Resource Breeze Ensure Clear
Intractable epilepsy	KetoCal (3:1 and 4:1)
Blended formulas (using real foods)[a]	Pediasure Harvest Compleat Pediatric Compleat Organic Blends Compleat Pediatric Organic Blends Nourish Liquid Hope Kate Farms (Standard 1.0, Pediatric Standard 1.2, Peptide 1.5 and Pediatric Peptide 1.5)
C. OLDER CHILDREN AND ADULTS ENTERAL NUTRITION (TUBE FEEDING)	
For malabsorption of protein and/or fat	Peptamen, Peptamen w/Prebio, Peptamen 1.0 and 1.5 Pediasure Peptide 1.0 and 1.5 Vital Peptide 1.5 Perative Tolerex Vital High Protein Vital 1.0 Cal and AF 1.2 Cal, 1.5 Cal Vivonex Plus and Vivonex T.E.N.
For critically ill and/or malabsorption	Pulmocare Pivot 1.5 Cal Perative

Continued

TABLE 21.13

ADDITIONAL FORMULAS FOR SPECIAL CLINICAL CIRCUMSTANCES—Cont'd

For impaired glucose tolerance	Glucerna Glytrol Store-brand diabetic nutritional drink
For dialysis patients	Magnacal Renal Nepro NutriRenal
For patients with acute renal failure not on dialysis	Renalcal Suplena
INCREASED CALORIC NEEDS (ORAL)	
With a normal gastrointestinal (GI) tract	Boost, Boost with fiber Boost Plus, Boost High Protein Carnation Instant Breakfast Essentials with whole milk Ensure Original NUTRA Shake
For clear liquid diet	Resource Breeze Ensure Clear
For patients with cystic fibrosis (CF)	Scandishake with whole milk

[a]Some blended formulas can also be used for older children and adults. Tube bore size (French) and gravity versus bolus feeding recommendations vary and should review each formula company's recommendations. Calories and nutrient information vary among formulas. If changing from a nonblended formula, gradual transition may be beneficial for optimal tolerance.

4. Abnormal gastrointestinal tract (e.g., congenital malformations, esophageal stenosis, intestinal pseudo-obstruction)
5. Injury/critical illness (e.g., burn, trauma, surgery, sepsis)

D. Features of the Most Common Oral Rehydration Solutions (Table 21.14)

VIII. PARENTERAL NUTRITION

A. Indications for the Use of Parenteral Nutrition[38]

1. Inability to feed enterally or when alimentation via gastrointestinal tract is restricted >3 to 5 days (or earlier for premature infants and neonates)
2. Chronic gastrointestinal dysfunction and/or malabsorption
3. Increased gastrointestinal losses or requirements

B. Starting and Advancing Parenteral Nutrition (Table 21.15)

C. Frequency of Monitoring Growth Parameters and Laboratory Studies in Patients on Parenteral Nutrition (Table 21.16)

D. Recommended Formulations of PN (Table 21.17)

IX. WEB RESOURCES

A. Professional and Government Organizations

1. Growth Charts and Nutrition Information: http://www.cdc.gov

TABLE 21.14

ORAL REHYDRATION SOLUTIONS

Solution	Kcal/mL (kcal/oz)	Carbohydrate (g/L)	Na (mEq/L)	K (mEq/L)	Osmolality (mOsm/kg H_2O)
CeraLyte-50	0.16 (4.9)	Rice digest (40)	50	20	N/A
CeraLyte-70	0.16 (4.9)	Rice digest (40)	70	20	N/A
CeraLyte-90	0.16 (4.9)	Rice digest (40)	90	20	N/A
Enfalyte	0.12 (3.7)	Rice syrup solids (30)	50	25	160
Oral Rehydration Salts (WHO)	0.06 (2)	Dextrose (20)	90	20	330
Pedialyte (unflavored)	0.1 (3)	Dextrose (25)	45	20	250

g, Gram; *kcal*, kilocalorie; *kg*, kilogram; *L*, liter; *mL*, milliliter; *mOsm*, milliosmole; *oz*, ounce.

TABLE 21.15

INITIATION AND ADVANCEMENT OF PARENTERAL NUTRITION FOR INFANTS THROUGH ADOLESCENTS[a,b]

Nutrient	Initial Dose	Advancement	Goals
Glucose	3.5%–10%	1%–5%/day	5–12 (max 14–18) mg/kg/min rate of infusion
Protein	0.8–3 g/kg/day	1 g/kg/day	0.8–4 g/kg/day 10%–16% of calories
Fat[c]	1–2 g/kg/day	0.5–1 g/kg/day	1–3.5 g/kg/day[d] 0.17 g/kg/hr (maximum rate of infusion)

[a]Acceptable osmolarity of parenteral nutrition through a peripheral line varies between 900 and 1050 osm/L by institution. An estimate of the osmolarity of parenteral nutrition can be obtained with the following formula: Estimated osmolarity = (dextrose concentration × 50) + (amino acid concentration × 100) + (mEq of electrolytes × 2). Consult individual pharmacy for hospital limitations.

[b]In general, infants require the higher concentration and/or rate of glucose, protein, and fat compared to older children and adolescents

[c]Essential fatty acid deficiency may occur in fat-free parenteral nutrition within 2 to 4 weeks in infants and children and as early as 2 to 14 days in neonates. A minimum of 2% to 4% of total caloric intake as linoleic acid and 0.25% to 0.5% as linolenic acid is necessary to meet essential fatty acid requirements.

[d]If parenteral nutrition–associated cholestasis occurs, lipid minimization and/or use of fish oil or composite lipids should be considered.[41]

Modified from Corkins M, Balint J, Plogested S, eds. *The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum*. Maryland: American Society for Parenteral and Enteral Nutrition; 2010; Table 34.4.

g, Gram; *hr*, hour; *kg*, kilogram; *L*, liter; *mg*, milligram; *min*, minute; *osm*, osmole.

2. American Academy of Pediatrics (AAP) Children's Health Topics: http://www.healthychildren.org
3. Academy of Nutrition and Dietetics: http://www.eatright.org
4. American Society for Parenteral and Enteral Nutrition: http://www.nutritioncare.org

TABLE 21.16

MONITORING SCHEDULE FOR PATIENTS RECEIVING PARENTERAL NUTRITION[a]

Variable	Initial Period[b]	Later Period[c]
GROWTH		
Weight	Daily	2 times/week
Height	Weekly (infants) Monthly (children)	Monthly
Head circumference (infants)	Weekly	Monthly[d]
LABORATORY STUDIES		
Electrolytes and glucose	Daily ×3 or until stable	1–2× weekly
BUN/creatinine	Daily ×3 or until stable	1–2× weekly
Albumin or prealbumin	Weekly	Weekly
Ca^{2+}, Mg^{2+}, P	Daily ×3 or until stable	Weekly
ALT, AST, ALP	Weekly	Weekly
Total and direct bilirubin	Weekly	Weekly
CBC with differential	Daily x3 or until stable	1–2× weekly
Triglycerides	Daily until stable	Weekly
Vitamins	—	As indicated
Trace minerals	—	As indicated

[a]For patients on long-term parenteral nutrition, monitoring every 24 weeks is adequate in most cases.

[b]The period before nutritional goals are reached or during any period of instability.

[c]When stability is reached, no changes in nutrient composition.

[d]Weekly in preterm infants.

Modified from Worthington P, Balint J, Bechtold M, et al. When is parental nutrition appropriate? *J Parent Enter Nutr.* 2017;41(3), Table 13.2.

ALP, Alkaline phosphatase; *ALT*, alanine transaminase; *AST*, aspartate transaminase; *BUN*, blood urea nitrogen; *CBC*, complete blood cell count; *Ca*, calcium; *Mg*, magnesium; *P*, phosphorous.

TABLE 21.17

PARENTERAL NUTRITION FORMULATION RECOMMENDATIONS

Electrolyte	Preterm	Term Infants/Children	Adolescents and Children >50 mg
Sodium (mEq/kg)	2–5	2–5	1–2
Potassium (mEq/kg)	2–4	2–4	1–2
Calcium	2–4 mEq/kg	0.5–4 mEq/kg	10–20 mEq/day
Phosphorus	1–2 mmol/kg	0.5–2 mmol/kg	10–40 mmol/day
Magnesium	0.3–0.5 mEq/kg	0.3–0.5 mEq/kg	10–30 mEq/day
Acetate and Chloride	As needed for acid base balance		

Trace Element	Preterm Neonate <3 kg (mCg/kg/day)	Term Neonate 3–10 kg (mCg/kg/day)	Children 10–40 kg (mCg/kg/day)	Adolescent > 40 kg (per day)
Zinc	400	50–250	50–125	2–5 mg
Copper[a]	20	20	5–20	200–500 mg
Manganese[a]	1	1	1	40–100 mCg
Chromium	0.05–0.2	0.2	0.14–0.2	5–15 mCg
Selenium	1.5–2	2	1–2	40–60 mCg

[a]Copper and manganese needs may be lowered in cholestasis.

From Mirtallo J, Canada T, Johnson D et al. Safe practices for parenteral nutrition. *J Parenter Enteral Nutr.* 2004;28(6):S29–S70; and Corkins M, Balint J, Plogested S, eds. *The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum.* Maryland: American Society for Parenteral and Enteral Nutrition; 2010, Tables 34.5 and 34.7.

5. U.S. Department of Agriculture Healthy Eating Guidelines: http://www.choosemyplate.gov
6. Bright Futures: Nutrition and Pocket Guide: https://brightfutures.aap.org
7. AAP Committee on Nutrition: https://www.aap.org/

B. Infant and Pediatric Formula Company Websites

1. Enfamil, Enfacare, Nutramigen, and Pregestimil: http://www.meadjohnson.com
2. Carnation, Good Start, Nutren, Peptamen, Vivonex, Boost, Alfamino, and Resource: https://www.nestlehealthscience.us/ and http://medical.gerber.com/
3. Alimentum, EleCare, Ensure, NeoSure, PediaSure, Pedialyte, and Similac: http://www.abbottnutrition.com
4. Bright Beginnings: http://www.brightbeginnings.com
5. America's Store Brand: http://www.storebrandformula.com
6. KetoCal, Neocate, and Pepdite: http://www.nutricia-na.com
7. Liquid Hope and Nourish: https://www.functionalformularies.com/
8. Kate Farms: https://www.katefarms.com/

C. Breastfeeding Resources

1. LactMed is an online resource from the National Library of Medicine/National Institutes of Health (N/IH) that provides information on the safety of maternal medications and breastfeeding: http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
2. Video instruction on breastfeeding techniques from Stanford Newborn Nursery: http://newborns.stanford.edu/Breastfeeding/FifteenMinuteHelper.html
3. Academy of Breastfeeding Medicine Protocols for the Care of Breastfeeding Mothers and Infants. Management of common breastfeeding-related challenges discussed: https://www.bfmed.org/protocols
4. National Institute of Child Health and Human Development—Breastfeeding: https://www.nichd.nih.gov/health/topics/breastfeeding/Pages/default.aspx

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A complete list of references can be found online at www.expertconsult.com.

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Chapter 22

Oncology

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See additional content on Expert Consult

I. OVERVIEW OF PEDIATRIC MALIGNANCIES[1-4]

A. Epidemiology

1. **Incidence**
   a. Annual rate of 18.8 cases per 100,000 person-years for children under 20 years of age.
   b. Incidence rate has increased by 0.6% per year since 1975.
2. **Survival**
   a. Five-year survival has improved from 61% to 83.6% over the past 40 years.
   b. Malignant neoplasms remain the leading cause of disease-related mortality in children.

B. Presenting Signs and Symptoms

1. **General:** Fever of unknown origin, fatigue, malaise, irritability, weight loss, failure to thrive
2. **Neurologic:** See Section IV.B.
3. **Cardiorespiratory:** Cough, dyspnea, stridor, hypertension
4. **Gastrointestinal (GI):** Anorexia, emesis, hepatosplenomegaly, abdominal mass
5. **Musculoskeletal:** Localized bone/joint pain, limp, soft tissue mass
6. **Dermatologic:** Bruising, bleeding, petechiae, pallor
7. **Hematologic:** Epistaxis, gingival bleeding, hematuria
8. **Lymphatic:** Features of a pathologic lymph node include:
   a. Size: <2 cm usually insignificant unless >1 cm in supraclavicular fossa or increase in size over time >2 to 4 weeks
   b. Consistency: Rubbery (classically lymphoma), hard (malignant, granulomatous infection)
   c. Sensation: Nontender more concerning for malignancy

II. PEDIATRIC HEMATOLOGIC MALIGNANCIES[1-2] (TABLE 22.1)

III. PEDIATRIC SOLID TUMOR MALIGNANCIES[1-2] (TABLE 22.2)

IV. PEDIATRIC CENTRAL NERVOUS SYSTEM (CNS) TUMORS[1-2,5-8] (TABLE 22.3)

A. Epidemiology

1. Most common solid tumors in children.

TABLE 22.1

COMMON PEDIATRIC HEMATOLOGIC MALIGNANCIES[1-2]

Malignancy	Clinical Presentation	Initial Workup	Epidemiology, Prognosis
ALL, AML	Fever, pallor, petechiae/ecchymoses, lethargy, malaise, anorexia, bone/joint pain **Exam:** Lymphadenopathy, hepatosplenomegaly, abnormal neurologic exam, testicular enlargement; AML may include subcutaneous nodules, gingival hyperplasia, chloromas (solid collection of leukemic cells) **T-cell ALL:** can present with anterior mediastinal mass	CBC with differential, peripheral smear; CMP with phosphate, uric acid, LDH important to assess for tumor lysis CXR to assess for mediastinal mass Blood and urine cultures if febrile Definitive diagnosis requires lumbar puncture (evaluate for CNS involvement), bone marrow biopsy, flow cytometry	**ALL:** Most common pediatric cancer (approximately 25% in <15 years). Peaks at age 2–5 years. Overall five-year survival rate exceeds 90%. **AML:** Peaks in first year of life, risk increases again after adolescence. Survival rate ~60%–70%; acute promyelocytic leukemia best prognosis.
Lymphoma HD, NHL	Painless, firm lymphadenopathy (often supraclavicular or cervical nodes) Cough, shortness of breath "B symptoms" (fevers, night sweats, weight loss)	CBC with differential, peripheral smear, electrolytes; include CRP, UA, LDH CXR to assess for mediastinal mass Diagnosis requires tissue and fluid sampling, lymph node biopsy	15% of childhood malignancies HD peak incidence occurs in bimodal distribution (15–34 years old and >55 years) NHL incidence increases with age, more common in second decade of life Prognosis: HD highly curable (95% survival with stage I disease and 75% for stage IV); NHL prognosis varies with histology and stage
Histiocytic Disease	Scaly rash, long bone pain, fever, weight loss, diarrhea, dyspnea, painless lymphadenopathy, polydipsia, polyuria	Triglycerides, fibrinogen, ferritin, urine osmolality Imaging to detect lytic lesions: Skeletal survey, followed by CT/MRI, bone scan/PET	**Langerhans Cell Histiocytosis:** Median age at presentation 30 months

Note: Laboratory testing and imaging suggestions are meant as a guide for evaluation of a potential malignancy. Patients warranting definitive testing should be referred to an oncologist.

ALL, Acute lymphocytic leukemia; *AML*, acute myeloid leukemia; *CBC*, complete blood count; *CMP*, complete metabolic panel; *CNS*, central nervous system; *CRP*, c-reactive protein; *CT*, computed tomography; *CXR*, chest x-ray; *HD*, Hodgkin disease; *IV*, intravenous; *LDH*, lactate dehydrogenase; *MRI*, magnetic resonance imaging; *NHL*, non-Hodgkin lymphoma; *PET*, positron emission tomography; *UA*, urinalysis.

TABLE 22.2

COMMON PEDIATRIC SOLID TUMOR MALIGNANCIES[1-2]

Malignancy	Clinical Presentation	Initial Workup	Epidemiology, Prognosis
Neuroblastoma: Malignant tumor of neural crest cell origin	Abdominal pain or mass (hard, nontender) Periorbital ecchymoses, spinal cord compression, Horner syndrome Paraneoplastic syndromes (secretory diarrhea, diaphoresis, opsoclonus-myoclonus)	Abdominal ultrasound Definitive diagnosis requires CT chest/abdomen/pelvis, urine catecholamines (HVA, VMA), MIBG scan, biopsy	Most common malignancy in infancy; median age of diagnosis 17 months 8% childhood malignancies, 15% of deaths caused by childhood malignancy **Prognosis**: Favorable prognosis if age of diagnosis <1 year, Stage I, II, IV-S, absence of N-myc amplification
Wilms Tumor: Nephroblastoma	Abdominal mass with or without abdominal pain May see hypertension, hematuria, anemia (bleeding within the tumor)	Liver and renal function tests, urinalysis Abdominal ultrasound, chest/abdominal CT or MRI Diagnosis requires biopsy	Peaks at age 3–4 years Survival rate 90% (poor prognosis with diffuse anaplasia)
Bone Sarcoma: Osteosarcoma, Ewing sarcoma	**Osteosarcoma**: Bone pain or mass (typically in epiphysis/metaphysis of long bones) not relieved with conservative treatment **Ewing Sarcoma**: Bone pain and swelling, most commonly in femur or pelvis	X-ray of primary site, followed by MRI Metastatic evaluation: CT of chest, PET scan	**Osteosarcoma**: Peaks in adolescence during maximum growth velocity **Ewing**: Peaks between 10 and 20 years **Prognosis**: Cure rate for localized disease: 60%–70%; poor prognosis with metastatic disease, primary tumor of axial skeleton, necrosis at time of resection (osteosarcoma)

Continued

TABLE 22.2—cont'd

COMMON PEDIATRIC SOLID TUMOR MALIGNANCIES[1-2]

Malignancy	Clinical Presentation	Initial Workup	Epidemiology, Prognosis
Rhabdomyosarcoma: Soft tissue malignant tumor of skeletal muscle origin	Rapidly growing mass, may be painful Symptoms based on location HEENT: Periorbital swelling, proptosis, chronic otitis media, dysphagia, neck mass GU tract: Paratesticular swelling, hematuria, urinary frequency/retention	CT or MRI of primary site Diagnosis requires tissue biopsy, immunohistochemical staining	Peaks at 2–6 years and in adolescence **Prognosis**: Based on stage, extent of surgical resection, and histopathology (alveolar histopathology poorer prognosis than embryonal); favorable prognostic factors include localized disease, >90% tumor necrosis at resection, age between 1 and 10 years at presentation
Retinoblastoma (Rb)	Leukocoria (retrolental mass), strabismus, hyphema, irregular pupil(s)	Ophthalmology referral MRI brain to evaluate pineal gland if bilateral	Peaks at age 2 years Survival at 5 years >90% 66%–75% tumors are unilateral *Rb1* mutations carries risk for second malignancies (osteosarcoma, soft tissue sarcoma, malignant melanoma)
Hepatic Tumors: Hepatoblastoma, Hepatocellular carcinoma (HCC)	Painless abdominal mass, anorexia, emesis, abdominal pain, fever Hepatoblastoma may be associated with anemia, thrombocytosis	CBC, LFTs, AFP, hepatitis B and C titers Abdominal ultrasound	Hepatoblastoma peaks at age <3 years HCC peaks after 10 years of age (associated with hepatitis B and C) **Prognosis**: Hepatoblastoma favorable prognosis pending tumor resection at diagnosis; HCC carries poor prognosis
Gonadal/Germ Cell Tumor	**Testicular tumors**: Nontender scrotal mass, hydrocele **Ovarian tumors**: typically asymptomatic until quite large **Hormone-producing tumors**: Amenorrhea, precocious puberty, hirsutism	AFP, β-hCG CXR, abdominal ultrasound, followed by CT or MRI	Peaks <4 years, then again in adolescence Overall cure rate >80% Favorable prognostic factors include <12 years of age, lack of thoracic involvement

Note: Laboratory testing and imaging suggestions are meant as a guide for evaluation of a potential malignancy. Patients warranting definitive testing should be referred to an oncologist.

AFP, α-Fetoprotein; *β-hCG*, beta human chorionic gonadotropin; *CBC*, complete blood cell count; *CT*, computed tomography; *CXR*, chest x-ray; *GU*, genitourinary; *HEENT*, head eyes ears nose throat; *HVA/VMA*, homovanillic acid/vanillylmandelic acid (urine catecholamines); *LFTs*, liver function tests; *MIBG*, metaiodobenzylguandidine; *MRI*, magnetic resonance imaging; *PET*, positron emission tomography.

TABLE 22.3

PEDIATRIC CENTRAL NERVOUS SYSTEM TUMORS BY INCIDENCE[1-2,5-7]

Tumor	Epidemiology	Location	Prognosis
Glioma (40%)	**Low-grade**: Average age of diagnosis: 6.5–9 years; male predominance **High-grade**: 9–10 years; 1:1 male-female ratio	Occur throughout the CNS Low-grade astrocytomas commonly occur in cerebellum, hypothalamic, third ventricular region, optic nerve	Low-grade: 50%–100% depending on ability to resect
Embryonal Tumor: Most commonly medulloblastoma (20%)	Most common group of malignant CNS tumors Bimodal distribution, peaking at 3–4 years, then again between 8 and 10 years	Commonly located in midline cerebellar vermis Older patients can present in cerebellar hemisphere	5-year survival 50%–80% Poor outcome if presents under 4 years of age
Ependymal Tumor: Derived from ependymal lining of ventricular system (10%)	Median age 6 years	~70% occur in the posterior fossa Can occur in supratentorial region, spinal cord Usually noninvasive, can extend into ventricular lumen	Long-term survival ~40% after undergoing gross total resection
Craniopharyngioma: Arise from embryonic remnant of Rathke pouch (5%–10%)	In childhood, peaks between 8 and 10 years of age Rarely occurs in infancy	Occur in suprasellar region adjacent to optic chiasm Minimally invasive	5-year survival 70%–90% Associated with significant morbidity (panhypopituitarism, growth failure, visual loss)
Germ Cell Tumor (3%–5%)	Peak incidence 10–12 years of age	Commonly arise in midline locations (pineal and suprasellar region)	5-year survival 40%–70%

CNS, Central nervous system.

2. Leading cause of childhood cancer deaths.
3. Highest incidence in infants and children under 5 years old.

B. Clinical Presentation

1. Early/generalized symptoms: Headache, lethargy/fatigue, nausea/emesis, gait abnormalities; increased head circumference in infants
2. Later symptoms related to tumor location: Seizures, altered language, encephalopathy, hemiplegia/hemi-sensory deficit, facial weakness, neuroendocrine effects (precocious/delayed puberty, diabetes insipidus), visual changes, abnormal movements, back pain, sphincter disturbance

C. Initial Workup

1. Thorough neurologic exam, including fundoscopic exam.
2. Neurosurgery/Neuro-oncology consultation.
3. Labs: Presurgical tests (complete blood count [CBC], electrolytes, blood type, coagulation factors, cross-matching); endocrine tests for suprasellar tumors; α fetoprotein (AFP) and β human chorionic gonadotropin (β hCG) if germinoma suspected.
4. Imaging: Magnetic resonance imaging (MRI) of brain (sometimes spine) with and without intravenous (IV) contrast.

D. Management Principles

1. High-dose dexamethasone: Often administered to reduce tumor-associated edema.
2. Consider seizure prophylaxis for those at high risk of seizures or seizure history.

V. ONCOLOGIC EMERGENCIES[2,9-16]

A. Fever and Neutropenia (Fig 22.1)

1. **Etiology:** Fever with temperature ≥38.3°C (some centers and medical associations also use 38.0°C sustained over an hour to define fever) in the setting of neutropenia (absolute neutrophil count [ANC] <500 cells/μL or <1000 cells/μL but expected to drop to <500 cells/μL in the next 48 hours). Presumed serious infection in a neutropenic host. While fevers may be caused by other etiologies including medications, presume infection until proven otherwise.
2. **Presentation:** May appear ill with fatigue, lethargy, or localized pain. Can also appear well, yet have subtle signs of compensated shock, including chills, rigors, tachypnea, or tachycardia. May deteriorate after initial doses of antibiotics.
3. **Management:** Broad-spectrum antibiotics with antipseudomonal coverage should be administered within 60 minutes of presentation to medical facility. Note: Antibiotic administration may lead to clinical sepsis secondary to release of endotoxin from gram-negative bacteria.

B. Hyperleukocytosis/Leukostasis

1. **Etiology:** Elevated white blood cell (WBC) count (usually >100,000/μL) in leukemia patients leads to leukostasis in the microcirculation and diminished tissue perfusion (notably in CNS and lungs). Leukostasis occurs more commonly and at lower WBC counts in acute myeloid leukemia (AML) than in acute lymphocytic leukemia (ALL).
2. **Presentation:** Hypoxia, tachypnea, dyspnea, and pulmonary hemorrhage from pulmonary leukostasis. Mental status changes, headaches, seizures, and papilledema from cerebral leukostasis. May also see GI bleeding, abdominal pain, renal insufficiency, priapism, and/or intracranial hemorrhage. Hyperleukocytosis may be asymptomatic.

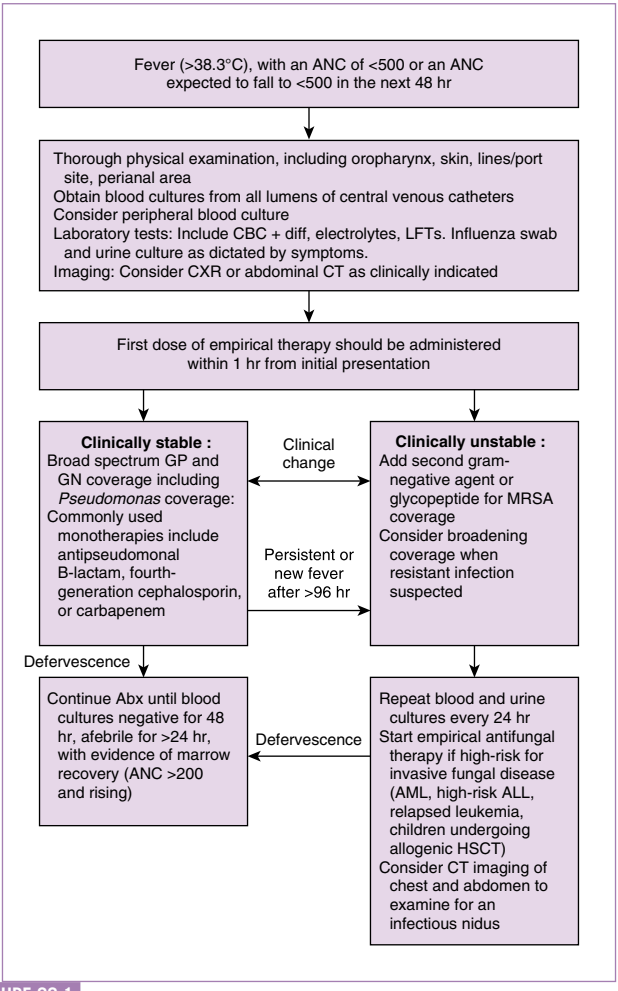

FIGURE 22.1

Algorithm for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem cell transplantation. Note: some centers and medical associations also use 38.0°C sustained over an hour to define fever. *Abx*, Antibiotics; *ALL*, acute lymphocytic leukemia; *AML*, acute myeloid leukemia; *ANC*, absolute neutrophil count; *CBC*, complete blood cell count; *CT*, computed tomography; *CXR*, chest x-ray; *diff*, differential; *GN*, gram-negative; *GP*, gram-positive; *HSCT*, hematopoietic stem cell transplantation; *LFTs*, liver function tests; *MRSA*, methicillin-resistant *Staphylococcus aureus*. (Data from Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. *J Clin Oncol.* 2017;35:2082–2094).

3. **Management**
   a. Prompt initiation of chemotherapy is the most effective approach.
   b. Consider leukapheresis or exchange transfusion if evidence of symptomatic leukostasis.
   c. Transfuse platelets to keep count above 20,000/μL to prevent hemorrhage.[1]
   d. Avoid red blood cell (RBC) transfusions, which raise viscosity. If required, consider partial exchange transfusion.
   e. Hydration and allopurinol should be initiated, as hyperleukocytosis increases the risk of tumor lysis syndrome.
   f. Treat coagulopathy.

C. Tumor Lysis Syndrome

1. **Etiology:** Rapid lysis of tumor cells releases intracellular contents into the blood stream spontaneously before treatment or during early stages of chemotherapy (especially Burkitt lymphoma, T-cell leukemia/lymphoma, acute leukemias with hyperleukocytosis).
2. **Presentation:** Hyperuricemia, hyperkalemia, hyperphosphatemia (with secondary hypocalcemia). Can lead to acute kidney injury. Symptoms include nausea, anorexia, arrhythmias, seizures, and altered mental status.
3. **Diagnosis:** CBC, basic metabolic panel (BMP), phosphorus, uric acid, lactate dehydrogenase (LDH), electrocardiogram (ECG).
4. **Prevention and Management**
   a. Hydration: Dextrose-containing IV fluids (without potassium, calcium, phosphate) at twice maintenance rate. Keep urine-specific gravity <1.010 and urine output >100 mL/m^2/hr. Alkalinization is no longer recommended, given increased risk of calcium phosphate precipitation.
   b. Hyperuricemia: Allopurinol inhibits formation of uric acid and should only be given PO (see Formulary for dosing). Rasburicase converts uric acid to the more soluble allantoin. Use in high-risk patients, especially those with uric acid >7.5 mg/dL. Do not use rasburicase with patients with known G6PD deficiency, as it may result in methemoglobinemia.
   c. Monitor potassium, calcium, phosphorous, uric acid, and urinalysis closely (up to Q2 hours for high-risk patients). There is an increased risk of calcium phosphate precipitation when Ca × Phos > 60. Consider early use of sevelamer.
   d. See Chapter 11 for management of abnormal electrolytes and Chapter 19 for dialysis indications.

D. Spinal Cord Compression

1. **Etiology:** Intrinsic or extrinsic compression of spinal cord. Occurs most commonly with metastases from brain tumors, spinal tumors, soft tissue sarcomas, neuroblastoma, lymphoma.
2. **Presentation:** Back pain (localized or radicular), weakness, sensory loss, bowel or bladder dysfunction, gait abnormalities. Prognosis for recovery based on duration and level of disability at presentation.

3. **Diagnosis:** MRI (preferred) or computed tomography (CT) scan of spine. Spine radiography is less sensitive.
4. **Management**
   a. In the presence of neurologic abnormalities, strong history, and rapid progression of symptoms, consider immediate dexamethasone. Note: Steroids may prevent accurate diagnosis of leukemia/lymphoma; plan diagnostic procedure as soon as possible.
   b. If tumor type is known and chemosensitive, emergent chemotherapy is indicated.
   c. If tumor type is unknown or debulking may remove most/all of tumor, emergent neurosurgery consultation is indicated to decompress the spine.

E. Increased Intracranial Pressure (ICP)

1. **Etiology:** Ventricular obstruction or impaired cerebral spinal fluid (CSF) flow. Most commonly seen with brain tumors, but also with intracranial hemorrhage, thrombosis, meningeal involvement by tumor or infection.
2. **Presentation:** Headaches, altered mental status, irritability, lethargy, nuchal rigidity, emesis, abnormal vision; Cushing triad and pupillary changes are late and ominous findings.
3. **Diagnosis**
   a. Evaluate for vital sign changes [i.e., Cushing triad (↓ heart rate, ↑ systolic blood pressure, irregular respirations)].
   b. Funduscopic evaluation for papilledema.
   c. Obtain CT or MRI of the head (MRI more sensitive for diagnosis of posterior fossa tumors).
4. **Management**
   a. See Chapter 1 for management principles.
   b. Obtain emergent neurosurgical consultation.
   c. If tumor is the cause, start IV dexamethasone (see Formulary for dosing).

F. Other Neurologic Emergencies: Cerebrovascular Accident (CVA), Seizures

1. **CVA Etiology:** Hyperleukocytosis, coagulopathy, thrombocytopenia, radiation (fibrosis) or chemotherapy-related (e.g., L-asparaginase–induced hemorrhage or thrombosis, methotrexate). Most common in patients with AML or any form of leukemia with hyperleukocytosis.
2. **Seizure Etiology**: Most common in primary CNS tumors, tumors metastatic to CNS, meningeal leukemia, chemotherapy-related (intrathecal [IT] cytarabine, IT/IV methotrexate).
3. See Chapters 1 and 20 for diagnosis and management.

G. Superior Vena Cava Syndrome/Superior Mediastinal Syndrome

1. **Etiology:** Compression of venous drainage and trachea, most commonly caused by mediastinal mass. Usually seen with T-lymphoblastic lymphoma, Hodgkin lymphoma, mature B-cell lymphoma, and germ cell tumors.
2. **Presentation:** Dyspnea, cough, wheeze, stridor, orthopnea, headaches, facial swelling, dizziness, plethora.

3. **Diagnosis:** Two-view chest radiograph. If mediastinal mass present, obtain neck radiograph to further assess. Avoid sedation if unstable, high risk for airway obstruction.
4. **Management**
   a. Control airway, place in upright position, and administer supplemental oxygen.
   b. Biopsy (e.g., bone marrow, pleurocentesis, lymph node biopsy) before therapy if patient can tolerate sedation.
   c. Empiric therapy: Radiotherapy, steroids, chemotherapy. **Note:** can confound diagnosis.

H. Typhlitis (Neutropenic Enterocolitis)

1. **Etiology:** Inflammation of bowel wall, typically localized to cecum. Associated with bacterial or fungal invasion. Associated with prolonged neutropenia, often secondary to induction therapy in leukemia.
2. **Presentation:** Right lower quadrant abdominal pain, nausea/emesis, diarrhea, fever (may be absent early in course). Risk for perforation.
3. **Diagnosis**
   a. Careful serial abdominal examinations.
   b. Abdominal ultrasound may be considered (may show pneumatosis intestinalis, bowel wall edema). CT abdomen with IV and PO contrast is most sensitive form of imaging.
4. **Management**
   a. Bowel rest: NPO on IV fluids; consider nasogastric decompression.
   b. Broad anerobic and gram-negative antibiotic coverage.
   c. Surgical consultation.

I. Cytokine Release Syndrome

1. **Etiology**: Newer immunologic agents (e.g., chimeric antigen receptor T [CAR-T] therapy and specific antibodies) can provoke release of cytokines associated with systemic inflammation and hemodynamic instability.
2. **Presentation**: Early symptoms include fever, diaphoresis, or mild evidence of hemodynamic instability (tachycardia) that can progress quickly to cardiovascular collapse and multi-organ dysfunction.
3. **Diagnosis:** Based on clinical features. Consider obtaining CRP and ferritin, although nondiagnostic.
4. **Management**
   a. Tocilizumab: recombinant humanized monoclonal antibody targeting the IL-6 receptor.
   b. Treat hypotension with IV fluids. If refractory, may require vasopressors, intensive care unit (ICU)-level care.
   c. Closely monitor neurologic status because these agents are associated with neurotoxicity. Patient should be on seizure prophylaxis.

VI. COMMONLY USED CHEMOTHERAPEUTIC DRUGS AND ASSOCIATED ACUTE TOXICITIES (TABLE 22.4)

TABLE 22.4

COMMONLY USED CHEMOTHERAPEUTIC AGENTS[a]

Drug Name (By Class)	Toxicity	Monitoring and Care
ALKYLATORS	**Significant myelosuppression, severe nausea, impaired fertility**	**Myelosuppression supportive care, aggressive antiemetics, pretreatment fertility consult**
Busulfan	Seizures, SOS, acute/chronic lung injury	Monitor weight, abdominal girth, bilirubin; seizure prophylaxis
Carmustine	Hypotension, chronic lung injury	Slow infusion, PFTs
Cyclophosphamide	Myocardial necrosis, hemorrhagic cystitis, SIADH	Hyperhydration and **mesna** to prevent hemorrhagic cystitis; ECG
Ifosfamide	Mental status changes, encephalopathy (rarely progressing to death), renal tubular damage, hemorrhagic cystitis, Fanconi syndrome	Monitor creatinine, magnesium, phosphate, potassium; hyperhydration and **mesna** to prevent hemorrhagic cystitis; methylene blue for neurotoxicity
Lomustine	Disorientation, fatigue	
Melphalan	Severe mucositis, pulmonary fibrosis	Aggressive oral hygiene, ophthalmologic examination
Procarbazine	Encephalopathy; adverse effects with tyramine-rich foods, ethanol, MAOIs, meperidine, and many other drugs	Avoid serotonergic agents/modulators, diet low in tyramine (avoid aged cheese/meats, beer, pickled food, soy sauce)
Temozolomide	Headache, seizures, thrombocytopenia	
Thiotepa	Encephalopathy, rash, burns, desquamation of skin, lower extremity weakness	Frequent bathing
NUCLEOTIDE ANALOGS	**Myelosuppression, mucositis, transaminitis**	**Supportive care, monitor LFTs**
Clofarabine	Capillary leak syndrome, SOS, nephrotoxicity, hyperbilirubinemia	Monitor creatinine; monitor weight, abdominal girth, bilirubin
Cytarabine (Ara-C)	Ara-C syndrome (maculopapular rash, fever), conjunctivitis, severe mucositis, ataxia, respiratory distress rapidly progressing to pulmonary edema	Corticosteroid eye drops; coverage for viridans streptococci with fever, systemic steroids for Ara-C syndrome
Fludarabine	Transaminitis, neurotoxicity, immunosuppression (nonmyelosuppressive)	Monitor creatinine (decreased clearance results in increased risk of neurotoxicity)
Mercaptopurine (6-MP)	Hepatotoxicity (increased risk in TPMT deficiency), pancreatitis	LFTs
Thioguanine	Hepatotoxicity (increased risk in TPMT deficiency), SOS	LFTs
DNA MODIFYING AGENTS		
Bleomycin *(DNA strand breaker)*	Anaphylaxis, pneumonitis, pulmonary fibrosis	PFTs

Continued

TABLE 22.4—cont'd

COMMONLY USED CHEMOTHERAPEUTIC AGENTS[a]

Drug Name (By Class)	Toxicity	Monitoring and Care
Carboplatin *(DNA cross-linker)*	Nephrotoxicity, ototoxicity, peripheral neuropathy	Monitor creatinine, adjust dose based on creatinine clearance, audiology evaluation
Cisplatin *(DNA cross-linker)*	Nephrotoxicity (related to cumulative dose), severe emesis, hypomagnesemia, hypophosphatemia, ototoxicity	Monitor creatinine, magnesium, phosphorous; audiology evaluation; aggressive antiemetic regimen
Etoposide *(Topoisomerase inhibitor)*	Anaphylaxis (rare), hypotension, hyperbilirubinemia, transaminitis, secondary malignancy (AML)	Slow infusion if hypotension; change formulation to etoposide phosphate if anaphylaxis; monitor bilirubin and LFTs
OTHER CHEMOTHERAPEUTIC AGENTS		
Asparaginase *(Enzyme)*	Pancreatitis, hypersensitivity reactions (acute and delayed), coagulopathy (thrombosis and bleeding), hyperammonemia	Monitor serum asparaginase activity levels, high index of suspicion for clots/bleeds, consider amylase/lipase with abdominal pain
Dactinomycin *(Antibiotic)*	Rash, hypocalcemia, radiation recall (rash), SOS	Monitor calcium; monitor weights, abdominal girth, bilirubin
Daunorubicin and Doxorubicin, Mitoxantrone (adriamycin) *(Anthracyclines)*	Arrhythmia, cardiomyopathy/heart failure (related to cumulative dose), severe mucositis, severe emesis, red urine and bodily fluids (dauno/doxo), blue–green urine (mitoxantrone), radiation recall	Limit cumulative dose; echocardiogram; consider **dexrazoxane** for cardioprotection
Methotrexate (MTX) *(Folate antagonist)*	Mucositis, diarrhea, renal dysfunction, encephalopathy, chemical arachnoiditis (intrathecal), photosensitivity, leukoencephalopathy, osteoporosis	**Leucovorin** to reduce mucositis with high-dose therapy; oral hygiene; monitor neurologic exam and developmental milestones
Vinblastine, Vincristine, and Vinorelbine *(Microtubule inhibitors)*	Constipation, bone and jaw pain, peripheral and autonomic sensory and motor neuropathy, foot drop, SIADH (rare), hyperbilirubinemia, transaminitis	Bowel regimen; monitor for neuropathy; fatal if given intrathecally, bilirubin and LFTs
MOLECULARLY TARGETED AGENTS		
Alemtuzumab (Campath) *(Monoclonal Ab binds CD52 on mature lymphocytes)*	Severe infusion reactions (hypotension, bronchospasm, ARDS, anaphylaxis), infections	Antimicrobial prophylaxis
Blinatumomab *(Bi-specific T-cell engager)*	CRS, neurotoxicity	Dexamethasone
Brentuximab *(Chimeric monoclonal Ab binds CD30)*	Peripheral neuropathy, diarrhea	

TABLE 22.4—cont'd

COMMONLY USED CHEMOTHERAPEUTIC AGENTS[a]

Drug Name (By Class)	Toxicity	Monitoring and Care
CAR T-Cells *(Immune cells genetically modified to bind tumor-specific antigens)*	CRS, neurotoxicity (headache, confusion, encephalopathy, seizure)	**Tocilizumab** (anti-IL-6R), steroids if severe/refractory
Dinutuximab *(Monoclonal Ab binds GD-2; for use in neuroblastoma)*	Rash/hives, rigors, severe pain, neuropathy, hyponatremia, hepatotoxicity, hypocalcemia, capillary leak syndrome, ocular neurologic disorders	Monitor sodium, calcium, LFTs; aggressive pain management
Imatinib (Gleevec), Dasatinib, Nilotinib *(Tyrosine kinase inhibitors)*	Congestive heart failure, edema, pleural effusions, rash, night sweats	ECG, serial echocardiograms
Nivolumab *(PD-1 checkpoint inhibitor)* and Pembrolizumab *(CTLA-4 checkpoint inhibitor)*	Autoimmune manifestations (colitis, dermatitis, hepatitis, nephritis, pneumonitis, etc.)	
Rituximab (Rituxan) *(Chimeric monoclonal Ab binds CD20 on B cells)*	Infusion reaction, urticaria	Hep B testing before use, slow infusion for first dose, immune reconstitution may be very delayed post therapy

[a]All chemotherapeutic medications may cause nausea, vomiting, fever, immunosuppression, mucositis, gastrointestinal upset. *AML*, Acute myeloid leukemia; *ARDS*, acute respiratory distress syndrome; *CAR T-cells*, chimeric antigen receptor T-cell therapy; *CRS*, cytokine release syndrome; *ECG*, electrocardiogram; *LFTs*, liver function tests; *PFTs*, pulmonary function tests; *SIADH*, syndrome of inappropriate antidiuretic hormone; *SOS*, sinusoidal obstruction syndrome; *TPMT*, thiopurine S-methyltransferase. Data from *Physician's Desk Reference*. 64th ed. Montvale, NJ: Medical Economics; 2010; and Taketomo CK, Hodding JH, Kraus DM. *American Pharmaceutical Association Pediatric Dosage Handbook*. 16th ed. Hudson, OH: Lexi-Comp, *Pediatric & Neonatal Dosage Handbook*, 25th edition; and Micromedex 2.0 (2018).

VII. COMMON CHEMOTHERAPY COMPLICATIONS AND SUPPORTIVE CARE[1,11]

Note: Transfuse only irradiated and leukoreduced packed red blood cells (pRBCs) and single-donor platelets; cytomegalovirus (CMV)-negative or leukofiltered pRBCs/platelets for CMV-negative patients. Use leukofiltered pRBCs/platelets for those who may undergo transplant in the future to prevent alloimmunization or for those who have had nonhemolytic febrile transfusion reactions. Many oncology patients have nonhemolytic reactions (fever, rash, hypotension, respiratory distress) to pRBCs and/or platelet transfusion and should subsequently be premedicated with diphenhydramine and/or acetaminophen.

A. Cytopenias: Anemia, Thrombocytopenia, Neutropenia

1. **Etiology:** Chemotherapy, medication, radiation, marrow infiltration, blood loss, hemolysis, consumptive coagulopathy.
2. **Management**
   a. See Chapter 14 for details on transfusion.

b. Anemia: Hemoglobin thresholds for pRBC transfusions in cancer patients are based on clinical status and symptoms (often ≤8 g/dL).
c. Thrombocytopenia: In general, maintain platelet count above 10,000/μL. Patients with active bleeding, fever, or before selected procedures (e.g., lumbar puncture, intramuscular injection) may require higher thresholds. Consider maintaining at higher levels for patients who have brain tumors, recent brain surgery, or history of stroke.
d. Neutropenia:
(1) Broad-spectrum antibiotics with concomitant fever (see Fig. 22.1).
(2) GCSF to assist in recovery of neutrophils.

B. Mucositis

1. **Etiology:** Damage to endothelial cells of the GI tract from chemotherapy, leading to breakdown of the mucosa. Typically peaks in the first 1 to 2 weeks after chemotherapy.
2. **Presentation:** Oropharyngeal pain, abdominal pain, nausea, vomiting, diarrhea, intolerance of PO intake.
3. **Prevention and Management:** Supportive care aimed at pain control and nutrition. Local pain control with lidocaine-containing mouthwashes and bicarbonate rinses. Systemic pain control often requires patient-controlled analgesia (PCA) infusion. Total parenteral nutrition (TPN) is commonly required.

C. Nausea and Emesis

1. **Etiology**: Chemotherapy side effect. Also suspect opiate therapy, GI and CNS radiotherapy, obstructive abdominal process, elevated ICP, certain antibiotics, or hypercalcemia.
2. **Presentation:** Can be acute (within 24 hours of chemotherapy initiation), delayed (beyond 24 hours), or anticipatory in subsequent cycles.
3. **Therapy:** Hydration plus one or more antiemetic medications (Table 22.5; see Formulary for dosing).

VIII. ANTIMICROBIAL PROPHYLAXIS IN ONCOLOGY PATIENTS (TABLE 22.6)[17-19]

Note: Treatment length and dosage may vary per protocol.

IX. HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)[1,2,20]

A. Goal

Administer healthy functioning hematopoietic stem cells from the bone marrow, peripheral blood, or umbilical cord blood to a patient whose bone marrow is diseased (e.g., hematologic malignancy) or depleted (after treatment with intense myeloablative chemotherapy). HSCT is also used for some congenital and acquired hematologic, immunologic, and metabolic disorders.

B. Preparative Regimens

1. **Myeloablative**: Elimination of recipient's diseased marrow with high-dose chemotherapy or chemotherapy plus total body irradiation (TBI) prior

TABLE 22.5

ANTIEMETIC THERAPIES[1]

Antiemetic Classes	Common Agents	Common Adverse Effects
Serotonin (5-HT_3) antagonists	Ondansetron, granisetron	QT prolongation, QRS widening, constipation
Histamine-1 antagonist	Diphenhydramine, scopolamine	Sedation, urinary retention, blurred vision
Benzodiazepines	Lorazepam	Sedation
Dopamine antagonists	Metoclopramide, prochlorperazine, promethazine	Sedation, extrapyramidal effects, QT prolongation; rarely, seizures or neuroleptic malignant syndrome. Consider diphenhydramine to reduce risk of extrapyramidal symptoms.
Substance P receptor antagonists	Aprepitant fosaprepitant	Exercise caution with agents metabolized by CYP3A4
Steroids (helpful in patients with brain tumors and prophylaxis for delayed nausea/vomiting)	Dexamethasone	Hypertension, hyperglycemia, bradycardia, osteoporosis/ osteonecrosis
Cannabinoids (also an appetite stimulant)	Dronabinol	Hallucinations, dizziness
Antipsychotics (useful in patients with refractory vomiting, can help comorbid depression)	Olanzapine	Weight gain, sedation, insulin resistance, QT prolongation; extrapyramidal side effects (rare)

TABLE 22.6

ANTIMICROBIAL PROPHYLAXIS IN ONCOLOGY PATIENTS[1,17-19]

Organism	Medication	Indication
Pneumocystis jirovecii	TMP-SMX: 2–3 consecutive days per week Alternatives: atovaquone, dapsone, or pentamidine	Chemotherapy and HSCT per protocol (usually at least 3–6 months after therapy completion)
HSV, CMV, VZV	Acyclovir or valacyclovir (dosing is different for zoster, varicella, and mucocutaneous HSV)	At risk for prolonged neutropenia (HSCT, AML, induction chemotherapy for high-risk leukemia, or reinduction therapy for relapsed leukemia)
Candida albicans	Fluconazole Alternatives: voriconazole or micafungin	Patients with leukemia or after HSCT (usually at least 28 days)
Gram-positive and gram-negative organisms	Levofloxacin	HSCT or leukemias with prolonged severe neutropenia until counts normalize

AML, Acute myeloid leukemia; *CMV*, cytomegalovirus; *HSCT*, hematopoietic stem cell transplantation; *HSV*, herpes simplex virus; *TMP-SMX*, trimethoprim–sulfamethoxazole; *VZV*, varicella zoster virus.

to stem cell infusion. Generally, provides greater anticancer activity but carries a higher risk of treatment-related organ injury.

2. **Nonmyeloablative**: Reduced-intensity conditioning regimen where marrow is not fully ablated, allowing recovery of autologous hematopoiesis if patient fails to engraft. Associated with decreased treatment-related mortality but higher risk of relapse or transplant rejection.

C. Types of HSCT

1. **Allogeneic**
   a. Recipient is transfused with donor stem cells from genetically similar but nonidentical donor, following a preparative regimen that includes chemotherapy and often radiation. Donors are screened for human leukocyte antigen (HLA) subtype matching to recipient. Possible donors include HLA-matched siblings, fully or partially HLA-matched unrelated donors, umbilical cord blood units, and HLA-haploidentical (half-matched) related donors.
   b. Increased level of mismatch between donor and recipient increases the risk for graft-versus-host disease (GVHD) but may offer greater graft-versus-leukemia (GVL) immunologic treatment effect.
   c. Used commonly for leukemias, myelodysplastic syndrome, hemophagocytic lymphohistiocytosis, and a number of nonmalignant hematologic, immunologic, and metabolic disorders.
2. **Autologous**
   a. Donor is recipient. After several cycles of conventional chemotherapy, stem cells from patient are harvested from the patient, stored, and given back after the patient has received intense myeloablative doses of chemotherapy.
   b. Generally, lacks GVHD or GVL effect.
   c. Used for high-risk neuroblastoma, lymphoma, and various high-risk solid tumors, which have demonstrated improved disease control after higher intensity chemotherapy that would otherwise be limited by excessive marrow suppression.

D. Engraftment

1. Recipient's bone marrow is repopulated with donor stem cells that proliferate and mature.
2. Usually starts within 2 to 4 weeks of transplant and may present with an inflammatory response, but can be significantly delayed with certain conditions, drug toxicity, or infection.
3. Defined as an ANC more than 500/μl for 3 consecutive days.

X. COMPLICATIONS OF HSCT[1,2,20-22]

A. Graft-Versus-Host Disease

1. **Etiology:** Donor T-cell-mediated reaction to unique host antigens. Risk factors include HLA disparity, source of stem cells (peripheral blood > bone marrow > umbilical cord blood), magnitude of conditioning-related tissue injury, and posttransplant infections.

2. **Presentation:** *Acute* GVHD most commonly occurs within 6 weeks of transplantation, typically within 100 days of transplantation; rarely, it may occur or persist beyond this time. *Chronic* GVHD traditionally presents >100 days after transplant but may occur earlier and persist.
   a. Maculopapular skin rash. Can progress to bullous lesions resembling toxic epidermal necrolysis.
   b. GI symptoms: Anorexia, dyspepsia, nausea, vomiting, abdominal cramping, secretory diarrhea.
   c. Laboratory findings: Direct hyperbilirubinemia.
   d. Chronic GVHD can involve nearly any organ. Commonly includes sclerodermatous skin changes, cholestasis/hepatitis, lung involvement (restrictive or obstructive), and/or dry eyes and mouth.
3. **Diagnosis:** Triad of rash, abdominal cramping with diarrhea, hyperbilirubinemia. Tissue biopsy of skin or mucosa can provide histologic confirmation, demonstrating lymphocytic infiltration and apoptosis. See Section XIII for clinical staging.
4. **Prevention and Management**
   a. Prophylaxis: Immunosuppression with posttransplant cyclophosphamide, cyclosporine, mycophenolate mofetil, tacrolimus, and/or sirolimus; adjuvants include methotrexate and prednisone.
   b. First-line treatment: Grade 1 and 2 GVHD may be treated locally with topical steroids (skin) or nonabsorbable enteral steroids (gut). First-line systemic treatment is corticosteroids, often with an additional immunosuppressant.
   c. Note: Patients with cGVHD are functionally asplenic and significantly immunosuppressed, requiring antimicrobial prophylaxis.

B. Sinusoidal Obstructive Syndrome (SOS); Veno-Occlusive Disease (VOD)

1. **Etiology:** Injury to endothelial cells leads to activation of the clotting cascade in liver sinusoids, causing erythrocyte congestion and occlusive fibrosis of terminal intrahepatic venules and sinusoids. Occurs as a consequence of hematopoietic cell transplantation, hepatotoxic chemotherapy, and/or high-dose liver radiation. Typically occurs within 3 weeks of the insult, most common at the end of the first week after transplant.
2. **Presentation:** Tender hepatomegaly, hyperbilirubinemia, edema, ascites, unexplained weight gain, thrombocytopenia refractory to transfusions.
3. **Diagnosis**: There are two established clinical diagnostic criteria, the Modified Seattle and Baltimore. Updated criteria based on growing understanding of the pathophysiology have recently been proposed.[26,30] As each has limitations, consideration of all factors enables earlier diagnosis, treatment, and improved outcomes.
   a. Modified Seattle Criteria: Two of the following events within 20 days of HSCT: Bilirubin >2 mg/dL; tender hepatomegaly; weight gain >2%.
   b. Baltimore Criteria: Bilirubin >2 mg/dL within 21 days of HSCT plus two of the following: Hepatomegaly; ascites; weight gain >5%.

c. Proposed updated criteria, unpublished as of this writing, have an expanded time frame with no time restriction to symptom development and broaden the definition by including transfusion refractory thrombocytopenia and imaging/biopsy results as eligible criteria.
d. Severe SOS is defined by the above, plus pulmonary and/or renal organ failure.
e. Imaging: Doppler US showing reversal of flow in the portal venous system is often found with severe SOS (although its absence does not rule out SOS).

4. **Prevention and Treatment**
   a. Prevention: Ursodeoxycholic acid from conditioning through 90 days post transplant.
   b. Treatment: Mild/moderate SOS can be managed with supportive care, including fluid and sodium restriction and diuretics. Defibrotide is the only approved pharmacologic treatment modality, with improved outcomes with earlier initiation and a 50% response rate. Maintain coagulation factors, platelets, and RBCs in stable range secondary to consumption.
   c. See Section XIII, for discussion of additional complications, including engraftment syndrome, thrombotic microangiopathy, hemorrhagic cystitis, and idiopathic pneumonia syndrome.

XI. CANCER SURVIVORSHIP[3,23-25]

A. Understand the Diagnosis

Obtain comprehensive treatment summary from oncologist summarizing diagnosis, chemotherapeutic agents, radiation, surgeries, history of HSCT, and adverse drug reactions.

B. Monitoring

1. Determine any potential problems by organ system, and devise plan for routine evaluation.
2. See Table 22.7 and www.survivorshipguidelines.org for common late effects of therapy.

C. Vaccinations in Oncology and HSCT Patients: see **Chapter 16**

XII. WEB RESOURCES

- National Cancer Institute (NCI): http://www.cancer.gov/cancertopics/pdq/pediatrictreatment
- NCI Clinical Trial Database: http://www.cancer.gov/clinicaltrials
- Surveillance, Epidemiology, and End Results (SEER) from NCI: http://seer.cancer.gov/
- Children's Oncology Group: http://www.childrensoncologygroup.org
- Long-term follow-up guidelines for survivors of pediatric cancer: http://www.survivorshipguidelines.org/
- Children's Oncology Camping Association, International: http://www.cocai.org/

TABLE 22.7

LATE EFFECTS OF CANCER TREATMENT BY ORGAN SYSTEM/SITE[1,23-25]

Organ System/Site	Specific Treatment Modality	Associated Late Effects	Suggested Monitoring (Frequency)
CNS	Cranial irradiation, intrathecal high-dose methotrexate	Cognitive dysfunction, peripheral neuropathy	Neuropsychological testing
Psychiatric	Any cancer experience	Mental health disorders, risky behaviors, psychosocial disability from pain, fatigue	Psychosocial assessment (yearly)
Vision		Cataracts, optic neuropathy	Routine ophthalmology follow-up (yearly for radiation >30 Gy; Every 3 years if <30 Gy)
Hearing	Platinum agents	Ototoxicity, sensorineural hearing loss	Regular audiology follow-up and evaluation (every 5 years if received radiation)
Thyroid		Malignancy, hyperthyroid, hypothyroid	Thyroid function testing (yearly)
Endocrine		Precocious puberty, growth hormone deficiency	Neuroendocrine monitoring, Tanner staging, BMI (twice a year until growth completed, then yearly)
Cardiac	Anthracyclines	Cardiomyopathies, pericarditis, ASCD/MI, arrhythmias	ECG, echocardiogram (every 1–5 years as indicated), HgA1C, lipid profile (every 2 years if received radiation)
Pulmonary	Bleomycin, various alkylating agents	Pulmonary fibrosis, restrictive lung disease	Pulmonary function tests with D_{LCO}
Hepatic	6-TG, methotrexate, 6-MP	Hepatic fibrosis, portal hypertension, VOD	LFTs, liver ultrasound with Doppler
Renal	Platinum agents, high-dose methotrexate, ifosfamide	Renal insufficiency/failure	UA and blood pressure (yearly), electrolytes, creatinine clearance, GFR
Urologic	Cyclophosphamide, ifosfamide	Cancer, fibrosis, hemorrhagic cystitis	UA (yearly), cystoscopy, bladder ultrasound, urine culture
Gonadal/ reproductive	Alkylating agents	Delayed puberty, ovarian failure, infertility, testosterone deficiency	Tanner staging, LH, FSH, estradiol, gynecologic evaluation Semen analysis, testosterone
Musculoskeletal	Methotrexate, corticosteroids	Osteoporosis/osteopenia, osteonecrosis, short stature, scoliosis, avascular necrosis	Serial heights and spine exam (yearly); DEXA scan; calcium and vitamin D supplementation may be recommended for high-risk patients

Continued

TABLE 22.7—cont'd

LATE EFFECTS OF CANCER TREATMENT BY ORGAN SYSTEM/SITE[1,23-25]

Organ System/Site	Specific Treatment Modality	Associated Late Effects	Suggested Monitoring (Frequency)
Secondary malignancies	Radiation therapy, alkylating agents, anthracyclines, topoisomerase II inhibitors, platinum agents, cyclophosphamide	For radiation, location is site-dependent; asssociated secondary malignancies include CNS, breast, thyroid, melanoma, solid tumors, and sarcomas Leukemia (alkylating agents) Bladder cancer (cyclophosphamide)	Yearly comprehensive history and physical, routine blood work, recommended follow-up for specific treatment modalities

ASCD, Atherosclerotic cardiac disease, *BMI*, body mass index, *CNS*, central nervous system; *DEXA*, dual-energy x-ray absorptiometry; D_{LCO}, diffusing capacity of lung for carbon monoxide; *ECG*, electrocardiogram; *FSH*, follicle-stimulating hormone; *GFR*, glomerular filtration rate; *Gy*, Gray; *HgA1C*, hemoglobin A1C; *LFT*, liver function test; *LH*, luteinizing hormone; *MI*, myocardial infarction; *UA*, urinalysis; *VOD*, veno-occlusive disease.

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A complete list of references can be found online at www.expertconsult.com.

XIII. ONLINE CONTENT

A. Complications of HSCT[1,2,19-21,25-29]

1. **Graft-Versus-Host Disease (GVHD)**

See Table EC 22.A for grading of acute GVHD. Acute GVHD should be graded weekly through day +100. If systemic treatment is started, it should be graded twice weekly while on treatment.

2. **Engraftment Syndrome**
   a. **Etiology:** Occurs several days prior to donor cell engraftment and in days following white blood cell recovery owing to endothelial injury and activated granulocytes in the setting of proinflammatory cytokines. Occurs in approximately 20% of HSCT patients.
   b. **Presentation:** Fever and rash; can have pulmonary infiltrates, diarrhea, or signs of shock.
   c. **Diagnosis:** Similar presentation to GVHD and infection. Imperative to rule out infection while treating empirically with antibiotics. Often mild and self-limited. However, if symptoms continue for ≥ 48 hours or are severe, consider initiation of corticosteroids. If insufficient steroid response after 72 hours, can biopsy for alternative diagnoses.
   d. **Treatment:** Treatment with supportive care and corticosteroids; optimization of GVHD prophylaxis. If biopsy confirms immune-mediated pathology, can treat with additional immunosuppressive agents.
3. **Transplant-Associated Thrombotic Microangiopathy (TA-TMA)**
   a. **Etiology:** Associated with immunosuppressants (e.g., cyclosporine, tacrolimus) and infection.
   b. **Presentation:** Microangiopathic hemolytic anemia and consumptive thrombocytopenia. Often associated with renal insufficiency/failure; may be associated with neurologic symptoms.
   c. **Diagnosis:** Anemia and thrombocytopenia on CBC, schistocytes on peripheral blood smear, hematuria, proteinuria, casts on urinalysis, elevated LDH, decreased haptoglobin, impaired renal function, elevated D-dimer on coagulation panel.
   d. **Treatment**: Supportive care with blood products, fluid management, and dialysis. Address underlying etiology—consider alternative immunosuppressant and treat any underlying infection. For progressive or severe TA-TMA, consider neutralization of compliment with eculizumab.[31]
4. **Hemorrhagic Cystitis**
   a. **Etiology:** Pretransplant conditioning regimens (specifically those that include cyclophosphamide, pelvic or total body irradiation [TBI]) or viral reactivation (adenovirus, BK virus).
   b. **Presentation:** Hematuria, dysuria, difficulty voiding due to clots.
   c. **Diagnosis:** Urine polymerase chain reaction (PCR) assay for adenovirus and BK virus, bacterial cultures, bladder ultrasound, CBC, coagulation studies.
   d. **Treatment**: Hydration, analgesics, platelet transfusion, treatment of any underlying infections. For obstruction, Foley catheter with bladder irrigation.

5. **Idiopathic Pneumonia Syndrome**
   a. **Etiology:** Widespread alveolar injury in the absence of infection or other known etiology. Thought to occur from a variety of insults, including toxic effects of the conditioning regimen, immunologic cell–mediated injury, and inflammation secondary to cytokine release following engraftment. Most commonly occurs within the first 120 days after transplant.
   b. **Presentation:** Rapidly progressive dry cough, dyspnea, hypoxemia, diffuse radiographic opacities; may progress to ARDS.
   c. **Diagnosis:** Imaging; bronchoalveolar lavage with transbronchial biopsy, if tolerated.
   d. **Prevention and Management:** Supportive care together with broad-spectrum antibiotics while infectious studies pending. IV corticosteroids and tumor necrosis factor-α inhibitor etanercept if no infection identified.[32]

TABLE EC 22.A

CLINICAL STAGING AND GRADING OF ACUTE GRAFT-VERSUS-HOST DISEASE

CLINICAL STAGING			
Stage	Skin (Rash)	Liver (Bilirubin)	GI System (diarrhea) [a]
1	<25% of BSA	2.1–3 mg/dL	500–1000 mL/day (10–19.9 mL/kg/day); OR severe nausea/vomiting
2	25%–50% of BSA	3.1–6 mg/dL	1001–1500 mL/day (20–30 mL/kg/day)
3	>50% of BSA	6.1–15 mg/dL	>1500 mL/day (or >30 mL/kg/day)
4	Erythroderma with bullous formation	>15 mg/dL	Severe abdominal pain and/or ileus
CLINICAL GRADE (BASED ON HIGHEST INDIVIDUAL TARGET ORGAN STAGING)			
I	Skin only (stage 1–2)		
II	Stage 3 skin OR stage 1 liver OR stage 1 GI		
III	Stage 2–3 liver OR stage 2–4 GI		
IV	Stage 4 skin OR stage 4 liver		

[a]Measured in mL/day if ≥50 kg or mL/kg/day if <50 kg.
BSA, Body surface area; *GI*, gastrointestinal.

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Chapter 23

Palliative Care

Joshua Natbony, MD

I. INTRODUCTION TO HOSPICE AND PALLIATIVE MEDICINE

A. Definition of Palliative Care[1,2]

1. Palliative care is the active total care of the child's body, mind, and spirit with the intent to prevent and relieve suffering, with a special focus on symptom control.
2. Palliative medicine supports the best quality of life for the child and family. It can be provided along with disease-directed treatment from the time of diagnosis of serious illness.
3. See Fig. 23.1 for the current accepted model of palliative care.

B. Definition of Hospice

1. Hospice care is an insurance benefit that may be initiated for patients who have a terminal illness with a life expectancy estimated to be 6 months or less.
2. It specializes in care at the end of life to promote a child's comfort and to support loved ones in their bereavement.

C. Team Composition

1. Hospice and palliative care teams are often robust and interdisciplinary.
2. They generally include physicians, nurses, nurse practitioners, physician assistants, social workers, child life specialists, pastoral care, patient care coordinators, and bereavement coordinators.

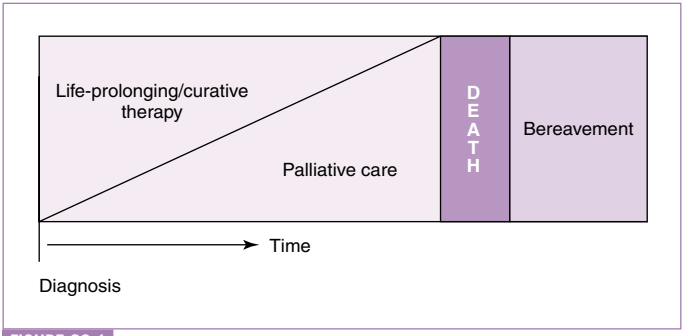

FIGURE 23.1
Current accepted model for palliative care.

II. COMMUNICATION AND DECISION MAKING

A. Decision-Making Tools[3]

1. Provide framework for discussion with families regarding medical issues, quality of life, family goals, preferences, and other contextual preferences, such as spirituality and culture.
2. Advance directives:
   a. Adolescents aged 18 years and older, if they are unable to speak for themselves, can name another adult to make healthcare decisions.
   b. Children and adolescents younger than 18 years of age can actively participate in decision making by using helpful tools such as "Five Wishes" and "Voicing My Choices" (see in Section IV).

B. Structuring Family Meetings[4]

1. Make sure that all necessary individuals are present and understand the purpose of the meeting.
2. Make sure that all clinicians are in agreement about the patient's condition and the recommendations.
3. Identify the individual who will facilitate the meeting.
4. Choose a private location with minimal distraction.
5. Always have water and tissues available.
6. Begin by introducing all participants and the purpose of the meeting.
7. Assess what the family knows and expects with respect to the patient's condition.
8. Describe the clinical situation, providing the big picture and then asking family members if they would like or are ready for more details.
9. Encourage each member of the family to express concerns and questions.
10. Explore the patient's and family's values and how they influence decision making.
11. Propose goals for the patient's care that reflect the stated values.
12. Provide a concrete follow-up plan.

C. Breaking Bad News[5]

1. Prepare yourself: Know the medical information, know what you will say, ask the patient/family if they want someone in particular present with them for the discussion.
2. Prepare the family/patient: Give a brief, calm statement that leads into the news.
3. State the news: Do this clearly and concisely, and be as definitive as possible.
4. Wait for the patient/family's reaction: Resist the urge to say more; allow others to speak first.
5. Reflect the response back: "This news is clearly very upsetting to you."
6. Legitimize the reaction: "It is understandable that you would be upset."
7. Explore: "What upsets you the most about this news?"
8. Provide realistic hope.

9. Discuss next steps (if appropriate at this time): "May I address your concerns now and talk about the next steps for treatment, or would you like more time?"

D. Other Tools for Difficult Conversations

1. Assess spirituality according to the "FICA" tool[6]:
   a. **F**aith and belief: "Do you consider yourself spiritual or religious?"
   b. **I**mportance in life: "What importance does your faith or belief system have in your life?"
   c. **C**ommunity: "Are you a part of a spiritual or religious community?"
   d. **A**ddress in care: "How would you like me, your healthcare provider, to address these issues in your healthcare?"
2. "Ask-tell-ask"[7]
   a. **Ask** the patient or family to describe their understanding of the situation or issue.
   b. **Tell** them what you need to communicate in a straightforward manner.
   c. **Ask** them questions to assess their understanding.
3. "Hope together" with the patient and family while also preparing for all possible outcomes.

III. CARE OF THE DYING CHILD

A. Limiting Interventions

The following options should be considered.

1. Do not attempt resuscitation (DNAR)—foregoing cardiopulmonary resuscitation (CPR) and other resuscitative interventions as part of an overall care plan that emphasizes comfort and quality of living.
2. Do not intubate (DNI)—although, if clinically appropriate, intubation may still allow the initiation of continuous positive-pressure ventilation or may help in managing symptoms.
3. Do not escalate treatment—the choice to forego changes in treatment, even as a patient's condition worsens, because death is expected. Examples of such requests include the following:
   a. Do not increase the dose of current medications (e.g., vasopressors).
   b. Do not add new medications (e.g., antibiotics).
   c. Do not initiate new interventions (e.g., dialysis, mechanical ventilation).
   d. However, one may still initiate and increase interventions to treat pain and reduce suffering.
4. Discontinuing current interventions—the option of discontinuing interventions that prolong the dying process must also be discussed.
5. Medical orders for life-sustaining treatment and physician orders for life-sustaining treatment (POLST) forms:
   a. These are portable and enduring medical order forms completed by patients or their authorized decision makers and are signed by a physician.

b. They contain orders regarding CPR and other life-sustaining treatments.
c. If a state offers one of these forms, the orders are valid for emergency medical service providers as well as healthcare providers and facilities within that state.
d. A copy must be provided to the patient or authorized decision maker within 48 hours of completion or sooner if the patient is to be transferred.
e. Refer to your state's laws prior to completing any documentation.
f. Additional information for US providers can be found at **www.polst.org.**

B. Involving the Child in Conversations About Death[8-11]

1. See Table 23.1 for the development of death concepts in children.[12]
2. A minor child has the capacity to meaningfully participate in medical decision making if he or she demonstrates the ability to do all of the following:
   a. Communicate understanding of the medical information.
   b. State his or her preference.
   c. Communicate understanding of the consequences of decisions.
3. Helpful documents are available for purchase from the nonprofit Aging with Dignity (see Section IV.B).
   a. Five Wishes: This is a legal advance directive with versions tailored for adolescents.
   b. Voicing My Choices: A workbook for adolescents intended to complement Five Wishes.
   c. My Wishes: A simple booklet for younger children to help them share their preferences.

TABLE 23.1

CONCEPTUALIZATION OF DEATH IN CHILDREN

Age Range	Characteristics	Concepts of Death	Interventions
0–2 years	Achieve object permanence May sense something is wrong	None	Provide maximal comfort with familiar persons and favorite toys
2–6 years	Magical thoughts	Believe death is temporary Do not personalize death Believe death can be caused by thoughts	Minimize separation from parents, correct perceptions that the illness is punishment
6–12 years	Concrete thoughts	Understand death can be personal Interested in details of death	Be truthful, evaluate fears, provide concrete details if requested, allow participation in decision making
12–18 years	Reality becomes objective Capable of self-reflection	Search for meaning, hope, purpose, and value of life	Be truthful, allow expression of strong feelings, allow participation in decision making

TABLE 23.2

SYMPTOMATIC MANAGEMENT OF THE DYING PATIENT

System	Changes as Death Approaches	Interventions
Neurologic	Pain	Morphine as needed
	Overactive senses (hearing last to diminish)	Dim lights and reduce noise, provide soft background music
	Increased need for sleep with occasional surge of energy to play or socialize	
Cardiovascular	Heart rate increases, blood pressure decreases, pulse weakens, and skin becomes cooler	Inform family that death is near
Respiratory	Increased secretions	Turn every few hours, elevate head of bed, frequent mouth care (avoid deep suctioning)
		Hyoscyamine
	Air hunger	Positive pressure through handheld fan
		Supplemental room air or oxygen as needed
		Morphine
Gastrointestinal	Nausea and vomiting	Ondansetron or prochlorperazine
	Decreased appetite, preference for liquids	Ice chips, moist mouth swabs
	Natural dehydration, fevers	Antipyretics per rectum
Dermatologic	Pruritus	Diphenhydramine
Psychiatric	Decreased interactions with outside world as thoughts and emotions are increasingly directed inward	Provide reassurance to family
		Frequently orient child to surroundings, surround with family and speak calmly
	Agitation or delirium	Lorazepam and haloperidol if needed

C. Supporting Patients Throughout the Dying Process

1. See Table 23.2 for normal changes that occur as death approaches and their recommended management.[12,13]
2. See Table 23.3 for appropriate dosing of recommended medications (NOTE: doses may be different for other indications).[12]

D. Pronouncing Death[14]

1. Preparation
   a. Know the child's name and gender.
   b. Be prepared to answer simple, pertinent questions from family and friends.
   c. Consult with nursing staff for relevant information, such as recent events and family dynamics.
   d. Determine the need and call for interdisciplinary support, such as social work, child life, pastoral care, and/or a bereavement coordinator.
2. Entering the room
   a. Enter quietly and respectfully along with the primary nurse.
   b. Introduce yourself and identify your role.

TABLE 23.3

DOSING FOR MEDICATIONS USED IN PALLIATIVE CARE[12,16-20]

Indication	Medication	Initial Regimen
Pain	Morphine	0.2–0.4 mg/kg/dose PO, SC, SL, PR Q2–4 hr[a] 0.1–0.2 mg/kg/dose IV Q2–4 hr[a] **NOTE:** Morphine should be titrated to symptomatic relief.
	Hydromorphone[b]	0.03–0.08 mg/kg/dose PO Q2–4 hr 0.015–0.02 mg/kg/dose IV, SC Q2–4 hr
	Oxycodone	0.05–0.2 mg/kg/dose PO 4hr (adult dose 5-10 mg)
Neuropathic pain	Gabapentin[b]	3–5 mg/kg/dose QHS day 1, BID day 2, then TID day 3 (titrate to effect, max dose per day 3600 mg)
Dyspnea	Morphine	0.1–0.25 mg/kg/dose PO, SC, SL, PR Q2–4 hr 0.05–0.1 mg/kg/dose IV Q2–4 hr
Agitation	Lorazepam	0.02–0.05 mg/kg/dose PO, IV, SL, PR Q4–8 hr
	Haloperidol	0.01–0.02 mg/kg/dose PO, IM, SC, IV Q8–12 hr
Pruritus	Diphenhydramine	0.5–1 mg/kg/dose PO, IV Q6–8 hr
Nausea/Vomiting	Prochlorperazine	0.1–0.15 mg/kg/dose PO, PR Q6–8 hr
	Ondansetron	0.15 mg/kg/dose PO, IV Q6–8 hr (max dose 8 mg)
	Granisetron	0.01 mg/kg IV/PO Q12hr (max 1 mg/dose)
	Olanzapine	0.1 mg/kg PO once daily (max 10 mg, titrate down in cases of oversedation)
Seizures	Diazepam	0.3–0.5 mg/kg/dose PR Q2–4 hr
	Lorazepam	0.05–0.1 mg/kg/dose SC, SL, IV Q2–4 hr
Secretions	Glycopyrrolate	0.04–0.1 mg/kg PO (max 8 mg/day) 0.004–0.01 mg/kg (4–10 mCg/kg) IV, SC

[a]Infants <6 months should receive one-third to one-half the dose. For adolescents, consider starting adult dosing of 10 to 30 mg/dose PO, 2 to 15 mg/dose IV.

[b]Medication has not been studied in neonates.

BID, twice daily; *IV*, intravenous; *PO*, oral; *PR*, rectal; *SC*, subcutaneous; *SL*, sublingual; *TID*, three times daily; *QHS*, nightly. Adapted from Himelstein BP, Hilden JM, Boldt AM, et al. Pediatric palliative care. *N Engl J Med.* 2004;350:1752–1762.
Note: For adult-sized patients, see Formulary for adult dosing recommendations.

   c. Determine the relationship of those in the room.
   d. Inform the family of the purpose of your visit ("I am here to examine your child") and invite them to remain in the room.
3. Procedure for pronouncement
   a. Check ID bracelet and pulse.
   b. Respectfully check response to tactile stimuli.
   c. Check for spontaneous respirations for a minimum of 1 minute.
   d. Check for heart sounds for a minimum of 1 minute.
   e. Record the time of death.
   f. Inform the family of death ("[Child's name] has died").
   g. Remember to convey sympathy ("I'm so sorry for your loss").
   h. Offer to contact other family members.
4. Documentation of death in the chart
   a. Write date, time of death, and the provider pronouncing the death.
   b. Document absence of pulse, respirations, and heart sounds.
   c. Identify family members who were present and informed of death.
   d. Document notification of the attending physician.

E. Explaining Autopsies[15]

1. Definitions
   a. An **autopsy** is a definitive examination of a deceased patient to determine the cause of death.
   b. A **forensic autopsy** is a legally mandated examination to determine cause of death in a criminal investigation.
   c. A **rapid autopsy** involves the urgent removal of tissues for research uses.
2. Frequently asked questions
   a. A voluntary autopsy can look at all parts of a patient's body or only some.
   b. An autopsy will not affect the patient's body cosmetically and should not affect funeral or viewing arrangements.
   c. An autopsy takes 2 to 4 hours to perform and should not delay funeral/burial arrangements.
3. Benefits of autopsy
   a. For families:
      (1) Provides closure regarding diagnosis.
      (2) Identifies possible genetic etiologies for unexplained death.
   b. For providers: clarifies potential diagnostic errors and uncertainties.

F. Organ Donation

   a. Most hospitals have a special third-party team that coordinates organ donations.
   b. Inform family members, if they are interested, that this team may be visiting soon to explain the process.

G. Completing Death Certificates[14]

1. Locate a copy of a sample death certificate for reference.
2. Cardiopulmonary arrest or respiratory arrest is NOT an acceptable primary cause of death.
3. For specific instructions for your state and/or institution, contact the Office of Decedent Affairs at your institution.
4. If you are completing a handwritten death certificate:
   a. Use BLACK INK ONLY and complete *Physician sections*.
   b. DO NOT use abbreviations (e.g., spell out the month: January 31, not 1/31).
   c. DO NOT cross out or use correction fluid; you must begin again if mistakes are made.

H. Interacting with Loved Ones After a Child's Death

1. It is appropriate to send condolence cards, contact families, or attend funerals after a child has died. These are all appropriate physician activities that are deeply valued by bereaved families. Families want to know that their children are not forgotten.
2. Numerous services are available for families, including: pastoral care, social work, bereavement coordinators, community support groups, counseling services, and bereavement follow-up programs.

IV. WEB RESOURCES

A. Center to Advance Palliative Care—capc.org

B. Aging with Dignity—https://agingwithdignity.org/

C. The American Academy of Hospice and Palliative Medicine—www.aahpm.org

D. The National Hospice and Palliative Care Organization—www.nhpco.org

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Chapter 24

Psychiatry

Christopher Morrow, MD

I. OVERVIEW

A. Epidemiology and General Approach

1. **Prevalence:** 15% to 20% of children in primary care practices require psychiatric care.[1]
2. **Surveillance and Screening:**
   a. Surveillance for mental health issues should occur at all routine well-child visits from early childhood through adolescence.
   b. The Pediatric Symptom Checklist (PSC) is a general mental health checklist that screens for a broad array of disorders (Table 24.1).
3. See the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), for full list of psychiatric diagnoses.[2]
4. Pharmacotherapy for many disorders may be managed or monitored by the pediatrician. See Riddle et al., "Pediatric Psychopharmacology for Primary Care."[3]

B. Mental Status Exam

1. General appearance: dress, self-care, demeanor, attitude, behavior
2. Motor activity: activity level (restless, fidgety, stereotyped or ritualized movements)
3. Speech and language: fluency, comprehension, rate, rhythm, volume, expressive and receptive skills
4. Mood and affect: stated and observed
5. Thought form/content
   a. What patient is thinking about
   b. Goal-directed nature of thoughts, coherence, organization, delusional content
6. Abnormal perceptual phenomena: illusions, hallucinations
7. Insight, judgment, cognition

II. POSTPARTUM DEPRESSION

A. Epidemiology[4]:

Prevalence in most studies is between 10% and 15%

B. Screening:

1. Universal screening is recommended for all postpartum women.
2. A history of depression doubles the risk of postpartum depression and should prompt careful assessment for postpartum symptoms.[5]

TABLE 24.1

MENTAL HEALTH SCREENING TESTS BY DIAGNOSIS

Symptoms or Diagnosis Evaluated	Screening Test	Age	Administration Time	Completed by	Comments	Weblink
General psychosocial screening	Pediatric Symptom Checklist (PSC)	4–16 years	<5 min	Parent or child/ adolescent	Assesses attention, externalizing, and internalizing symptoms	https://www.massgeneral.org/psychiatry/treatments-and-services/pediatric-symptom-checklist
Attention-deficit/hyperactivity disorder (ADHD)	Vanderbilt Diagnostic Rating Scales	6–12 years	10 min	Parent or teacher	Separate scales for functioning in different domains (home, school)	http://www.nichq.org/childrens-health/adhd/resources/vanderbilt-assessment-scales
Anxiety	Self-Report for Childhood Anxiety Related Emotional Disorders (SCARED)	8+ years	5 min	Parent or patient	Separate scales for parent and patient Does not assess for OCD, PTSD	http://www.midss.org/content/screen-child-anxiety-related-disorders-scared
	Spence Children's Anxiety Scale	2.5–12 years	5–10 min	Parent or patient if 8–12 years of age	Multiple subscales of anxiety	http://www.scaswebsite.com/
Depression	Patient Health Questionnaire-2 (PHQ-2) and Patient Health Questionnaire-9 (PHQ-9)	13+ years	1 min	Patient	Brief screening tool for adolescents or parents (e.g., postpartum depression)	http://www.cqaimh.org/pdf/tool_phq2.pdf http://www.cqaimh.org/pdf/tool_phq9.pdf
	Center for Epidemiological Studies Depression Scale for Children (CES-DC)	6–17 years	5–10 min	Child/adolescent	Originally used in adult populations	http://www.brightfutures.org/mentalhealth/pdf/professionals/bridges/ces_dc.pdf

OCD, obsessive-compulsive disorder; *PTSD*, posttraumatic stress disorder.

Modified from the American Academy of Pediatrics. Mental health screening and assessment tools for primary care. From Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit. 2010

C. Diagnosis:

1. Depression occurring in the 12-month period after birth.
2. Maternal depression is important to identify and treat, given the substantial impact on the health of the developing infant. Impaired maternal attachment may compromise the social, cognitive, and behavioral development of the infant.[4]
3. The Edinburgh Postnatal Depression Scale is a 10-item questionnaire which can be completed in 5 minutes or less.[6]

D. Treatment:

1. Referral to mother's primary care physician or mental health expert is preferred.
2. Integrating maternal mental health into pediatrics practice is ideal.[6]

III. COMMON PSYCHIATRIC CONDITIONS IN CHILDREN (2 TO 12 YEARS)

A. Attention-Deficit/Hyperactivity Disorder

1. **Epidemiology:**
   a. Persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development.
   b. Prevalence continues to rise. This disorder affected 11.0% (6.4 million) of children in the United States in 2011, marking an increase from 9.5% (5.4 million) of children in 2007.[7,8]
   c. Most affected children continue to meet the diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD) through adolescence.
2. **Screening:** Evaluate all children aged 4 to 18 years who have academic and/or behavioral concerns for ADHD and common comorbid conditions (depression, anxiety, oppositional defiant disorder, conduct disorder).[9]
3. **Diagnosis[2]:**
   a. DSM-5 diagnostic criteria: inattention, impulsivity/hyperactivity that are more frequent and severe than typically observed in children of the same developmental age.
   b. Symptoms must persist for 6 months or more, occur before the age of 12 years, and should be evident in two or more settings (e.g., home and school). [2,10]
   c. Subtypes: Combined, predominantly inattentive, or predominantly hyperactive/impulsive.
   d. Diagnosis is made using history, observation, and behavioral checklists such as the Vanderbilt Assessment Scale (see Table 24.1).
   e. If the medical history is unremarkable, no further laboratory or neurologic testing is required. Psychological and neuropsychological testing is not required for diagnosis but is recommended if other academic or developmental concerns are present.[10]

4. **Treatment:**
   a. Pharmacologic treatment works best with behavioral therapy as an adjunct.[9]
   b. Behavioral therapy may be tried alone in preschool-age children (4 to 5 years old), but for older children or in preschool-age children where behavioral therapy is ineffective, combination therapy with pharmacologic and behavioral interventions is most effective.[11]
   c. Before starting a stimulant medication, a history should be taken to exclude cardiac symptoms, Wolff-Parkinson-White syndrome, a family history of sudden death, hypertrophic cardiomyopathy, and long-QT syndrome. Screening electrocardiography is not required if there is no personal or family history of cardiac disease.[12]
   d. See Table 24.2 for recommended pharmacologic treatments. The ADHD Medication Guide provides visual information (see Section VI).
      (1) For preschool-age children (4 to 5 years old), start with behavioral therapy and, if necessary, a methylphenidate stimulant.[3,11]
      (2) For elementary-age children (6 or more years old), start with behavioral and stimulant therapy (methylphenidate or amphetamine).[3,11]
   e. Titrate medications to maximal symptom control with minimal side effects.
   f. Common side effects of stimulants to monitor include appetite suppression, abdominal pain, headaches, palpitations, and sleep disturbance.[9]
   g. If the first stimulant is ineffective, consider an alternative class of stimulant. Second-line options as alternative therapy or as an augmenting agent to stimulant therapy include guanfacine, clonidine, and atomoxetine.[3,11]
   h. If multiple medication trials prove ineffective, consultation with a pediatric psychiatrist is suggested.

B. Anxiety Disorders

1. **Epidemiology:**
   a. A group of disorders characterized by excessive fear, anxiety, and related behavioral disturbances.
   b. An estimated 4.7% of all children 3 to 17 years of age are affected, with onset most often before the age of 25 and increased prevalence (15% to 20%) among adolescents 13 to 17 years of age.[13-15]
2. **Clinical Presentation:**
   a. May present with fear or worry and without recognizing that their fear or anxiety is unreasonable.
   b. Commonly have somatic complaints of headache and abdominal pain. Patients with many primary care visits for such complaints may benefit from formal anxiety screening.
   c. Fear/anxiety may affect school performance or manifest as school avoidance.
   d. Crying, irritability, angry outbursts, and disruptive behavior are expressions of fear and an effort to avoid anxiety-provoking stimuli.

TABLE 24.2

COMMONLY USED PSYCHOTROPIC MEDICATIONS

Drug Name	Age of FDA Approval
ANTIDEPRESSANTS/ANXIOLYTICS	
Fluoxetine (Prozac)	7+ years (OCD) 8+ years (MDD)
Sertraline (Zoloft)	6+ years (OCD)
Escitalopram (Lexapro)	12+ years (MDD)
Duloxetine (Cymbalta)	7+ years (GAD)
ADHD MEDICATIONS	
METHYLPHENIDATE PREPARATIONS	
Methylphenidate (Concerta, Ritalin)	6+ years (Ritalin)
Dexmethylphenidate (Focalin)	6+ years
AMPHETAMINE PREPARATIONS	
Lisdexamfetamine (Vyvanse)	6+ years
Dextroamphetamine + amphetamine (Adderall)	3+ years (immediate release) 6+ years (extended release)
NONSTIMULANT OPTIONS	
Clonidine (Kapvay)	6+ years
Guanfacine (Tenex, Intuniv)	6+ years (Intuniv) 12+ years (Tenex)
Atomoxetine (Strattera)	6+ years
ANTIPSYCHOTICS	
Haloperidol (Haldol)	Not established
Aripiprazole (Abilify)	6+ years (irritability with ASD) 10+ years (BPD) 13+ years (schizophrenia)
Risperidone (Risperdal)	5+ years (irritability with ASD) 10+ years (BPD) 13+ years (schizophrenia)
Quetiapine (Seroquel)	10+ years (BPD) 13+ years (schizophrenia)

See Formulary for more detailed drug information, indications, and dosing.

ASD, Autism spectrum disorder; *BPD*, bipolar disorder; *GAD*, generalized anxiety disorder; *MDD*, major depressive disorder; *OCD*, obsessive-compulsive disorder.

Adapted from the Centers for Medicare and Medicaid Services factsheets (www.CMS.gov) and the US Food and Drug Administration.

3. **Screening:** Multiple tools, such as the Self-Report for Childhood Anxiety Related Emotional Disorders (SCARED) (Table 24.1), are available.
4. **Diagnosis:**
   a. DSM-5 diagnostic criteria vary based on the specific disorder[2]: (1) generalized anxiety disorder, (2) separation anxiety disorder, (3) social anxiety disorder, (4) selective mutism, (5) specific phobia, (6) panic disorder, (7) agoraphobia
   b. Differential diagnosis: obsessive-compulsive disorder, posttraumatic stress disorder.
5. **Treatment:** Cognitive behavioral therapy (CBT) with or without pharmacotherapy (see Table 24.2) based on the disorder and its severity.[16]

C. Oppositional Defiant Disorder (ODD)[17]

1. **Epidemiology:**
   a. Pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness.
   b. Prevalence estimated at approximately 3%. Increased prevalence in boys as compared with girls in the preteen years but not in the teens.
   c. Age of onset approximately 6 years of age, frequently comorbid with ADHD.
2. **Screening:** Many screening tools are available, including the Vanderbilt Assessment Scale (see Table 24.1).[18]
3. **Diagnosis[2]:**
   a. DSM-5 diagnostic criteria: angry/irritable mood with argumentative/defiant behavior and vindictiveness for 6 or more months.
   b. Behavior must be present with at least one nonsibling.
4. **Treatment:**
   a. No evidence for pharmacologic intervention as first-line therapy for ODD.
   b. Combination of CBT and parent management training may be most effective as first-line intervention.[17]

IV. COMMON PSYCHIATRIC CONDITIONS IN ADOLESCENTS

A. Depressive Disorders

1. **Epidemiology:**
   a. A group of disorders characterized by mood changes as well as somatic and cognitive symptoms that disrupt functioning.
   b. Prevalence of major depressive disorder: 2% of children, 4% to 8% of adolescents.[15]
   c. Subclinical symptoms: 5% to 10% of children.
   d. Common comorbid conditions: anxiety disorders, disruptive behavior disorders, ADHD, substance use.
2. **Screening:**
   a. Routine screening is recommended for patients 11 years of age or older.
   b. Multiple screening tools are available (see Table 24.1). The Patient Health Questionnaire (PHQ-2) is a brief but effective tool for use in adolescents.[19]
   c. All patients with suspected depressive symptoms should be screened for suicidal ideation and referred for emergency evaluation if serious thoughts and/or action plans are endorsed (see Section V.A).
3. **Diagnosis:**
   a. DSM-5 Major Depressive Disorder diagnostic criteria:
      (1) Five or more of the following symptoms for 2 or more weeks: Must include either depressed mood/irritability OR anhedonia; changes in appetite/weight, sleep, or activity; fatigue or loss of energy; guilt/worthlessness; decreased concentration; suicidality.
      (2) Symptoms cause significant impairment in functioning.

(3) Symptoms not due to substance use or a medical condition.
(4) No history of manic episodes.[20]

b. Other depressive disorders are defined by their own diagnostic criteria[2]: (1) disruptive mood dysregulation disorder; (2) persistent depressive disorder (dysthymia); (3) premenstrual dysphoric disorder.
c. Differential diagnosis: bipolar disorder, adjustment disorder.

4. **Treatment:**
   a. Selective serotonin reuptake inhibitors (SSRIs) may be initiated in the primary care setting. Referral to subspecialist may be required depending on severity or in the case of treatment failure (Fig. 24.1).
   b. Antidepressant medications (see Table 24.2) and CBT combined are the most effective treatments, followed by medication alone and then CBT alone.[21]

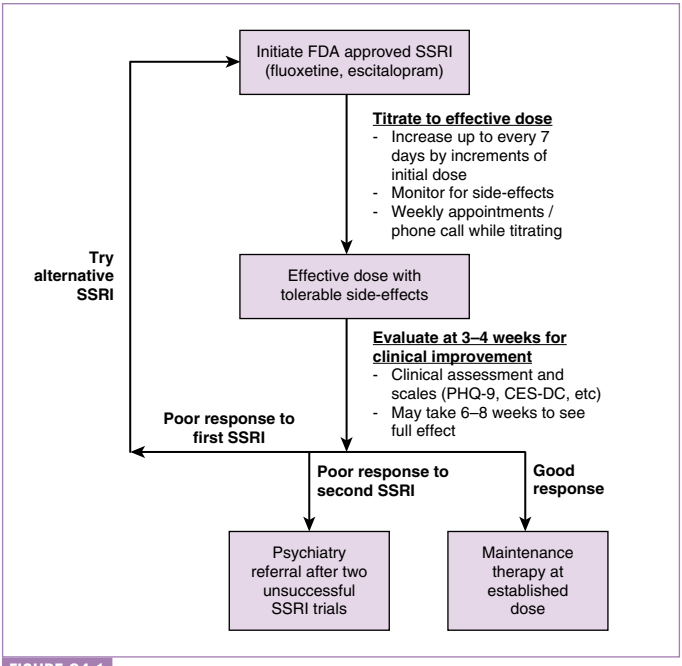

FIGURE 24.1
SSRI initiation algorithm. *CES-DC*, Center for Epidemiological Studies Depression Scale for Children; *FDA*, US Food and Drug Administration; *PHQ-9*, Patient Health Questionnaire-9; *SSRI*, selective serotonin reuptake inhibitor.

c. SSRIs have a black box warning from the US Food and Drug Administration (FDA) concerning a possible increase in suicidal thoughts or behaviors after initiation of medication.
   (1) The basis of this warning was a large meta-analysis that found no increase in completed suicides but a small increase in suicidal ideation.[22]
   (2) Multiple professional mental health groups support the continued use of SSRIs in treating depression in children and adolescents because the benefits appear to outweigh potential risks.[20,23,24]
d. Refer to the Physicians Med Guide prepared by the American Psychological Association (APA) and American Academy of Child and Adolescent Psychiatry (AACAP) for guidelines regarding medication use for depression in adolescents (see Section VI).[25]

B. Substance Use Disorders

1. **Epidemiology:**
   a. Lifetime diagnosis of alcohol abuse: 0.4% to 9%; alcohol dependence: 0.6% to 4.3%.[26]
   b. Lifetime diagnosis of drug abuse or dependence: 3.3% to 9.8%.[26]
   c. Common comorbid conditions: disruptive behavior disorders, mood disorders, anxiety disorders.
2. **Clinical Presentation:**
   a. Acute change in mood, behavior, and cognition.
      (1) Mood: low to elevated mood
      (2) Behavior: disinhibition, lethargy, hyperactivity, agitation, somnolence, hypervigilance
      (3) Cognition: impaired concentration, changes in attention span, perceptual and overt disturbances in thinking (e.g., delusions)
   b. Impairment in psychosocial and academic functioning (family conflict/dysfunction, interpersonal conflict, academic failure).
   c. Deviant or risk-taking behavior.[26]
3. **Diagnosis:**
   a. Establish standards of confidentiality.
   b. Administer CRAFFT Questionnaire (see Chapter 5).
   c. Evaluate age of onset of use; progression of use for specific substances; circumstances, frequency, and variability of use; types of agents used.
   d. Consider urine/serum toxicology evaluation if there is concern for substance use and patient consents to testing.
4. **Treatment:**
   a. Determine goals and readiness for change; promote behavioral change through motivational interviewing.[27]
   b. Families should be involved in treatment.
   c. Medications can be used to manage withdrawal symptoms and/or cravings.
   d. Treatment of comorbid conditions should occur at the same time.[26]

C. Eating Disorders

1. **Epidemiology:**
   a. Includes anorexia nervosa and bulimia nervosa as well as pica, rumination disorder (repeated regurgitation), avoidant/restrictive food intake disorder, and binge eating disorder.
   b. Twelve-month prevalence of 0.4% (anorexia nervosa) and 1% to 1.5% (bulimia nervosa); 10:1 female-to-male ratio.[5]
   c. Common comorbidities: affective and anxiety disorders.
2. **Diagnosis:**
   a. Anorexia nervosa
      (1) Restricted energy intake and low weight (body mass index [BMI] < 18.5 kg/m^2; severity stratified by BMI)
      (2) Fear of gaining weight
      (3) Disturbance in perception of body weight or shape
   b. Bulimia nervosa
      (1) Recurrent episodes of binge eating that occur at least once a week for 3 months
      (2) Recurrent inappropriate compensatory mechanisms to prevent weight gain (e.g., diuretic or laxative use, exercise) or purging (self-induced vomiting)
      (3) Self-evaluation excessively influenced by body shape or weight[5]
3. **Treatment:**
   a. Aimed at nutritional rehabilitation and therapy (family-based or as a component of day treatment programs). Hospitalization may be needed in cases of medical instability. See Chapter 21 for management of refeeding syndrome.
   b. SSRIs indicated in the treatment of bulimia nervosa (see Table 24.2). No medications have been approved for use in anorexia nervosa.[28]

V. PSYCHIATRIC EMERGENCIES

A. Suicide

1. **Epidemiology[29]:** Suicide is the **second** leading cause of death in children and adolescents.
2. **Screening:**
   a. Primary care setting: risk factor screening[30] (Fig. 24.2).
   b. Emergency department setting: the Ask Suicide-Screening Questions (ASQ) (Box 24.1) is validated for identifying pediatric patients at risk for suicide.
3. **Formal suicide assessment** (see Fig. 24.2)
   a. Any positive reply to a screening question warrants formal evaluation by a psychiatrist or other mental health professional.
   b. Goal is to determine disposition (inpatient versus outpatient) and develop a safety plan with caregivers.

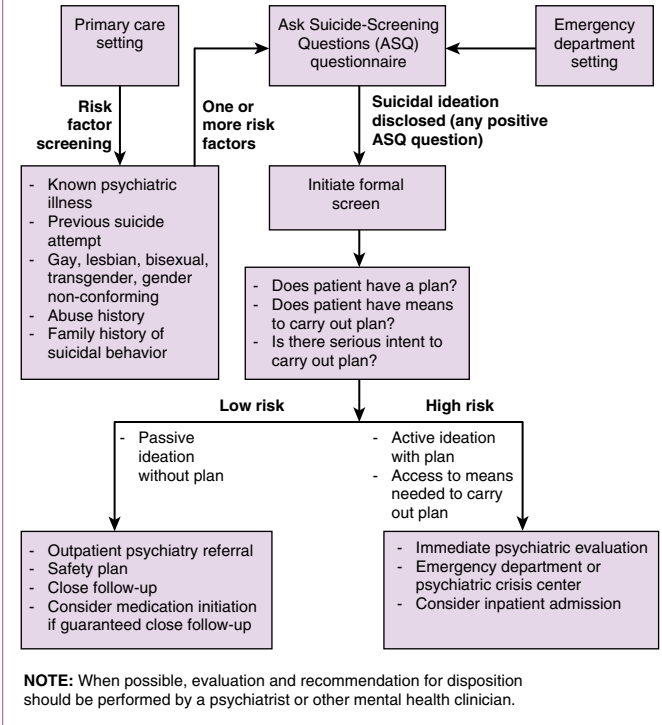

FIGURE 24.2
Suicide screening and assessment.

BOX 24.1

ASK SUICIDE-SCREENING QUESTIONS (ASQ)

Validated for identifying pediatric patients at risk for suicide.

1. In the past few weeks, have you wished you were dead?
2. In the past few weeks, have you felt that you or your family would be better off if you were dead?
3. In the past week, have you been having thoughts about killing yourself?
4. Have you ever tried to kill yourself?

Note: Any affirmative response constitutes a positive screen.

Adapted from the Ask Suicide-Screen Questions (ASQ) Toolkit. National Institute of Mental Health, National Institutes of Health. Available from: http://www.nimh.nih.gov/labs-at-nimh/asq-toolkit-materials/index.shtml

B. Agitation[31,32]

1. **Definition:**
   a. Agitation can be defined as disruptive behavior occurring during periods of emotional distress.
   b. Manifestations include
      (1) Excessive motor activity: pacing, fidgeting
      (2) Verbal aggression: yelling, shouting, rapid uninterruptable speech, threats
      (3) Physical aggression: hitting, throwing things
   c. Agitation frequently occurs as a manifestation of psychiatric illness, but it can also present in behaviorally disordered youth or as a result of organic neurologic disease.
   d. Agitation is a multifactorial symptom. Risk factors for agitation include history of aggression, history of physical abuse, past psychiatric hospitalizations, traumatic brain injury, autism spectrum disorder, delirium, and substance use.
2. **Management** (Fig. 24.3):
   Determine the etiology of agitation:
   a. Review vital signs, presenting history, past diagnoses, past episodes of agitation.
   b. Attempt to rule out underlying medical cause (e.g., ingestion, traumatic brain injury).
3. **Treatment**
   a. Nonpharmacologic
      (1) Low-stimulation environment (e.g., dim lights, move child away from busy areas, avoid unnecessary interventions).
      (2) Communicate in a calm, neutral, empathetic tone at eye level using simple language.
      (3) Utilize distraction techniques and Child Life services if available.
   b. Pharmacologic: therapy choice should target the etiology of agitation (see Fig. 24.3).
   c. Restraints and seclusion: reserved for cases where both nonpharmacologic and pharmacologic interventions fail. Regulations and requirements for use vary by state.
      (1) Close monitoring required.
      (2) Frequent reassessment of necessity of restraints.

VI. WEB RESOURCES

- ADHD Medication Guide: www.adhdmedicationguide.com
- Physicians Med Guide: parentsmedguide.org/physiciansmedguide.htm
- Substance Abuse and Mental Health Services Administration: www.samhsa.gov

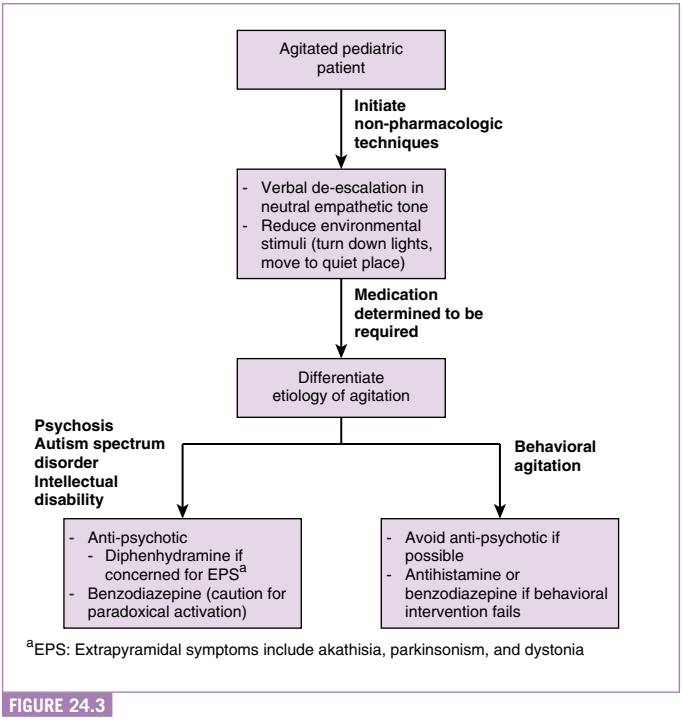

FIGURE 24.3
Agitation management algorithm.

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Chapter 25

Pulmonology and Sleep Medicine

Stephanie Tung, MD, MSc

See additional content on Expert Consult

I. EVALUATION OF PULMONARY GAS EXCHANGE

A. Pulse Oximetry[1-3]

1. Noninvasive and indirect measurement of arterial O_2 saturation (SaO_2) estimated by light absorption characteristics of oxygenated and deoxygenated hemoglobin in peripheral blood.
2. Limitations:
   a. Measures oxygen saturation, not O_2 delivery to tissues.
   b. Insensitive to hyperoxia. See Fig. EC 25.A for oxyhemoglobin dissociation curve.
   c. Artificially increased by carboxyhemoglobin levels >1% to 2%.
   d. Artificially decreased by intravenous dyes, opaque nail polish, and methemoglobin levels >1%.
   e. Unreliable when pulse signal is poor due to hypothermia, hypovolemia, shock, edema, and movement artifact.

B. Capnography[4,5]

1. Measures CO_2 concentration of expired gas by infrared or mass spectroscopy.
2. End-tidal CO_2 ($ETCO_2$) correlates with $PaCO_2$ (usually within 5 mmHg in healthy subjects).
3. Used to evaluate proper placement of an endotracheal tube, to monitor ventilation in mechanically ventilated patients, to assess effectiveness of cardiopulmonary resuscitation (CPR), and during polysomnography.

C. Blood Gases[6-8]

1. Arterial blood gas (ABG): Most accurate way to assess oxygenation (PaO_2), ventilation ($PaCO_2$), and acid-base status (pH and HCO_3^-). See Chapter 28 for normal mean values.
2. Venous blood gas (VBG): $PvCO_2$ averages 6 to 8 mmHg higher than $PaCO_2$; venous pH is slightly lower than arterial pH.
3. Capillary blood gas (CBG): Correlation with ABG is generally best for pH, moderate for PCO_2, and worst for PO_2.

D. Analysis of Acid-Base Disturbances[9-11]

The first step is to determine the primary disturbance (metabolic versus respiratory); the second step is to assess for a mixed disorder by calculating expected compensatory response. See Chapter 11 for details.

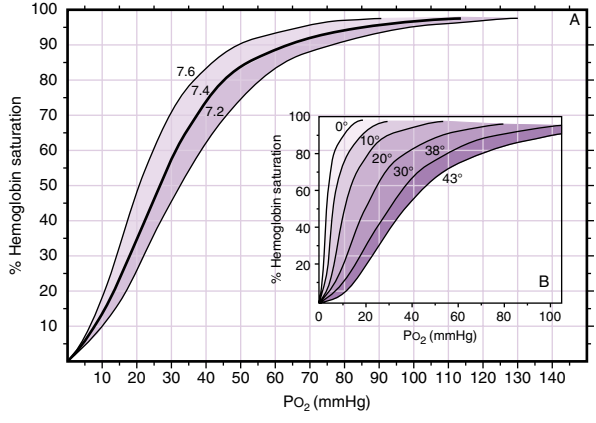


FIG. EC 25.A

Oxyhemoglobin dissociation curve. (A) Curve shifts to the left as pH increases. (B) Curve shifts to the left as temperature decreases. (Modified from Boron, WF. Transport of oxygen and carbon dioxide by the blood. Chapter 29, 647–659.e1. *Medical Physiology*. 4th edition; 2016.)

TABLE 25.1

PREDICTED AVERAGE PEAK EXPIRATORY FLOW RATES FOR NORMAL CHILDREN

Height, Inches (cm)	PEFR, L/min	Height, Inches (cm)	PEFR, L/min
43 (109)	147	56 (142)	320
44 (112)	160	57 (145)	334
45 (114)	173	58 (147)	347
46 (117)	187	59 (150)	360
47 (119)	200	60 (152)	373
48 (122)	214	61 (155)	387
49 (124)	227	62 (157)	400
50 (127)	240	63 (160)	413
51 (130)	254	64 (163)	427
52 (132)	267	65 (165)	440
53 (135)	280	66 (168)	454
54 (137)	293	67 (170)	467
55 (140)	307		

PEFR, Peak expiratory flow rate

Data from Voter KZ. Diagnostic tests of lung function. *Pediatr Rev.* 1996;17:53–63.

II. PULMONARY FUNCTION TESTS (PFT)

Provide objective and reproducible measurements of airway function and lung volumes. Used to characterize disease, assess severity, and follow response to therapy.

A. Peak Expiratory Flow Rate (PEFR)[12,13]

Maximal flow rate generated during a forced expiratory maneuver.

1. Used to follow the course of asthma and response to therapy by comparing current PEFR with the previous "personal best" and the normal predicted value.
2. Limitations: Normal values vary across racial groups, measurement is effort dependent, cannot be used reliably in many young children.
3. Normal predicted PEFR values for children are shown in Table 25.1.

B. Maximal Inspiratory and Expiratory Pressures[14,15]

Maximal pressure generated during inhalation and exhalation against a fixed obstruction. Used as a measure of respiratory muscle strength.

1. Maximal inspiratory pressure (MIP) is in the range of 80 to 120 cm H_2O at all ages. A low MIP may be an indication for ventilatory support.
2. Maximum expiratory pressure (MEP) increases with age and is greater in males. A low MEP correlates with decreased effectiveness of coughing.

C. Spirometry (for Children 6 Years of Age or Above)[16,17]

Plot of airflow versus time during rapid, forceful, complete expiration from total lung capacity (TLC) to residual volume (RV) is useful to characterize different patterns of airway obstruction (Fig. 25.1). Usually performed before and after bronchodilation to assess response to therapy or after bronchial challenge to assess airway hyperreactivity.

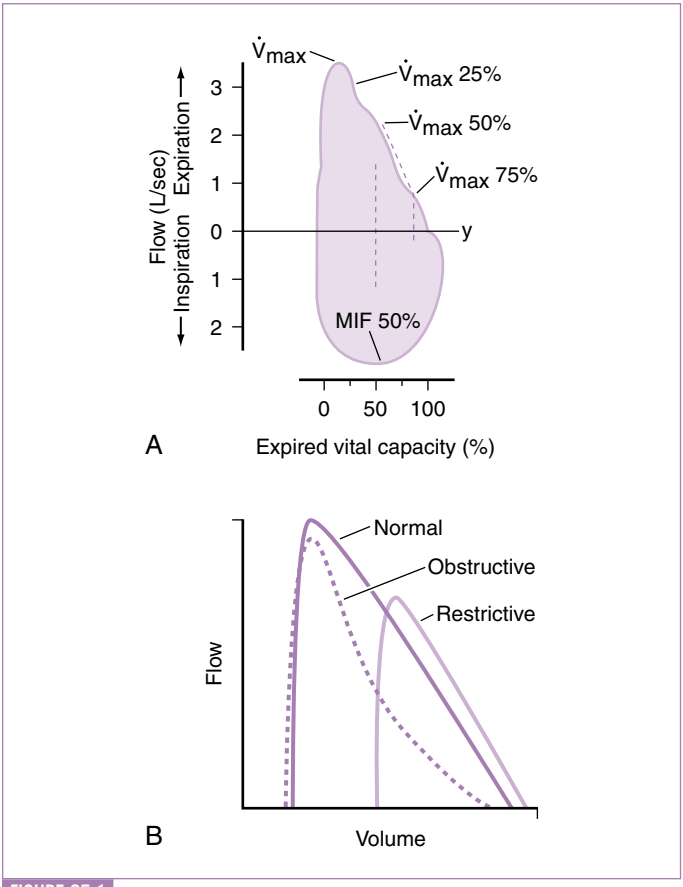


FIGURE 25.1

(A) Normal flow-volume curve. (B) Obstructive pattern seen in asthma or cystic fibrosis; restrictive pattern seen in interstitial lung disease. (B, Data from Baum GL, Wolinsky E. *Textbook of Pulmonary Diseases*. 5th ed. Boston: Little, Brown; 1994.)

1. Important definitions (Fig. 25.2)
   a. Forced vital capacity (FVC): maximal volume of air exhaled from the lungs after a maximal inspiration.
   b. Forced expiratory volume in 1 second (FEV_1): volume exhaled during the first second of the FVC maneuver.
2. Interpretation of spirometry and lung volume readings is shown in Table 25.2.

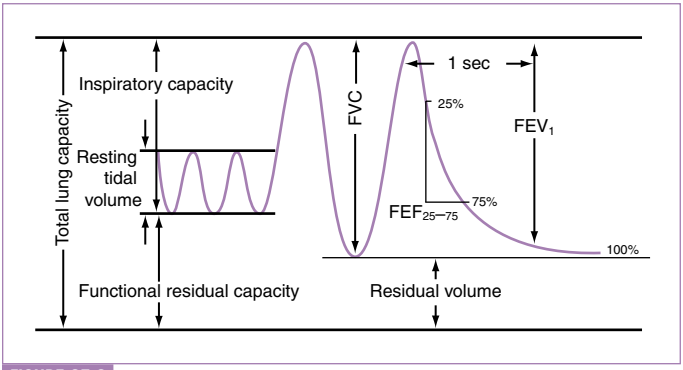


FIGURE 25.2

Lung volumes. $FEF_{25–75}$, Forced expiratory flow between 25% and 75% of FVC; FEV_1, forced expiratory volume in 1 second; *FVC*, forced vital capacity.

TABLE 25.2

INTERPRETATION OF SPIROMETRY AND LUNG VOLUME READINGS

	Obstructive Disease (Asthma, Cystic Fibrosis)	Restrictive Disease (Interstitial Fibrosis, Scoliosis, Neuromuscular Disease)
SPIROMETRY		
FVC[a]	Normal or reduced	Reduced
FEV_1[a]	Reduced	Reduced[b]
FEV_1/FVC[c]	Reduced	Normal
$FEF_{25–75}$	Reduced	Normal or reduced[b]
PEFR[a]	Normal or reduced	Normal or reduced[b]
LUNG VOLUMES		
TLC[a]	Normal or increased	Reduced
RV[a]	Increased	Reduced
RV/TLC[d]	Increased	Unchanged
FRC	Increased	Reduced

[a]Normal range: ±20% of predicted.
[b]Reduced proportional to FVC.
[c]Normal range: >85%.
[d]Normal range: 20 ± 10%.
$FEF_{25–75}$, Forced expiratory flow between 25% and 75% of FVC; FEV_1, forced expiratory volume in 1 second; *FRC*, functional residual capacity; *FVC*, forced vital capacity; *PEFR*, peak expiratory flow rate; *RV*, residual volume; *TLC*, total lung capacity.

III. ASTHMA[12,18]

A. Definition

A chronic inflammatory disorder of the airways resulting in reversible airway obstruction. It manifests as recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early

morning. The inflammation causes increased airway hyperreactivity to a variety of stimuli: viral infections, cold air, exercise, emotions, environmental allergens, and pollutants.

B. Clinical Presentation

1. Cough, increased work of breathing (tachypnea, retractions, accessory muscle use), wheezing, hypoxia, and hypoventilation. Crackles may also be present with asthma exacerbations.
2. No audible wheezing may indicate very poor air movement and severe bronchospasm.
3. Radiographic findings: peribronchial thickening, hyperinflation, patchy atelectasis.

C. Treatment

1. See Chapter 1 for acute management of status asthmaticus.
2. Initial classification and initiation of treatment for ages 0 to 4, 5 to 11, and 12 years and above (Figs. 25.3–25.5).
3. Stepwise approach to continued management for ages 0 to 4, 5 to 11, and 12 years and above (Figs. 25.6–25.8)
4. Additional management guidelines available from the Global Initiative for Asthma.[21]

D. Prevention of Exacerbations

1. Ensure up-to-date immunizations, including influenza.
2. Create an asthma action plan.
3. Identify and minimize asthma triggers and environmental exposures.
4. Assess symptom control, inhaler technique, and medication adherence with regular clinical evaluations.
5. Consider specialist referral for formal PFTs, monitoring, and allergy testing.
6. See Table EC 25.A for dosing guidelines for inhaled corticosteroids.

IV. BRONCHIOLITIS[19-23]

A. Definition

1. Lower respiratory tract infection common in infants and children aged 2 years and younger.
2. Characterized by acute inflammation, edema, and necrosis of airway epithelium, leading to increased mucus production and bronchospasm.
3. Most commonly caused by respiratory syncytial virus (RSV), but can also be seen with other viruses including parainfluenza virus, adenovirus, mycoplasma, and human metapneumovirus.

B. Clinical Presentation

1. Rhinitis and cough, which may progress to tachypnea, wheezing, rales, use of accessory muscles, and/or nasal flaring. Transient apnea may also be seen.
2. Radiographic findings: hyperinflation and atelectasis.
3. Radiographs and viral testing should NOT be routinely obtained.

CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 0–4 YEARS OF AGE

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Components of severity		Classification of asthma severity (0–4 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1–2×/month	3–4×/month	>1×/week
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time. Exacerbations of any severity may occur in patients in any severity category.			
Recommended step for initiating therapy (See Fig. 25.6 for treatment steps.)		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	
		In 2–6 weeks, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternative diagnoses.			

Key: EIB, exercise-induced bronchospasm

Notes

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 months, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 25.3

Guidelines for classifying asthma severity and initiating treatment in infants and young children (aged 0 to 4 years). (Adapted from National Asthma Education and Prevention Program (NAEPP)—Expert Panel Report 3. *Guidelines for the Diagnosis and Management of Asthma*. August 2007.)

CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 5–11 YEARS OF AGE

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Components of severity		Classification of asthma severity (5–11 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2×/month	3–4×/month	>1×/week but not nightly	Often 7×/week
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC >85%	• FEV_1 >80% predicted • FEV_1/FVC >80%	• FEV_1 = 60%–80% predicted • FEV_1/FVC = 75%–80%	• FEV_1 <60% predicted • FEV_1/FVC <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		Consider severity and interval since last exacerbation. ← Frequency and severity may fluctuate over time → for patients in any severity category.			
		Relative annual risk of exacerbations may be related to FEV_1.			
Recommended step for initiating therapy (See Fig. 25.7 for treatment steps.)		Step 1	Step 2	Step 3, medium-dose ICS option	Step 3, medium-dose ICS option, or step 4
				and consider short course of oral systemic corticosteroids	
		In 2–6 weeks, evaluate level of asthma control that is achieved, and adjust therapy accordingly.			

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids

Notes

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 25.4

Guidelines for classifying asthma severity and initiating treatment in children 5 to 11 years of age. (Adapted from National Asthma Education and Prevention Program (NAEPP)—Expert Panel Report 3. *Guidelines for the Diagnosis and Management of Asthma.* August 2007.)

CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN YOUTHS ≥12 YEARS OF AGE

Assessing severity and initiating treatment for patients who are not currently taking long-term control medications

Components of severity		Classification of asthma severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2×/month	3–4×/month	>1×/week but not nightly	Often 7×/week
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1 time on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		Consider severity and interval since last exacerbation. ← Frequency and severity may fluctuate over time → for patients in any severity category.			
		Relative annual risk of exacerbations may be related to FEV_1			
Recommended step for initiating treatment (See Fig. 25.8 for treatment steps.)		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

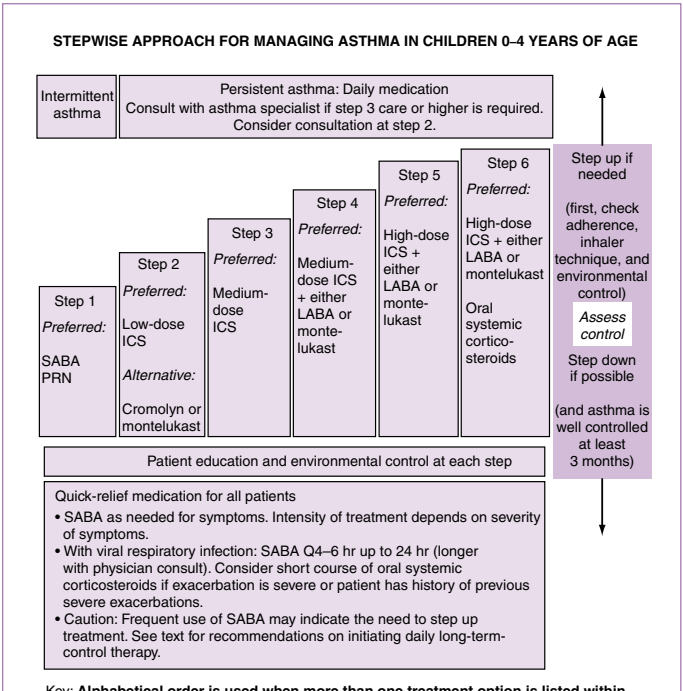
Key: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

Notes

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 25.5

Guidelines for classifying asthma severity and initiating treatment in youths 12 years of age and older. (Adapted from National Asthma Education and Prevention Program (NAEPP)—Expert Panel Report 3. *Guidelines for the Diagnosis and Management of Asthma*. August 2007.)



Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy**. ICS, inhaled corticosteroid; LABA, long-acting inhaled β_2-agonist; PRN, as needed; SABA, short-acting inhaled β_2-agonist

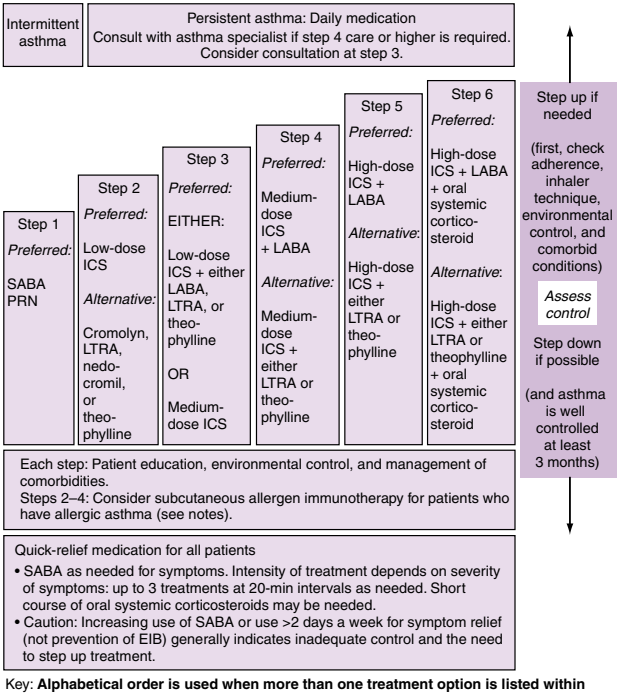
Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4–6 weeks and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children 0–4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.

FIGURE 25.6

Stepwise approach for managing asthma in infants and young children (aged 0 to 4 years). (Adapted from National Asthma Education and Prevention Program (NAEPP)—Expert Panel Report 3. *Guidelines for the Diagnosis and Management of Asthma*. August 2007.)

STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 5–11 YEARS OF AGE



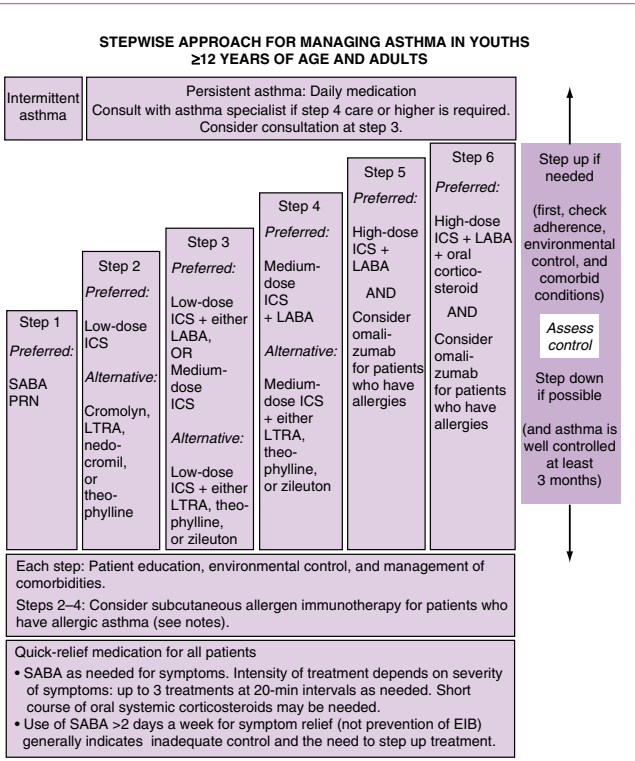
Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy**. ICS, inhaled corticosteroid; LABA, long-acting inhaled β_2-agonist; LTRA, leukotriene receptor antagonist; PRN, as needed; SABA, short-acting inhaled β_2-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
- Step 1 and step 2 medications are based on Evidence A. Step 3 ICS + adjunctive therapy and ICS are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; steps 4–6 are based on expert opinion and extrapolation from studies in older children and adults.
- Immunotherapy for steps 2–4 is based on Evidence B for house dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

FIGURE 25.7

Stepwise approach for managing asthma in children 5 to 11 years of age. (Adapted from National Asthma Education and Prevention Program (NAEPP)—Expert Panel Report 3. *Guidelines for the Diagnosis and Management of Asthma.* August 2007.)



Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, long-acting inhaled β_2-agonist; LTRA, leukotriene receptor antagonist; PRN, as needed; SABA, short-acting inhaled β_2-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Zileuton is a less-desirable alternative as adjunctive therapy due to limited studies and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.
- In step 6, before oral systemic corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.
- Step 1, 2, and 3 preferred therapies are based on Evidence A; step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. Step 4 preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and theophylline and Evidence D for zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on Expert Panel Report 2 (1997) and Evidence B for omalizumab.
- Immunotherapy for steps 2–4 is based on Evidence B for house dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

FIGURE 25.8

Stepwise approach for managing asthma in youths 12 years of age and older. (Adapted from National Asthma Education and Prevention Program (NAEPP)—Expert Panel Report 3. *Guidelines for the Diagnosis and Management of Asthma.* August 2007.)

TABLE EC 25.A

ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS

ICS	Strength	<12 Years Old			≥12 Years Old		
		Low Dose	Medium Dose	High Dose	Low Dose	Medium Dose	High Dose
Beclomethasone/ QVar MDI	40 mCg	2–4 puffs/day	5–8 puffs/day	>8 puffs/day	2–6 puffs/day	7–12 puffs/day	>12 puffs/day
	80 mCg	1–2 puffs/day	3–4 puffs/day	>4 puffs/day	1–3 puffs/day	3–6 puffs/day	>6 puffs/day
Budesonide/ Pulmicort DPI Flexhaler	90 mCg	2–4 puffs/day	4–8 puffs/day	>8 puffs/day	2–6 puffs/day	7–12 puffs/day	>12 puffs/day
	180 mCg	1–2 puffs/day	2–4 puffs/day	>4 puffs/day	1–3 puffs/day	4–6 puffs/day	>6 puffs/day
Ciclesonide	80 mCg	*See Formulary remarks for ciclesonide*			1 puff BID	2 puffs BID	4 puffs BID
	160 mCg	*See Formulary remarks for ciclesonide*			N/A	1 puff BID	2 puffs BID
Budesonide/ Pulmicort Respule	0.25 mg neb	2 nebs/day	4 nebs/day	8 nebs/day	N/A	N/A	N/A
	0.5 mg neb	1 neb/day	2 nebs/day	4 nebs/day	N/A	N/A	N/A
Flunisolide/Aerospan MDI	80 mCg	2 puffs/day	4 puffs/day	>8 puffs/day	4 puffs/day	5–8 puffs/day	>8 puffs/day
	250 mCg	2–3 puffs/day	4–5 puffs/day	>5 puffs/day	2–4 puffs/day	5–8 puffs/day	>8 puffs/day
Fluticasone/Flovent MDI	44 mCg	2–4 puffs/day	5–8 puffs/day	>8 puffs/day	2–6 puffs/day	7–10 puffs/day	>10 puffs/day
	110 mCg	1 puff/day	2–3 puffs/day	>3 puffs/day	1–2 puffs/day	3–4 puffs/day	>4 puffs/day
	220 mCg	N/A	1 puff/day	>1 puff/day	1 puff/day	2 puffs/day	>2 puffs/day
Fluticasone/Flovent Diskus DPI	50 mCg	2–4 puffs/day	5–8 puffs/day	>8 puffs/day	2–6 puffs/day	7–10 puffs/day	>10 puffs/day
	100 mCg	1–2 puffs/day	2–4 puffs/day	>4 puffs/day	1–3 puffs/day	4–5 puffs/day	>5 puffs/day
	250 mCg	N/A	1 puff/day	>1 puff/day	1 puff/day	2 puffs/day	>2 puffs/day
Mometasone/ Asmanex Twisthaler	220 mCg	N/A	N/A	N/A	1 puff	2 puffs	>2 puffs

TABLE EC 25.A

ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS—cont'd

ICS	Strength	<12 Years Old			≥12 Years Old		
		Low Dose	Medium Dose	High Dose	Low Dose	Medium Dose	High Dose
COMBINATION DRUGS: ICS + LABA[a]							
Fluticasone/ Salmeterol MDI (Advair)	45/21 mCg	2 puffs/day	2–3 puffs/day	4 puffs/day	2 puffs/day	3–4 puffs/day	
	115/21 mCg		2 puffs/day	2–4 puffs/day	2 puffs/day	2 puffs/day	3–4 puffs/day
	230/21 mCg			2–4 puffs/day			3–4 puffs/day
Fluticasone/ Salmeterol Diskus DPI (Advair)	100/50 mCg	1 puff/day	2 puffs/day	2 puffs/day		2 puffs/day	
	250/50 mCg			2 puffs/day		1 puff/day	2 puffs/day
	500/50 mCg			2 puffs/day			2 puffs/day
Budesonide/ Formoterol MDI (Symbicort)	80/4.5 mCg	1–2 puffs/day	2–4 puffs/day		1–3 puffs/day	4 puffs/day	
	160/4.5 mCg		1–2 puffs/day	2–4 puffs/day		2 puffs/day	4 puffs/day
Mometasone/ Formoterol (Dulera)	100/5 mCg	*No dosing information currently available for patients above 12 years of age*			N/A	2 puffs BID	N/A
	200/5 mCg	*No dosing information currently available for patients below 12 years of age*			N/A	N/A	2 puffs BID

[a]For ICS + LABA combination drugs, patient should not take more than two puffs per dose of the MDI, one puff per dose of the DPI, or two doses per day.

DPI, dry powder inhaler; *ICS*, inhaled corticosteroid; *LABA*, long-acting β agonist; *MDI*, metered-dose inhaler

Data from Expert Panel Report III. *Guidelines for the Diagnosis and Management of Asthma—Full Report 2007*; National Institutes of Health Pub. No. 08-4051. Bethesda, MD: National Asthma Education and Prevention Program; 2007.

C. Treatment

Mainstay is supportive care.

1. Assess risk factors for severe disease, such as age less than 12 weeks, a history of prematurity, underlying cardiopulmonary disease, or immunodeficiency.
2. Clinicians should NOT administer albuterol, epinephrine, systemic corticosteroids, or chest physiotherapy to previously healthy infants and children with a diagnosis of bronchiolitis. Antibiotics should be administered only for concomitant bacterial infection.
3. Nebulized hypertonic saline may be administered to hospitalized infants and children, although evidence of effectiveness is mixed.[20-22]
4. Evidence supporting continuous pulse oximetry and supplemental O_2 when SpO_2 is greater than 90% is currently lacking.
5. Nasogastric or intravenous fluid is necessary when infant is unable to maintain oral hydration.
6. High-flow nasal cannula supports breathing in infants requiring supplemental oxygen and may decrease the rate of escalation of care.[23]
7. RSV immunoprophylaxis with palivizumab for high-risk infants (see Chapter 16).

V. BRONCHOPULMONARY DYSPLASIA (BPD)[24-27]

A. Definition

1. Also known as chronic lung disease of prematurity or chronic lung disease of infancy.
2. Chronic pulmonary condition that usually evolves after premature birth, characterized by a need for oxygen supplementation >21% for at least 28 days after birth.
3. Thought to be a result of airway inflammation, damage from hyperoxia, hypoxia, or mechanical ventilation; results in interference with normal lung alveolar, airway, and vascular development.
4. Earlier gestational age in preterm infants is associated with a higher likelihood of BPD development.

B. Clinical Presentation

Children with BPD may have persistent respiratory symptoms, airway hyperreactivity, and supplemental oxygen requirements, especially during intercurrent illness.

C. Diagnosis

Severity based on oxygen requirement at time of assessment and characterized as mild if on room air, moderate if requiring <30% oxygen or severe if requiring >30% oxygen and/or positive pressure.

1. If gestational age at birth was <32 weeks, assess infant at 36 weeks' postmenstrual age or at discharge to home, whichever comes first.
2. If gestational age at birth >32 weeks, assess infant at 28 to 56 days postnatal age or at discharge to home, whichever comes first.

D. Treatment

1. Children with BPD often require some combination of the following for their lung disease:
   a. Bronchodilators
   b. Antiinflammatory agents (corticosteroids)
   c. Supplemental oxygen therapy
   d. Diuretics
   e. Tracheostomy and prolonged mechanical ventilation for severe cases
   f. RSV prophylaxis if indicated (see Chapter 16)
2. Children with BPD need close monitoring for complications, which can affect additional organ systems and processes, including pulmonary or systemic hypertension, electrolyte abnormalities, nephrocalcinosis (from chronic diuretics), neurodevelopmental or growth delay, aspiration from dysphagia and/or gastroesophageal reflux (GER), and more severe infections with RSV or influenza.

VI. CYSTIC FIBROSIS[28-37]

A. Definition

Autosomal recessive disorder in which mutations of the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene reduce the function of a chloride channel that usually resides on the surface of epithelial cells in the airways, pancreatic ducts, biliary tree, intestine, vas deferens, and sweat glands, resulting in progressive obstructive pulmonary disease and pancreatic exocrine insufficiency.

B. Clinical Manifestations (Fig. 25.9)

C. Diagnosis

Diagnosing CF is a multistep process (Fig. 25.10); a complete evaluation involves the following:

1. Newborn screening (NBS): utilizes blood immunoreactive trypsinogen (IRT) level and/or *CFTR* gene mutation analysis.
2. Quantitative pilocarpine iontophoresis (sweat chloride) test: gold standard for diagnosis. False-positive results can be seen in untreated adrenal insufficiency, glycogen storage disease type 1, fucosidosis, hypothyroidism, nephrogenic diabetes insipidus, ectodermal dysplasia, malnutrition, mucopolysaccharidosis, and panhypopituitarism.
3. Genetic analysis: over 2000 *CFTR* mutations have been described; the most common is F508del.

D. Treatment

Patients with CF should be managed within a CF Foundation accredited care center.

1. **Pulmonary**
   a. Airway clearance therapy to mobilize airway secretions and facilitate expectoration. Often manual/mechanical percussion and postural drainage is used. Older children may use high-frequency vest therapy, mechanical chest percussors, or oscillatory positive expiratory pressure (PEP) handheld devices.

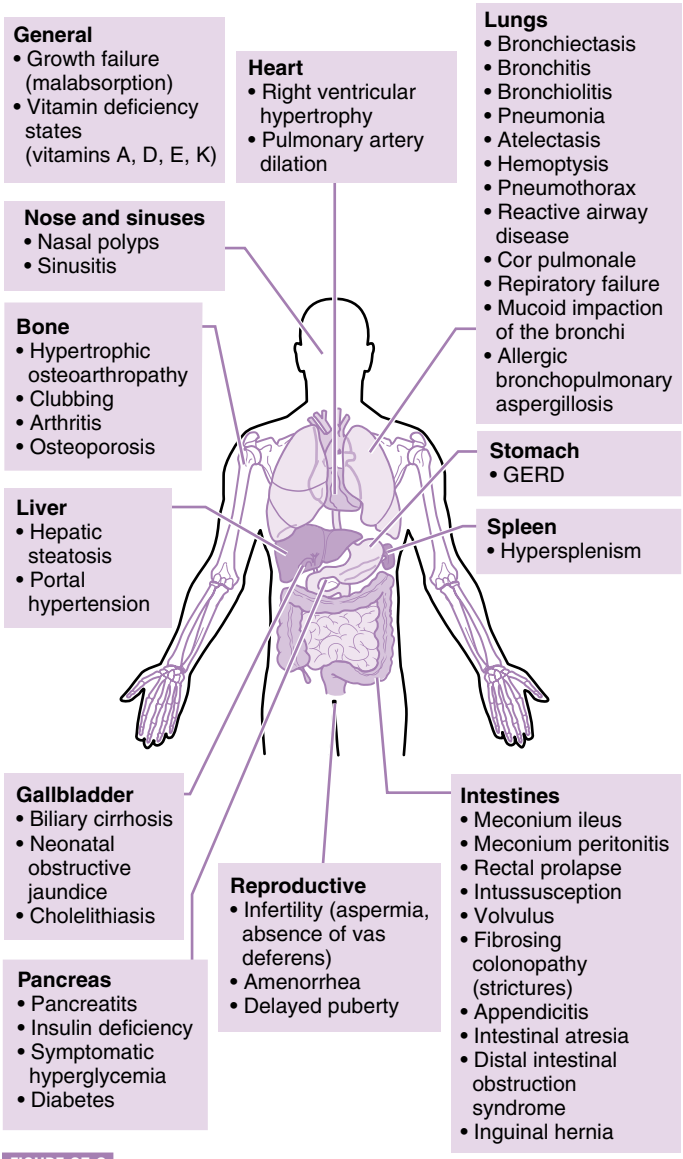


FIGURE 25.9

Clinical manifestations of cystic fibrosis. (Adapted from Kliegman R., Kliegman RM. *Nelson Essentials of Pediatrics.* St. Louis: Elsevier Saunders; 2019.)

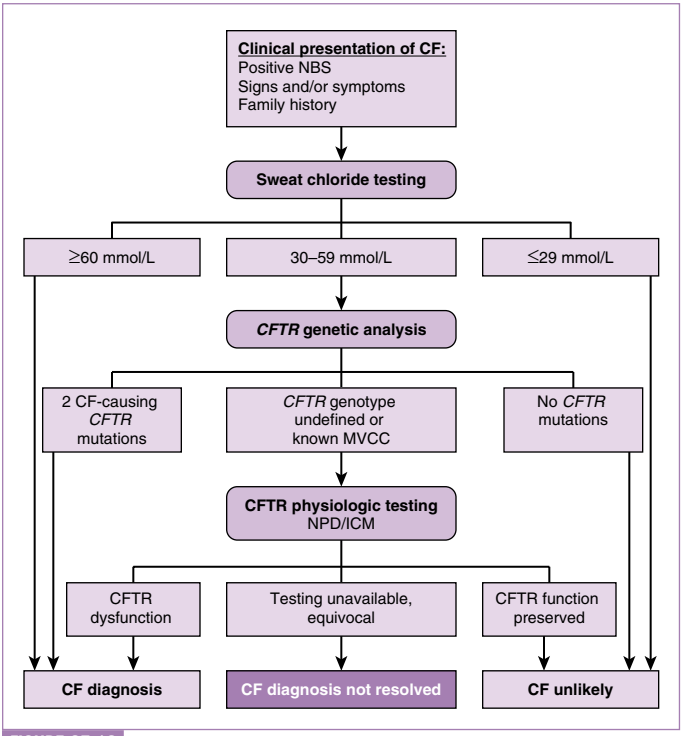


FIGURE 25.10

Diagnosis of cystic fibrosis. *CF,* Cystic fibrosis; *CFTR,* cystic fibrosis transmembrane conductance regulator; *ICM,* intestinal current measurement; *MVCC,* mutation of varying clinical consequence; *NBS,* newborn screen; *NPD,* nasal potential difference (Adapted from Farrell DW, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. *J Pediatr.* 2017;181S:S4–S15.e1. https://doi.org/10.1016/j.jpeds.2016.09.064, Figure 1.)

b. Aerosolized medications to enhance mucociliary clearance: Recombinant human DNAase (dornase alfa) and aerosolized hypertonic saline to hydrate airway mucus and stimulate cough.
c. Chronic antibiotics. If *Pseudomonas aeruginosa* is persistently present in airway cultures, chronic aerosolized antibiotic and/or oral macrolide therapy may be considered.
d. Intermittent use of intravenous antibiotics when patient is hospitalized for exacerbations. Common bacteria that cause exacerbations include *P. aeruginosa* and *Staphylococcus aureus.* There is no current consensus regarding antibiotic choice, dosing, or duration.

e. *CFTR* modulator therapy may be effective for patients with specific mutations (G551D, F508del/F508del). Can be used in combination. See Formulary for dosing.
f. Allergic bronchopulmonary aspergillosis (ABPA) treatment may include oral corticosteroids; antifungal therapy can be a helpful adjunct therapy.
g. Lung transplantation.

2. **Extrapulmonary**
   a. Pancreatic and liver disease
      (1) Pancreatic enzyme replacement therapy prior to meals to improve digestion and intestinal absorption of dietary protein and fat.
      (2) Fat-soluble vitamin A, D, E, and K supplementation.
      (3) Nutritional supplementation to maintain body mass index (BMI) at or above the 50th percentile.
      (4) Monitoring for CF-related diabetes or liver disease.
   b. Infertility
      (1) Men have absence of the vas deferens; however, assisted fertilization is possible using aspiration of viable sperm from testes.
      (2) Women who are healthy have relatively normal fertility.
   c. Decreased life expectancy. Survival continues to improve, and median predicted survival age is more than 47 years.[37]

VII. OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS)[38-42]

A. Definition

Disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction that disrupts normal ventilation during sleep and normal sleep patterns.

B. Clinical Presentation

1. Habitual snoring sometimes accompanied by snorts, gasps, or intermittent pauses in breathing. Increased respiratory effort during sleep.
2. Disturbed or restless sleep with increased arousals and awakenings.
3. Daytime cognitive and/or behavioral problems. Young children rarely present with daytime sleepiness.
4. Long-term complications: neurocognitive impairment, behavioral problems, poor growth, cardiac dysfunction, systemic and pulmonary hypertension.
5. Risk factors: adenotonsillar hypertrophy, obesity, family history of OSAS, craniofacial or laryngeal anomalies, prematurity, nasal/pharyngeal inflammation, cerebral palsy, and neuromuscular disease.

C. Diagnosis

1. All children and adolescents should be routinely screened for snoring.
2. If a child snores on a regular basis and has any of the complaints or findings shown in Box 25.1, clinicians should obtain a polysomnogram or, if polysomnography is not available, refer the patient to a sleep specialist or otolaryngologist for more extensive evaluation.

BOX 25.1

SYMPTOMS AND SIGNS OF OBSTRUCTIVE SLEEP APNEA SYNDROME

I. History

- Frequent snoring (≥3 nights a week)
- Labored breathing during sleep
- Gasping/snorting noises or observed episodes of apnea
- Sleep enuresis (especially secondary enuresis)
- Sleeping in a seated position or with the neck hyperextended
- Cyanosis
- Headache on awakening
- Daytime sleepiness
- Attention-deficit/hyperactivity disorder
- Learning problems

II. Physical examination

- Underweight or overweight
- Tonsillar hypertrophy
- Adenoidal facies
- Micrognathia/retrognathia
- High-arched palate
- Failure to thrive
- Hypertension

Adapted from Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2012;130:575–584.

3. Polysomnogrpaphy criteria for OSAS diagnosis (one of the following):
   a. One or more obstructive or mixed apnea or hypopnea events per hour (AHI ≥1).
   b. $PaCO_2$ >50 mmHg for >25% of sleep time coupled with snoring, paradoxical thoracoabdominal movement, or flattening of nasal airway pressure waveform implying flow limitation.
4. No standard severity classification. Commonly used: mild (1< AHI ≤5), moderate (5< AHI ≤10), and severe (AHI >10).

D. Treatment

1. Weight loss for patients who are overweight or obese.
2. Intranasal corticosteroids may be considered for children with mild OSAS.[38] Follow-up is needed to assess symptoms and monitor possible adverse effects of long-term intranasal steroids. Oral leukotriene inhibitor (e.g., montelukast) can also be considered.
3. Adenotonsillectomy is recommended as first-line treatment of patients with OSAS documented with an overnight polysomnogram.[42] Patients should be reevaluated postoperatively to determine whether further treatment is required.
   a. Risk factors for postoperative respiratory complications: age <3 years, severe OSAS on polysomnography (AHI ≥10, lowest oxygen

saturation <80%, and/or significant hypercapnia), cardiac complications of OSAS, failure to thrive, obesity, craniofacial anomalies, neuromuscular disorders, current respiratory infection.
   b. High-risk children warrant a more comprehensive evaluation and postoperative admission for monitoring.
4. Continuous positive airway pressure is recommended as treatment if adenotonsillectomy is not performed or if OSAS persists postoperatively.
5. Craniofacial surgery and tracheostomy are reserved for severe cases in children with syndromic craniofacial abnormalities.

VIII. INFANT AND CHILD SLEEP[43-46]

A. Sleep Duration

1. Recommended average sleep duration varies by age (Table 25.3).
2. Sleep concerns are common in childhood. Inadequate or poor-quality sleep can have negative impacts on health, behavior, and learning.
3. See Section XI for a discussion of common childhood sleep disorders.

TABLE 25.3

RECOMMENDED AVERAGE SLEEP DURATION

Age Group	Duration of Sleep (per 24 hr)
Infants (4–12 months)	12–16 hr[a]
Toddlers (1–2 years)	11–14 hr[a]
Preschool-age children (3–5 years)	10–13 hr[a]
School-age children (6–12 years)	9–12 hr
Teenagers (13–18 years)	8–10 hr

[a]Recommended sleep duration in 24-hour period includes naps. Adapted from Paruthi S, Brooks LJ, D'Ambrosio C, et al. Recommended amount of sleep for pediatric populations: a consensus statement of the American Academy of Sleep Medicine. *J Clin Sleep Med.* 2016;12(6):785–786.

B. Sleep-Related Infant Death

1. **Definition**
   a. Sleep-related infant death: sudden unexplained infant death occurring during an observed or unobserved sleep period.
   b. Sudden infant death syndrome (SIDS): cause assigned to infant death that cannot be explained after thorough case investigation.
2. **Epidemiology**
   a. Approximately 40 per 100,000 live births in 2013, more than double in African American and Native American populations.
   b. Peak incidence is at 1 to 4 months, with 90% occurring before 6 months.

3. **Safe Infant Sleep**

Evidence-based safe infant sleep recommendations to reduce the risk of sleep-related infant death from the 2016 AAP guidelines include the following[46]:

a. Back to sleep during every episode of sleep.
b. Using a firm sleep surface without soft objects or loose bedding.
c. Room sharing with the infant on a separate surface, ideally for the first year of life, but at least for the first 6 months.
d. Avoidance of overheating and head covering.
e. Avoidance of alcohol, illicit drugs, and smoke exposure during pregnancy and after birth.
f. Protective factors that should be recommended: Regular prenatal care, breastfeeding, routine immunizations.
g. Modeling of safe sleep by healthcare providers/staff, day care providers, and in advertising.

IX. BRIEF RESOLVED UNEXPLAINED EVENT (BRUE)[47,48]

A. Definition

Formerly termed an *apparent life-threatening event* (ALTE), a BRUE is defined as an event involving an infant below 1 year of age when the observer reports a sudden, brief (typically 20 to 30 seconds) and now resolved episode of at least one of the following:

1. Cyanosis or pallor
2. Absent, decreased, or irregular breathing
3. Marked change in muscle tone (hyper- or hypotonia)
4. Altered level of responsiveness

B. Differential Diagnosis

The three most common differential diagnoses are GER, seizure, and lower respiratory tract infection. If an explanation for the event is identified, then it is not a BRUE.

C. Management

An algorithm for the diagnosis, risk stratification, and management of BRUE patients is provided in Fig. 25.11.

X. WEB RESOURCES

- American Lung Association: www.lung.org
- Cystic Fibrosis Foundation: www.cff.org
- American Academy of Allergy, Asthma and Immunology: www.aaaai.org
- National Heart Lung and Blood Institute: www.nhlbi.nih.gov
- American Thoracic Society: www.thoracic.org
- American Academy of Sleep Medicine: www.aasm.org

REFERENCES

A complete list of references can be found online at www.expertconsult.com.

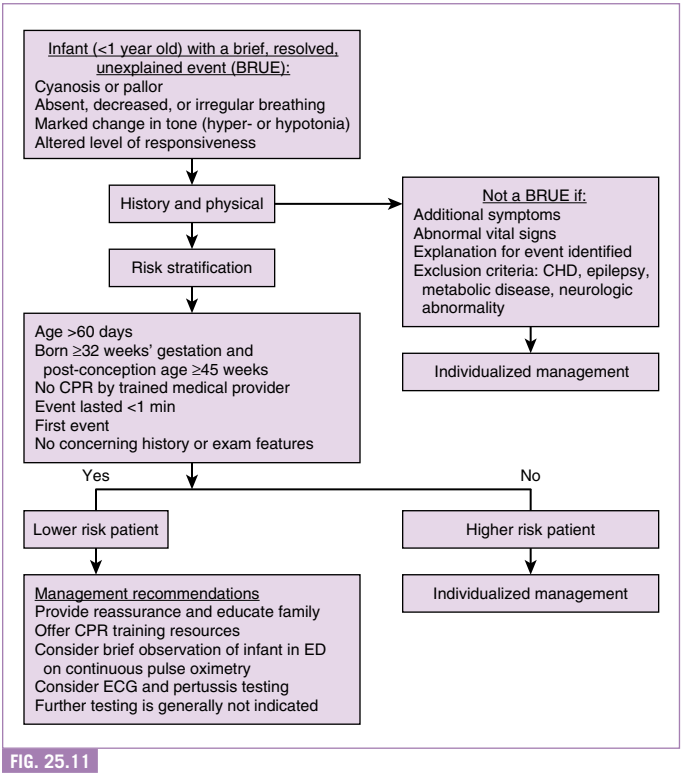


FIG. 25.11

Algorithm for diagnosis, risk stratification, and management of BRUE. *CHD,* Congenital heart disease; *CPR,* cardiopulmonary resuscitation; *ECG,* electrocardiogram; *ED,* emergency department (Adapted from *AAP Clinical Practice Guideline: Brief Resolved Unexplained Events (Formerly Apparent Life-Threatening Events) and Evaluation of Lower-Risk Infants*. May 2016.)

XI. ONLINE CONTENT

A. Evaluation of Pulmonary Gas Exchange

Oxyhemoglobin dissociation curve (see Fig. EC 25.A)

B. Asthma

Dosing of inhaled corticosteroids (see Table EC 25.A)

C. Childhood Sleep Disorders[44,45]

1. **Insomnia**
   a. Difficulty falling asleep, staying asleep, or both.
   b. In younger children, the common behavioral insomnias of childhood include limit-setting (bedtime resistance) and sleep-onset association disorder (night wakings). Treatment includes bedtime limits and appropriate sleep hygiene.
   c. In older children, psychosocial or primary insomnia is characterized by excessive worry about sleep and the consequences of inadequate sleep. Managed with behavioral interventions.
   d. Insomnia can be secondary to another sleep or medical disorder. A comprehensive evaluation is required. Referral to a sleep specialist or behavioral psychologist may be useful.
2. **Nighttime fears**
   a. Common condition that is part of normal development and stems from cognitive development.
   b. Characterized by tearful, fearful behavior at bedtime.
   c. Relieved by sleeping with member of household.
   d. Treatment involves reassurance, teaching coping skills, and use of security objects. Consider evaluation for anxiety disorder in older children/adolescents.
3. **Nightmares**
   a. Frightening dreams that result in awakening from sleep.
   b. Part of normal development.
   c. Peak at age 6 to 10 years.
   d. May be reduced by reducing stressors, avoiding exposure to frightening images, and ensuring adequate sleep.
4. **Delayed sleep phase syndrome**
   a. A circadian rhythm with a persistent, intractable shift in the sleep-wake cycle. Patients move to a late bedtime and late awakening.
   b. Seen most commonly in adolescent and young adults.
   c. Patients have daytime sleepiness and tardiness/absenteeism when unable to sleep during the day.
   d. Treatment includes behavioral therapy, bright light exposure, and melatonin. Consider evaluation by a sleep specialist.
5. **Parasomnias**
   a. Common and benign disorders of arousal.
   b. Includes sleepwalking, night terrors, and confusional arousals.
   c. Onset typically at age 4 to 6 years and usually disappear by adolescence.

d. Characterized by agitation and confusion. Child avoids comfort and does not recall event.
e. Usually occur in the first few hours of the night.
f. Treatment involves keeping child safe, ensuring adequate sleep, and avoiding triggers. Discourage parental intervention during an episode.

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Chapter 26

Radiology

Brittany Hunter, MD

See additional content on Expert Consult

I. GENERAL PEDIATRIC PRINCIPLES

A. Limit Radiation Exposure

1. Children are at increased radiation risk given their greater lifetime exposure, relatively small size, increased radiosensitivity, and longer lives during which to manifest side effects.[1]
2. Use evidence-based imaging guidelines to guide appropriate imaging choice and minimize radiation exposure.[1]
3. See Table 26.1 for relative radiation by imaging study.

B. Use Imaging Judiciously

1. Minimize use of ionizing radiation when possible.
2. Limit imaging to indicated areas to improve resolution and minimize radiation exposure.
3. Provide adequate clinical background when ordering imaging studies to assist radiologist.

II. CHOOSING THE RIGHT STUDY

1. See Table 26.2 for descriptions of imaging modalities.
2. Computed tomography (CT) versus magnetic resonance imaging (MRI): CT is often more readily available, can be performed quickly, and does not require sedation; however, CT raises safety concerns regarding radiation exposure. MRI uses nonionizing radiation and may require sedation.[1]
3. Contrast: Helps distinguish selected body areas from surrounding tissue. Oral and rectal contrast is used for bowel opacification. Intravenous is used to opacify vascular structures and solid organs.

III. HEAD

Head ultrasound (HUS) can be used for infants with open anterior fontanelles. **CT** is preferred for acute situations (e.g., trauma, hemorrhage) and for evaluating bone structure or calcifications. **MRI** offers better soft-tissue contrast and visualization of brain anatomy and is, therefore, preferred for most nontraumatic intracranial pathology. **MRI fast sequences** (such as ultrafast [UF] MRI) uses specialized sequencing to assess ventricular size and shunt position without requiring sedation. Does not allow for adequate delineation and diagnosis of other brain pathology.[1]

TABLE 26.1

COMPARATIVE RADIATION EXPOSURE

Radiation Source	mSv[17]	Equivalent Chest X-rays	Equivalent Flight Hours[18]	Equivalent Background Radiation
CXR (single view)	0.01	1	3	1 day
Abdominal XR (2 views)	0.05	5	17	5 days
Chest CT	3	300	1000	12 months
Head CT	2	200	670	8 months
Abdominal CT	5	500	1670	20 months
Upper GI series	3	300	1000	12 months
Contrast enema	4.5	450	1500	18 months

CT, Computed tomography; *CXR*, chest x-ray; *GI*, gastrointestinal.

A. Head Trauma

1. **Preferred imaging**: Noncontrast head CT. Use the Pediatric Emergency Care Applied Research Network (PECARN) rules to decide whether imaging is indicated (see Chapter 2).[2,3]

B. CSF Shunt Malfunction

1. **Preferred imaging:** Ultrafast brain MRI (UF MRI).
2. **Other imaging:** CT if UF MRI is not available or contraindicated. Shunt series (plain radiographs evaluating shunt tubing) are useful.

C. Orbital Cellulitis

1. **Preferred imaging**: Orbital contrast-enhanced CT (Fig. EC 26.A).[4]

IV. NECK AND AIRWAY

Conventional radiography (CR) anteroposterior (AP) and lateral neck views are preferred initial imaging.[5,6]

A. Normal Anatomy

1. Normal anatomy (Figs. 26.1 and 26.2).
2. Reading lateral C-spine films.
   a. Must visualize skull base, C1 to C7, top of T1.
   b. Assess alignment by evaluating four curvilinear contour lines: anterior vertebral, posterior vertebral, spinolaminar, tips of spinous process (Fig. 26.3).
   c. Evaluate vertebral bodies for fractures, displacement, subluxation, dislocations. Vertebral bodies should be same height and uniformity below C2.
   d. Evaluate predental and prevertebral spaces for widening.

B. Cervical Spine Trauma

1. **Initial imaging:** CR, lateral and AP.
2. **Other imaging:** MRI if high clinical suspicion of C-spine injury without CR findings.

TABLE 26.2

OVERVIEW OF IMAGING MODALITIES

Modality/Description	Ionizing Radiation	Advantages	Disadvantages/ Limitations	Relative Cost
Conventional radiographs (CR) Uses x-rays to create 2D images based on density	Yes	Fast, portable, readily available	2D only, poor soft-tissue contrast	+
Ultrasound (US) Uses high-frequency sound waves to produce image, can evaluate blood flow with Doppler or contrast	No	Portable, real-time imaging, multiplanar	Operator dependent, limited in obese patients, poor penetration of air-filled viscera and bone, may require preparation (e.g., fasting or full bladder), may be invasive (e.g., transvaginal)	++
Computed tomography (CT) Uses multiple x-rays to produce cross-sectional image, delineates bones, soft tissue, calcifications	Yes	Fast, cross sectional, more detailed than CR	Intermediate to high radiation dose, potential side effects from intravenous contrast if used (anaphylaxis, nephrotoxicity)	+++
Magnetic resonance imaging (MRI) Uses magnetic fields and radio waves to show detailed cross-sectional images	No	High resolution of soft tissue, multiplanar	Lengthy, slight movements can ruin image, may require sedation, contraindicated for certain implantable devices	++++
Fluoroscopy Uses x-rays and contrast to evaluate dynamic processes	Yes	Real-time imaging	Invasive, requires contrast, high radiation dose	++
Nuclear medicine (commonly PET, Meckel scan, SPECT) Uses radioactive tracer to delineate patterns of concentration or elimination of tracer, can be superimposed with MRI or CT	Yes	Functional	Intermediate to high radiation dose, may require sedation	++++

2D, two dimensional; *PET*, positron emission tomography; *SPECT*, single photon emission computed tomography

Modified from Zitelli and Davis' *Atlas of Pediatric Physical Diagnosis*. 7th ed. Philadelphia: Saunders; 2018.

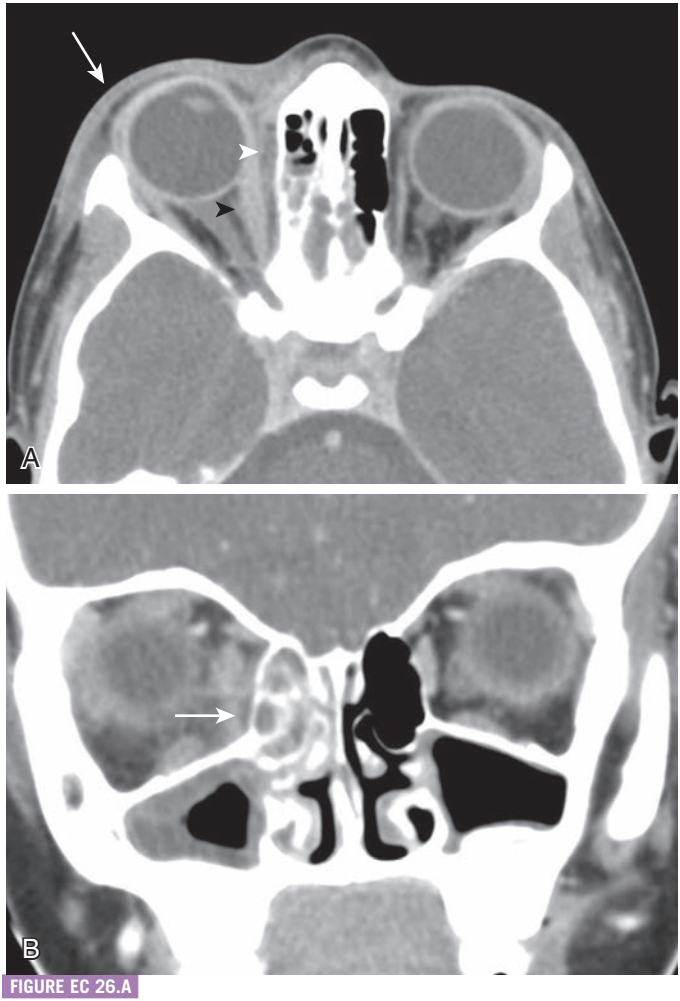

FIGURE EC 26.A

Preseptal and postseptal cellulitis. (A) Axial contrast-enhanced computed tomography (CT) of orbits shows asymmetric thickening of the right preseptal soft tissues *(arrow)*. There is also involvement of the medial extraconal postseptal soft tissues *(white arrowhead)*. The medial rectus muscle is enlarged *(black arrowhead)* due to reactive myositis. Note partial ethmoid sinus opacification. (B) Coronal contrast-enhanced CT of a different patient also showing right medial postseptal cellulitis with a small subperiosteal collection representing an early abscess *(arrow)*. Note again ethmoid sinusitis as the cause of orbital cellulitis. (From Donnelly, LF. *Fundamentals of Pediatric Imaging*. 2nd ed. Philadelphia: Elsevier; 2017, p. 308, Fig. 8.95.)

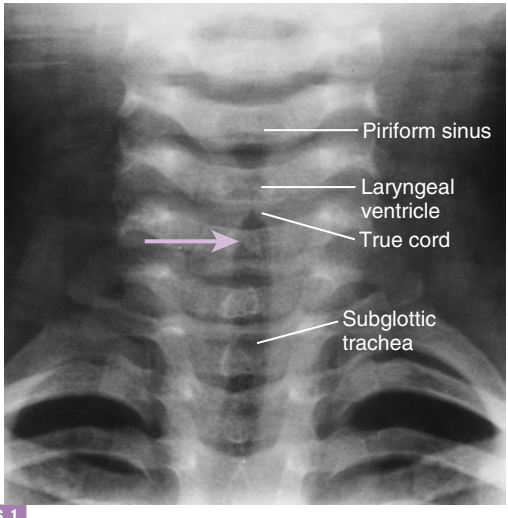

FIGURE 26.1
Anteroposterior neck film with normal anatomy. Note subglottic airway demonstrates rounded shoulders *(arrow)* that are convex outward. (Figure modified from Blickman JG, Van Die L. *Pediatric Radiology: The Requisites*. 3rd ed. Philadelphia: Elsevier; 2009, Fig. 2.17B.)

C. Classic Findings of Upper Airway Conditions on Conventional Radiographs

1. Croup: AP and lateral radiographs with subglottic narrowing (*steeple sign)* (Fig. EC 26.B).
2. Epiglottitis: Enlarged, indistinct epiglottis on lateral film (*thumbprint sign*).
3. Retropharyngeal abscess or pharyngeal mass: Soft-tissue air or enlargement of prevertebral soft tissues (Fig. EC 26.C).

D. Foreign Body

1. **Preferred imaging**: CR, AP and lateral of neck and chest. Obtain both expiratory and inspiratory films. Bilateral decubitus for younger children who cannot hold breath on command.[7]
2. **Findings**: Radiopaque foreign bodies visualized. *Indirect Signs*: hyperinflation of affected lung, atelectasis/consolidation distal to obstruction.[7]

E. Tracheoesophageal Fistula and Esophageal Atresia

1. **Initial imaging**: CR; upper GI (UGI) rarely needed.
2. **Findings**: Distended air-filled pharyngeal pouch indicates esophageal atresia (EA). Presence of distal bowel gas indicates concurrent distal TEF.[8]

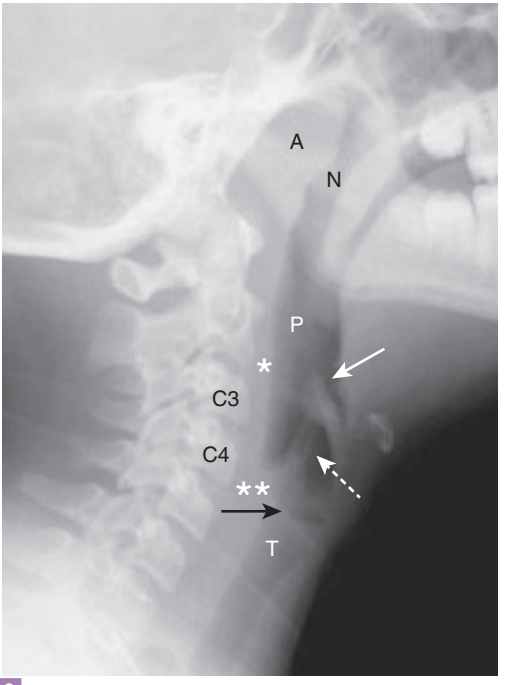

FIGURE 26.2

Normal soft tissue lateral neck radiograph. The adenoids *(A)* are seen at the base of the skull and are adjacent to the nasopharyngeal airway *(N)*. More distally is the pharynx *(P)*. The epiglottis *(solid white arrow)* is bounded superiorly by air in the vallecula. The aryepiglottic folds are thin, paired structures *(dotted white arrow)*. The normal-sized laryngeal ventricle *(black arrow)* separates the false vocal cords above from the true cords below. The trachea *(T)* starts below the true cords. The retropharyngeal soft tissue *(asterisks)* is less than one-half the width of the adjacent vertebral body above *C3/C4 (*)* and less than the width of the adjacent vertebral body below C3/C4 *(**)*. (Modified from Herring, W. *Learning Radiology: Recognizing the Basics*. 3rd ed. Philadelphia: Elsevier; 2016, Fig. 28.12.)

F. Vascular Rings and Pulmonary Slings

1. **Preferred imaging**: Contrast-enhanced CT angiography (CTA) or MR angiography (MRA).
2. **Other imaging:** Echocardiography (ECHO) in neonates and infants may be able to directly visualize vascular ring.[9] Neck and chest CR may show displacement or compression of tracheal air column. Barium swallow or UGI show extrinsic compression of esophagus.[7]

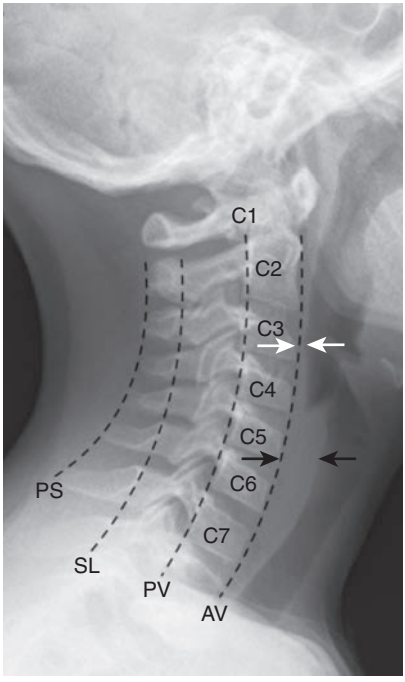

FIGURE 26.3
Normal lateral cervical spine radiograph. Four curvilinear lines can be used to help evaluate alignment: anterior vertebral line *(AV)*, posterior vertebral line *(PV)*, spinolaminar line *(SL)*, posterior spinous line *(PS)*. The retropharyngeal space should be less than one-half the width of the adjacent vertebral body above *C3/C4 (white arrows)* and the width of the adjacent vertebral body below C3/C4 *(black arrows)*.

V. CHEST

CR used for initial imaging. **CT** useful for evaluating lung parenchyma, pleura, and osseous thorax; important for identifying oncologic disease.[1,6] **US** can evaluate pleura, peripheral lung disease, and diaphragmatic motion.[6]

A. Normal Anatomy (Fig. 26.4 and Fig. EC 26.D)

B. Pulmonary Infections

1. **Preferred imaging**: CR, PA and lateral when possible.
2. **Other imaging**: CT with IV contrast for suspected complications including abscess, empyema, lung necrosis, or recurrent infection. US for parapneumonic effusions, empyema, and evaluating feasibility of percutaneous drainage.[6,9]

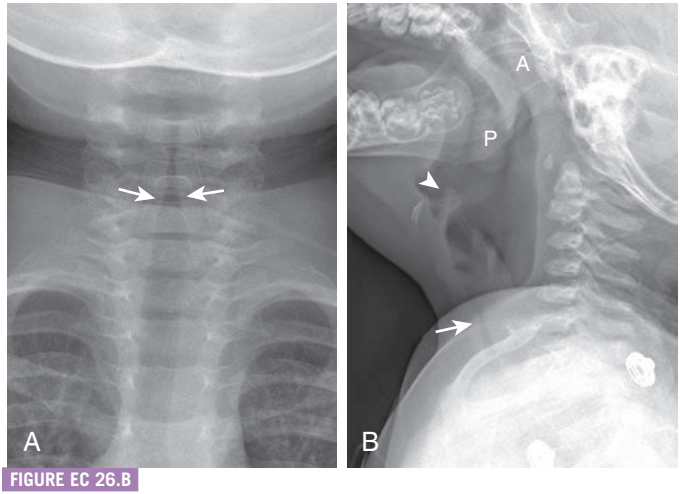

FIGURE EC 26.B

Croup. (A) Frontal radiograph showing symmetric subglottic narrowing *(arrows)* with loss of normal shouldering, "steeple sign." (B) Lateral radiograph showing subglottic narrowing *(arrow)*. Note normal-appearing epiglottis *(arrowhead)* and thin aryepiglottic folds. Also note mildly enlarged adenoid *(A)* and palatine *(P)* tonsils. (From Donnelly, LF. *Fundamentals of Pediatric Imaging*. 2nd ed. Philadelphia: Elsevier; 2017, p. 2, Fig. 2.1.)

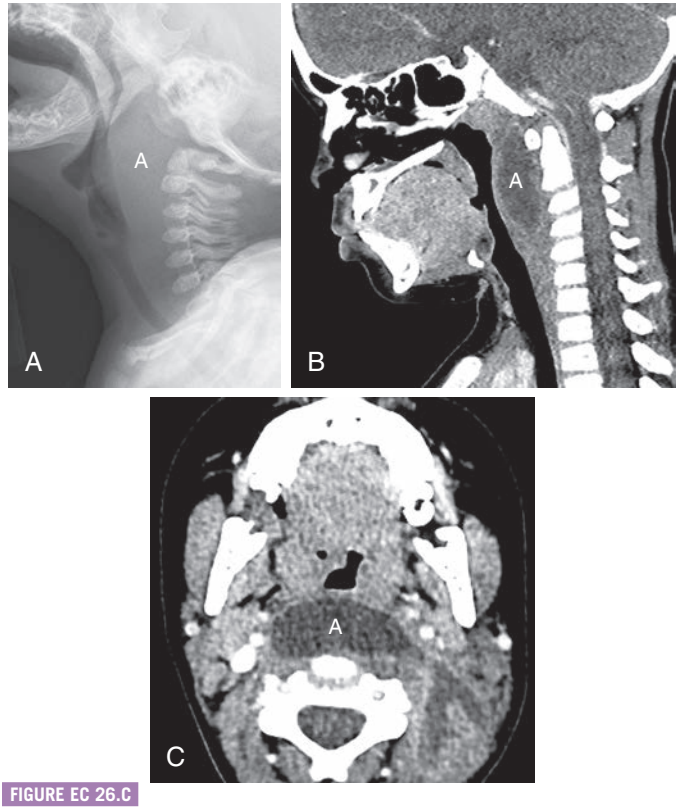

FIGURE EC 26.C

Retropharyngeal abscess. (A) Lateral radiograph showing marked thickening of the retropharyngeal soft tissues (A), which are wider than the adjacent vertebral bodies. Note the anterior convexity of soft tissues. (B and C) Contrast-enhanced computed tomography in sagittal and axial planes shows a low-attenuation region with enhancing rim (A), suggestive of a drainable abscess. (From Donnelly, LF. *Fundamentals of Pediatric Imaging*. 2nd ed. Philadelphia: Elsevier; 2017, p. 12, Fig. 2.7.)

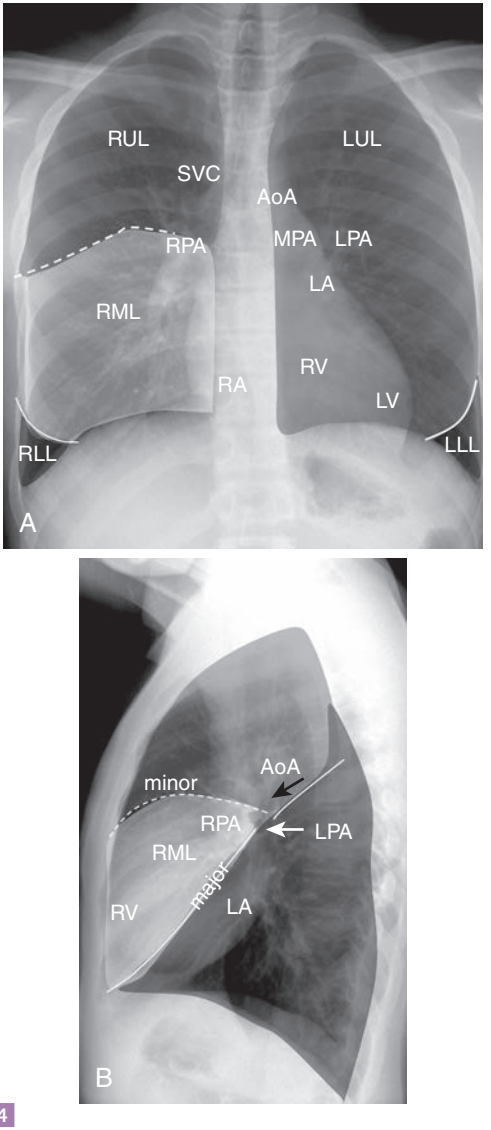

FIGURE 26.4

Normal lung and cardiac anatomy as seen on anteroposterior (A) and lateral (B) chest radiograph. *AoA*, Aortic arch; *RPA*, right pulmonary artery; *LPA*, left pulmonary artery; *RA*, right atrium; *RV*, right ventricle; *LA*, left atrium; *LV*, left ventricle; *black arrow*, posterior wall of bronchus intermedius; *white arrow*, left upper lobe airway; *RUL*, right upper lobe, *RML*, right middle lobe; *RLL*, right lower lobe; *LUL*, left upper lobe; *LLL*, left lower lobe

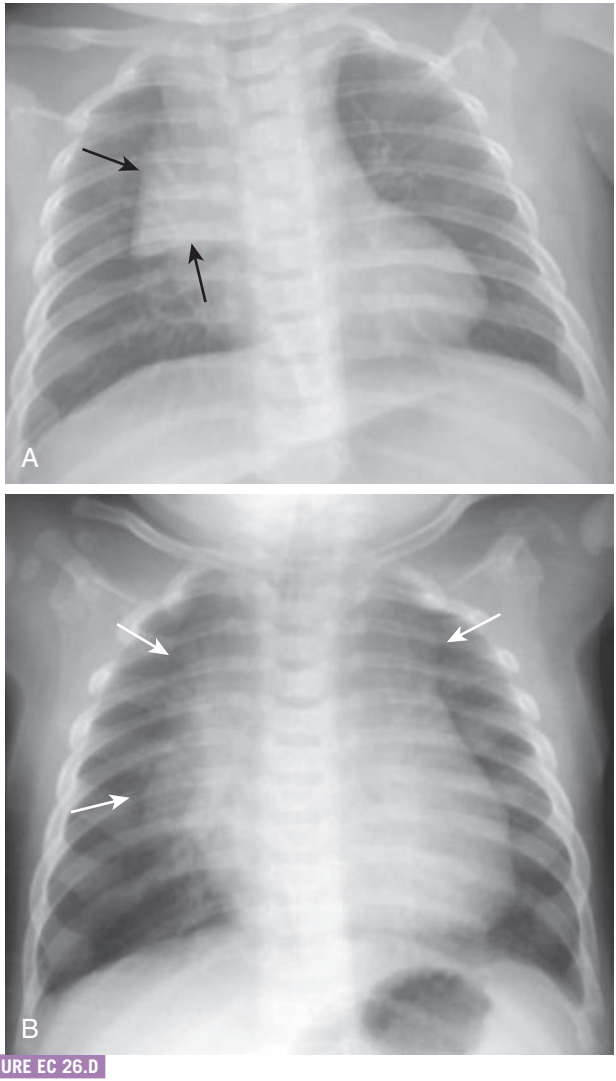

FIGURE EC 26.D

Normal thymus. (A) Radiograph shows prominent but normal thymus with rightward triangular extension, "sail sign" *(black arrows).* (B) One aid in identifying the thymus gland is that it is frequently lobulated in appearance *(white arrows).* Although the thymus gland will usually involute with age, it may still be normally visible in children as old as 3 years of age on conventional radiographs. (A from Herring, W. *Learning Radiology: Recognizing the Basics*. 3rd ed. Philadelphia: Elsevier; 2016, Fig. 28.19, B from Donnelly, LF. *Fundamentals of Pediatric Imaging*. 2nd ed. Philadelphia: Elsevier; 2017, p. 58, Fig. 3.44.)

2. Viral Infections
   a. **Nonspecific chest x-ray (CXR) findings** (often overlaps with bacterial infections): Bilateral interstitial opacities, peribronchial thickening (cuffing), hyperinflation, subsegmental atelectasis (Fig. EC 26.E).[9]
3. Bacterial Pneumonia
   a. **CXR findings**: Alveolar consolidation, air bronchograms (Fig. EC 26.F).[9,10]
   b. Localizing pneumonia on CXR:
      (1) *Silhouette sign*: Loss of normal borders between thoracic structures of same density; used to localize lung pathology (Table 26.3).[10]
      (2) *Spine sign*: Vertebral bodies of thoracic spine become less opaque (blacker) as moving inferiorly toward diaphragm. Soft tissue or fluid density involving posterior lower lobe adds density causing spine to become more opaque (whiter) above diaphragm.[1,10]
   c. Patterns of pneumonia
      Certain radiographic patterns are highly suggestive of particular microorganisms but impossible to identify with certainty (Table EC 26.A).[10]

C. Neonatal Lung Disease

1. Respiratory distress syndrome (or hyaline membrane disease): Hypoinflation, symmetrical hazy reticulogranular opacities, prominent air bronchograms, poor definition of pulmonary vessels.[6-8]
2. Transient tachypnea of the newborn (TTN): Interstitial edema, small pleural effusions, increased vascular markings, mildly enlarged cardiothymic silhouette, hyperinflation.[6,7]
3. Meconium aspiration syndrome: Bilateral, asymmetric areas of hyperinflation and atelectasis; asymmetric perihilar opacities, which can be associated with pneumothorax, pneumomediastinum, or pleural effusions.[7,8]
4. Neonatal pneumonia: Bilateral, patchy interstitial opacities, hyperinflation.[7]

D. Mediastinal Masses

1. **Preferred imaging**: CR followed by contrast-enhanced CT.
2. **Findings**: Middle mediastinal masses silhouetting the heart border and aorta.[1]

VI. HEART (SEE CHAPTER 7)

ECHO is the first-line imaging modality. **Cardiac MR (CMR)** evaluates extracardiac anatomy; gold standard for quantifying ventricular volume, mass, and ejection fraction; creates a three-dimensional reconstructions of complex congenital heart disease (CHD) without radiation. **Cardiac CT** is alternative if CMR is contraindicated (see Fig. 26.4 for normal cardiac findings on CXR).[1,8]

FIGURE EC 26.E

Chest radiograph of a child with viral bronchiolitis. CXR shows hyperinflated lungs with scattered areas of subsegmental atelectasis, most pronounced in the right upper and left lower lungs, as well as thickening of the peribronchial structures.

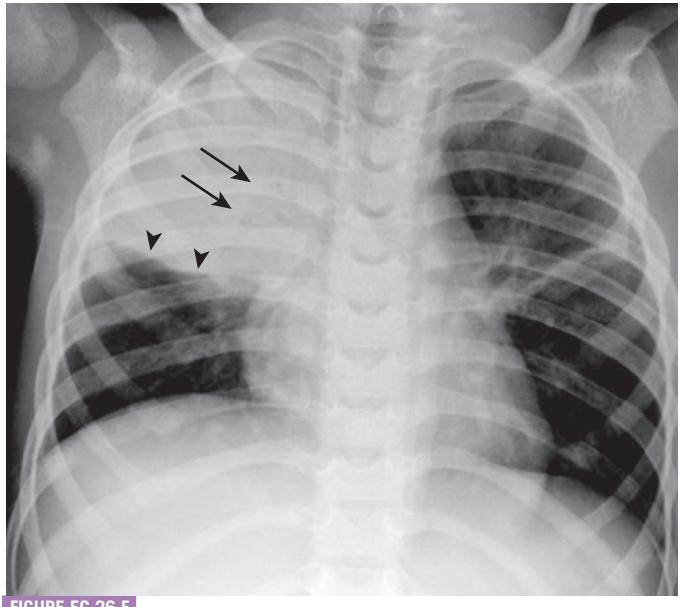

FIGURE EC 26.F

Pneumonia. Chest radiograph shows right upper lobe pneumonia with inferior bulging of the minor fissure (*arrowheads*) and air bronchograms *(arrows)*.

TABLE EC 26.A

PATTERNS OF PNEUMONIA AND ASSOCIATED ORGANISMS

Pattern	Characteristics	Typical Association
Lobar	Homogenous consolidation of a lobe. Normally contains air bronchograms.	*Streptococcus pneumoniae*
Segmental	Patchy appearance, often multifocal. Does not normally contain air bronchograms.	*Staphylococcus aureus*, *Pseudomonas aeruginosa*
Interstitial	Fine reticular pattern spread diffusely through lungs.	*Mycoplasma pneumoniae*, *Pneumocystis jirovecii* (PCP)
Round	Spherically shaped, normally located posteriorly in lower lung lobes. May be confused for a mass.	*Haemophilus influenzae*, *Streptococcus, Pneumococcus*
Cavitary	Lucent cavities (from necrosis) without air fluid levels, often seen in the upper lobe.	*Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*

Modified from Herring W. *Learning Radiology: Recognizing the Basics*. 3rd ed. Philadelphia: Elsevier; 2016, Tables 9.1 and 9.2.

TABLE 26.3

USING THE SILHOUETTE SIGN TO HELP LOCALIZE PNEUMONIA

Silhouetted Structure	Lobe
Ascending aorta	Right upper lobe
Right heart border	Right middle lobe
Right hemidiaphragm	Right lower lobe
Descending aorta	Left upper or lower lobe
Left heart border	Lingula of left upper lobe
Left hemidiaphragm	Left lower lobe

Modified from Herring W. *Learning Radiology: Recognizing the Basics.* 3rd ed. Philadelphia: Elsevier; 2016, Table 9.4.

VII. ABDOMEN

CR used for initial workup; two-view studies (supine and upright) are often preferred. Decubitus and cross-table lateral views can help localize free air, foreign bodies, and enteric tubes; may replace upright view if needed.[7] **US** is the initial modality for abdominal masses, ascites, appendicitis, abscesses, and biliary pathology.[1] **CT** is preferred for trauma and further evaluation.[1] **MRI** is becoming more frequently utilized, including magnetic resonance cholangiopancreatography (**MRCP**) for pancreatitis, biliary pathology, and trauma; and magnetic resonance enterography (**MRE**) in known or suspected inflammatory bowel disease to assess disease activity, extent of bowel involvement, and extraintestinal complications.[1] **Cross-sectional imaging** (US, CT, or MR) is preferred for suspected inflammation, infection, tumors, and lymphadenopathy. **Upper GI (UGI) series** can assess upper GI obstruction in neonates, malrotation, anatomic malformations, and motility problems.[7]

A. Normal Abdominal X-ray and Bowel Gas Pattern

1. Neonatal bowel gas pattern: Gas should be present in stomach by 15 minutes of life, in proximal small bowel by 30 to 60 minutes, in most of small intestine by 6 hours, and in colon by 12 to 24 hours (Fig. 26.5).[6,11] Bowel loop diameter and bowel wall thickness should be uniform.[5]
2. After infancy, pockets of gas should be visualized in small bowel, colon, and rectum.
3. Small bowel seen if contains gas, located centrally, has valvulae (extends across bowel), normal diameter smaller than 3 cm.
4. Large bowel contains gas and stool, located peripherally, has haustra (extends partially across bowel), normal diameter smaller than 5 cm.

B. Pneumoperitoneum (Free Intraperitoneal Air)

1. **Preferred imaging**: CR including upright imaging (cross-table or decubitus lateral if patient unable to stand or sit).
2. **Other imaging:** CT confirms diagnosis, detects small amounts of air not seen on CR.[10]
3. **Findings:** Air under diaphragm
   a. *Continuous diaphragm sign:* Air under entire diaphragm, including underneath heart silhouette

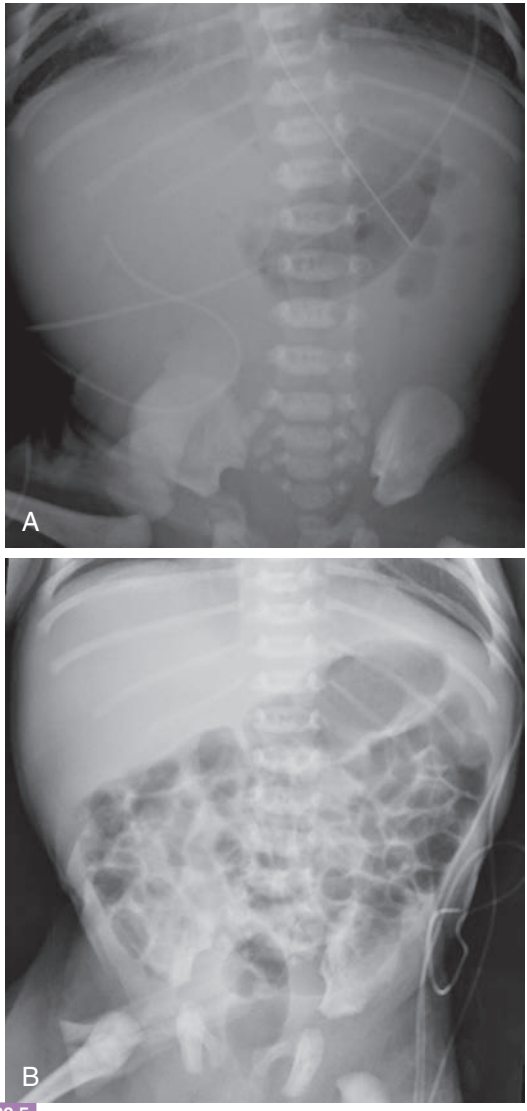

FIGURE 26.5

Normal bowel gas progression in neonates as seen on abdominal radiograph at 2 hours of life (A) and 24 hours of life (B). Note that by 12 hours of life air should have progressed through small bowel and by 24 hours of life (B) air can be visualized in the rectum.

b. *Falciform ligament sign*: Ability to visualize normally invisible falciform ligament as free air surrounds ligament (Fig. EC 26.G)
c. *Football sign*: Oval appearance of abdominal cavity outlined by gas with visualization of falciform ligament, seen in massive pneumoperitoneum (see Fig. EC 26.G)[10]

C. Neonatal Enterocolitis (see Chapter 18)

1. **Initial imaging**: CR, include cross-table lateral or left decubitus views to evaluate for free air.[7]
2. **Other imaging:** Intestinal US if high clinical suspicion for NEC and CR nonspecific or inconclusive, as can depict changes in intra-abdominal fluid, bowel wall thickness, and bowel wall perfusion before findings on CR.[12]
3. **CR findings**: *Nonspecific signs*: Diffuse gaseous distention (most common), loss of normal symmetrical distribution of gas, persistence of single dilated bowel loop (*fixed loop sign*). *Pathognomonic signs*: Pneumatosis intestinalis (intramural gas with "bubbly" appearance commonly in distal small bowel and colon), portal venous gas (branching lucencies seen projecting over liver) (Fig. 26.6).[7]

D. Neonatal Intestinal Obstruction

1. Difficult to distinguish small from large bowel in neonates.[5]
2. **Initial imaging**: CR to decipher high obstruction (stomach to proximal ileum) from low obstruction (distal ileum to colon).
3. **Further imaging:** UGI series or esophagram (obstruction proximal to ligament of Treitz), UGI series with small bowel follow-through (ligament of Treitz to ileocecal junction), contrast enema (distal to ileocecal junction).[5,7,9]
4. High intestinal obstruction
   a. CR findings: Few dilated loops of bowel.
   b. Duodenal atresia: Double bubble on CR (Fig. EC 26.H), reflecting air in dilated stomach and proximal duodenum with absence of air distally. If partial obstruction, UGI series further differentiates duodenal stenosis or web from midgut volvulus.[7]
   c. Malrotation: Malpositioned duodenojejunal junction/ligament of Treitz (normally at level of duodenal bulb and to left of spine). UGI series is the gold standard. US can be used for rapid screening.[5,7]
5. Low intestinal obstruction
   a. CR findings: Multiple dilated loops of bowel; assess further with contrast enema.
   b. Ileal atresia: Contrast enema shows opacification of diffusely small caliber large bowel (microcolon). Contrast refluxes into distal ileum, but unable to reflux further. Bowel proximal to distal ileum is air filled and dilated.
   c. Hirschsprung disease: Contrast enema shows "transition zone" between nondilated aganglionic distal colon and normal, relatively distended, proximal colon.[7]

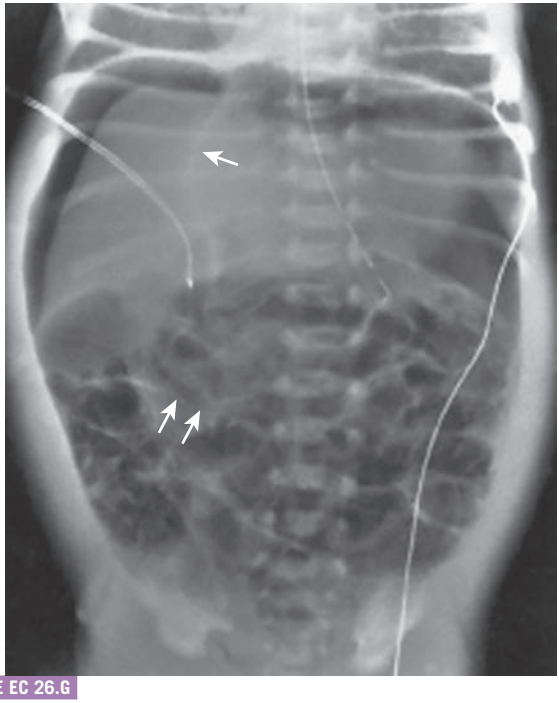

FIGURE EC 26.G

Free intraperitoneal air. An anteroposterior supine abdominal radiograph in a baby with necrotizing enterocolitis and free air demonstrates generalized lucency throughout the abdomen. Note that free air outlines the falciform ligament ("football sign") (*arrow*), and air is seen on both sides of the bowel wall ("Rigler sign") (*double arrows*). (From Walters, MM, Robertson RL. *Pediatric Radiology: The Requisites*. 4th ed. Philadelphia: Elsevier; 2017, p. 93, Fig. 4.4.)

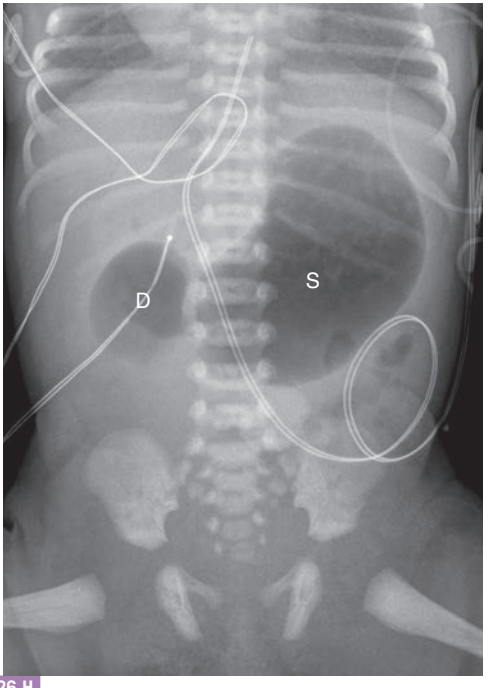

FIGURE EC 26.H

Duodenal atresia in a newborn infant. Radiograph shows air-filled, dilated stomach *(S)* and dilated duodenal bulb *(D)*, giving the appearance of a double bubble. There is no distal bowel gas. (From Donnelly, LF. *Fundamentals of Pediatric Imaging*. 2nd ed. Philadelphia: Elsevier; 2017, p. 95, Fig. 5.8.)

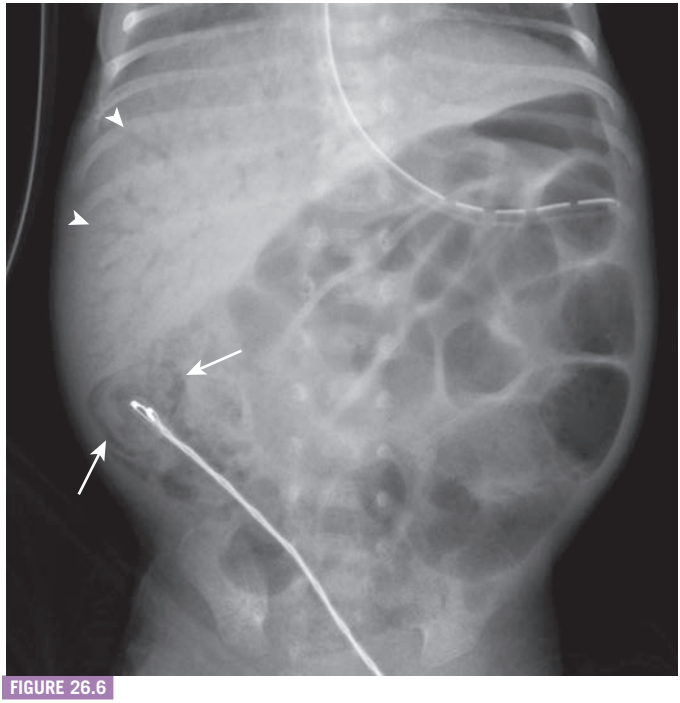

FIGURE 26.6
Necrotizing enterocolitis (NEC) in a premature infant. Radiography shows multiple dilatated bowel loops with multiple areas of linear lucency *(arrows)* along the bowel wall, consistent with pneumatosis. Note portal venous gas *(arrowheads)* as branching, tubular lucencies overlying the liver. (From Donnelly, LF. *Fundamentals of Pediatric Imaging*. 2nd ed. Philadelphia: Elsevier; 2017, p. 92, Fig. 5.1.)

d. Meconium ileus: Contrast enema shows opacification of diffusely small caliber large bowel. Contrast refluxes into nondilated terminal ileum, which contains impacted meconium pellets. Bowel proximal to terminal ileum is dilated.[5]

E. Pyloric Stenosis

1. **Preferred imaging**: Upper abdominal US.
2. **Findings**: Abnormal thickening of pyloric muscle (≥3 mm) and elongation of pyloric channel (>15 to 17 mm).[10]

F. Intussusception

1. **Preferred imaging:** RUQ US.[1]
2. **Findings**: Donut, target, or pseudo-kidney sign.[1]
3. **Treatment**: Pneumatic enema reduction under fluoroscopic guidance.[1]

G. Ileus

1. **Preferred imaging**: CR.
2. **Findings**: Small and large bowel distention.[1,10]

H. Mechanical Bowel Obstruction

1. **Initial imaging:** CR. Supine view for identifying gas pattern. Upright/erect, cross-table lateral, or lateral decubitus for identifying free air and air-fluid levels.
2. **Other imaging**: CT with oral contrast determines obstruction site. CT with IV contrast to detect complications such as ischemia.[10] *Note: CR has low sensitivity for identifying bowel obstruction; therefore, CT should be obtained if obstruction clinically suspected.*
3. **Findings**: Dilated loops of bowel proximal to obstruction, little to no air in rectum.[1]
   a. Small bowel obstruction: Numerous air-fluid levels. Distended bowel normally more central.
   b. Large bowel obstruction: Few to no air-fluid levels. Distended bowel normally more peripheral.

I. Appendicitis

1. **Preferred imaging**: RLQ US.
2. **Other imaging:** MRI if US equivocal. CT only if MRI unavailable or patient unstable or cannot tolerate MRI.[1,7]
3. **US findings:** Fluid-filled, noncompressible, blind-ending tubular structure greater than 6 mm in diameter.[1,7]

J. Esophageal Foreign Bodies

1. **Preferred imaging**: CR, evaluate entire GI tract (AP/lateral neck, chest, abdomen).
2. **Other imaging:** Esophagram with water-soluble contrast if suspicion high but CR negative.[7]
3. **Findings**: Most commonly lodged at thoracic inlet. Only radiopaque objects can be visualized on CR. May see mass effect on adjacent structures from swelling caused by foreign body.
   a. Coins (most common): Flat object on frontal view with edge visualized on lateral.
   b. Disk batteries: Bilaminar structure, must identify as may cause serious chemical injury.[7]

K. Abdominal Trauma

1. **Preferred imaging**: CT with IV contrast.
2. **Other imaging:** If hemodynamically unstable, rapid bedside US using focused assessment with sonography for trauma (FAST) protocol to evaluate for free fluid.[7] FAST evaluates bilateral upper quadrants, bilateral pericolic gutters, pelvis, and pericardium.[1]

L. Gallbladder Disease

1. **Preferred imaging**: US. Patients should fast for 6 hours prior to allow for gallbladder filling.[1]