

## Chapter 84 ◆ An Approach to Inborn Errors of Metabolism 635

**Table 84-1**

Disorders Recommended By the American College of Medical Genetics Task Force for Inclusion in Newborn Screening ("Primary Disorders")\*

**DISORDERS OF ORGANIC ACID METABOLISM**

Isovaleric acidemia  
Glutaric aciduria type I  
3-Hydroxy-3-methylglutaric aciduria  
Multiple carboxylase deficiency  
Methylmalonic acidemia, mutase deficiency form  
3-Methylcrotonyl-CoA carboxylase deficiency  
Methylmalonic acidemia, cblA and cblB forms  
Propionic acidemia  
 $\beta$ -Ketothiolase deficiency

**DISORDERS OF FATTY ACID METABOLISM**

Medium-chain acyl-CoA dehydrogenase deficiency  
Very-long-chain acyl-CoA dehydrogenase deficiency  
Long-chain 3-hydroxy acyl-CoA dehydrogenase deficiency  
Trifunctional protein deficiency  
Carnitine uptake defect

**DISORDERS OF AMINO ACID METABOLISM**

Phenylketonuria  
Maple syrup urine disease  
Homocystinuria  
Citrullinemia  
Argininosuccinic acidemia  
Tyrosinemia type I

**HEMOGLOBINOPATHIES**

Sickle cell anemia (hemoglobin S)  
Hemoglobin S- $\beta$ -thalassemia  
Hemoglobin SC disease

**OTHER DISORDERS**

Congenital hypothyroidism  
Biotinidase deficiency  
Congenital adrenal hyperplasia  
Galactosemia  
Hearing deficiency  
Cystic fibrosis

\*At this time, there is state-to-state variation in newborn screening; a list of the disorders that are screened for by each state is available at <http://genes-r-us.uthscsa.edu/sites/genes-r-us/files/nbsdisorders.pdf>.

cblA, Cobalamin A defect; cblB, cobalamin B defect; CoA, coenzyme A.

**Table 84-2**

Secondary Conditions Recommended By American College of Medical Genetics\* Task Force for Inclusion in Newborn Screening

**ORGANIC ACID METABOLISM DISORDERS**

Methylmalonic acidemia, cblC and cblD forms  
2-Methyl-3-hydroxybutyric aciduria  
Isobutyryl-CoA dehydrogenase deficiency  
2-Methylbutyryl-CoA dehydrogenase deficiency  
3-Methylglutaconic aciduria  
Malonic acidemia

**FATTY ACID OXIDATION DISORDERS**

Medium-/short-chain 3-OH acyl-CoA dehydrogenase deficiency  
Short-chain acyl-CoA dehydrogenase deficiency  
Medium-chain ketoacyl-CoA thiolase deficiency  
Glutaric acidemia type 2  
Carnitine palmitoyltransferase I deficiency  
Carnitine palmitoyltransferase II deficiency  
Carnitine acylcarnitine translocase deficiency  
Dienoyl-CoA reductase deficiency

**AMINO ACID METABOLISM DISORDERS**

Hyperphenylalaninemia, benign (not phenylketonuria)  
Tyrosinemia type II  
Tyrosinemia type III  
Defects of biotinidase cofactor biosynthesis  
Defects of biotinidase cofactor regeneration  
Argininemia  
Hypermethioninemia  
Citrullinemia type II

**HEMOGLOBINOPATHIES**

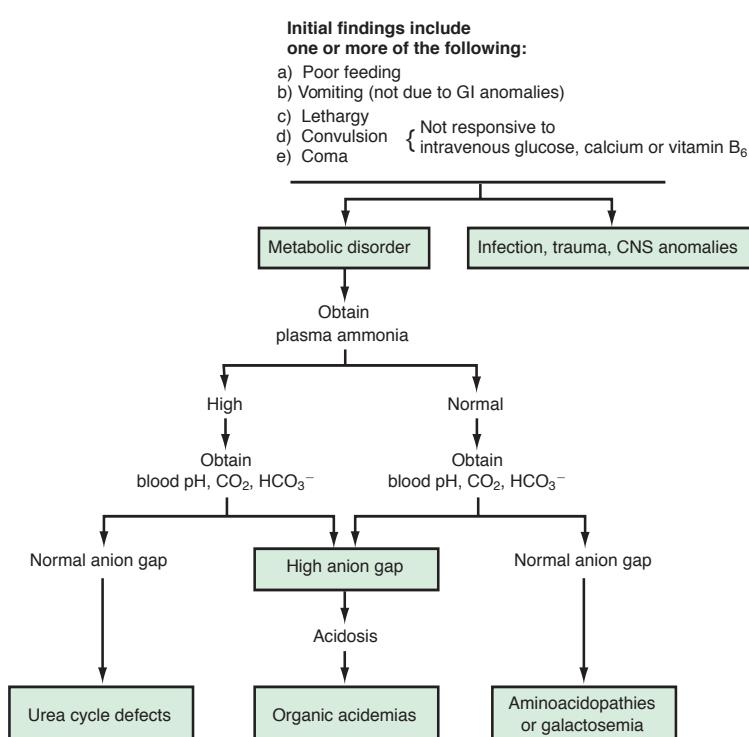
Hemoglobin variants (including hemoglobin E)

**OTHERS**

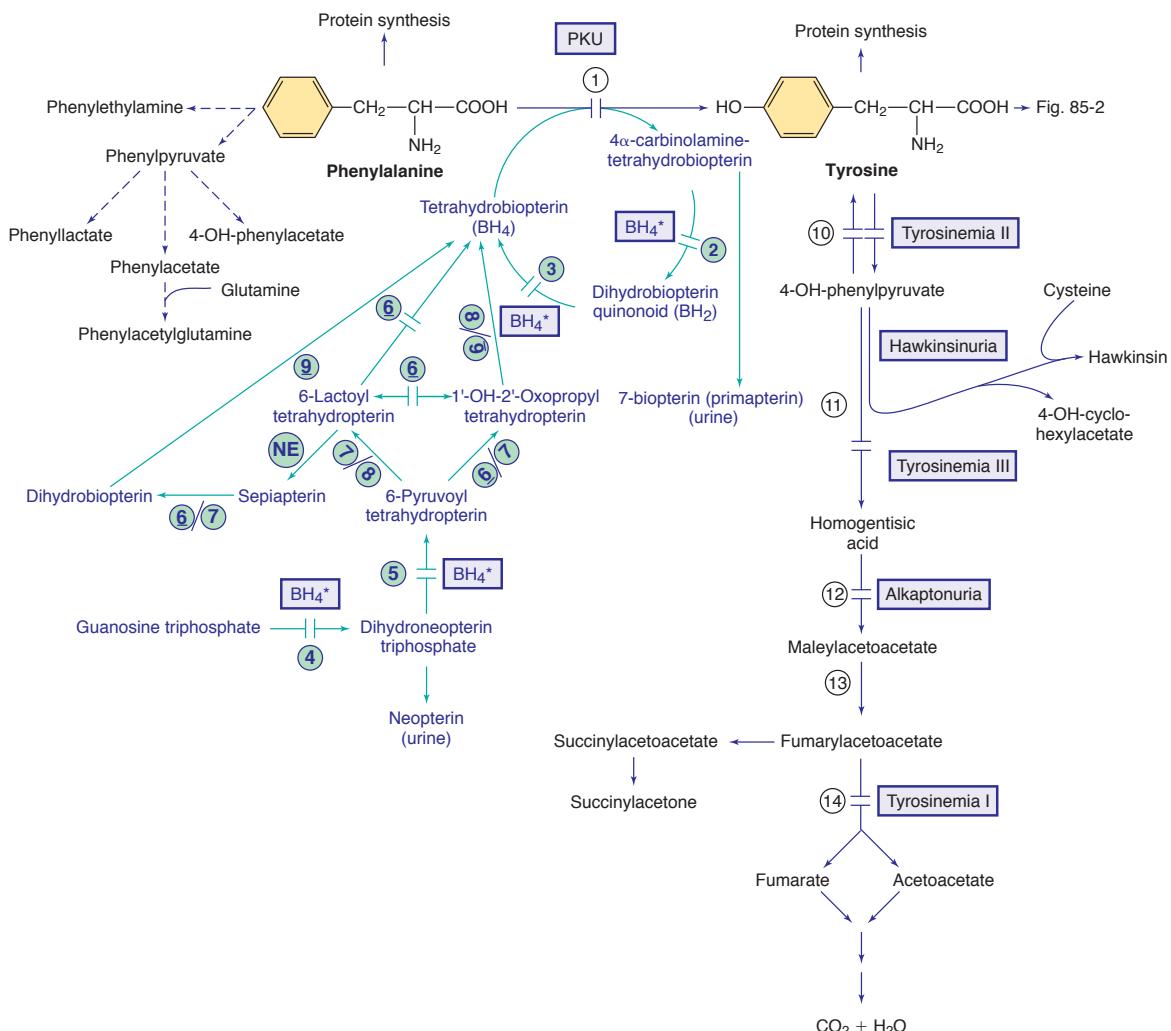
Galactose epimerase deficiency  
Galactokinase deficiency

\*The American College of Medical Genetics task force recommended reporting 25 disorders ("secondary targets") in addition to the primary disorders that can be detected through screening but that do not meet the criteria for primary disorders.

cblC, Cobalamin C defect; cblD, cobalamin D defect; CoA, coenzyme A.



**Figure 84-1** Initial clinical approach to a full term newborn infant with a suspected genetic metabolic disorder. This schema is a guide to the elucidation of some of the metabolic disorders in newborn infants. Although some exceptions to this schema exist, it is appropriate for most cases.



**Figure 85-1** Pathways of phenylalanine and tyrosine metabolism. Enzyme defects causing genetic conditions are depicted as horizontal bars crossing the reaction arrow(s). Pathways for synthesis of cofactor BH<sub>4</sub> are shown in purple. PKU\* refers to defects of BH<sub>4</sub> metabolism that affect the phenylalanine, tyrosine, and tryptophan hydroxylases (see Figs. 85-2 and 85-5). **Enzymes:** (1) Phenylalanine hydroxylase, (2) pterin-carbinolamine dehydratase, (3) dihydrobiopterin reductase, (4) guanosine triphosphate (GTP) cyclohydrolase, (5) 6-pyruvoyltetrahydropterin synthase, (6) sepiapterin reductase, (7) carbonyl reductase, (8) aldolase reductase, (9) dihydrofolate reductase, (10) tyrosine aminotransferase, (11) 4-hydroxyphenylpyruvate dioxygenase, (12) homogentisic acid dioxygenase, (13) maleylacetoacetate isomerase, (14) fumarylacetoacetate hydrolase, (NE) nonenzymatic.

#### Common features

Refusal to feed  
Vomiting  
Acidosis  
Dehydration  
Neutropenia  
Hypoglycemia

Ketosis

No ketosis or mild ketosis

No skin manifestations

Skin manifestations

Multiple carboxylase deficiency\*

1. 3-Hydroxy-3-methylglutaric aciduria
2. Acyl CoA dehydrogenase deficiencies
3. HMG CoA synthetase deficiency

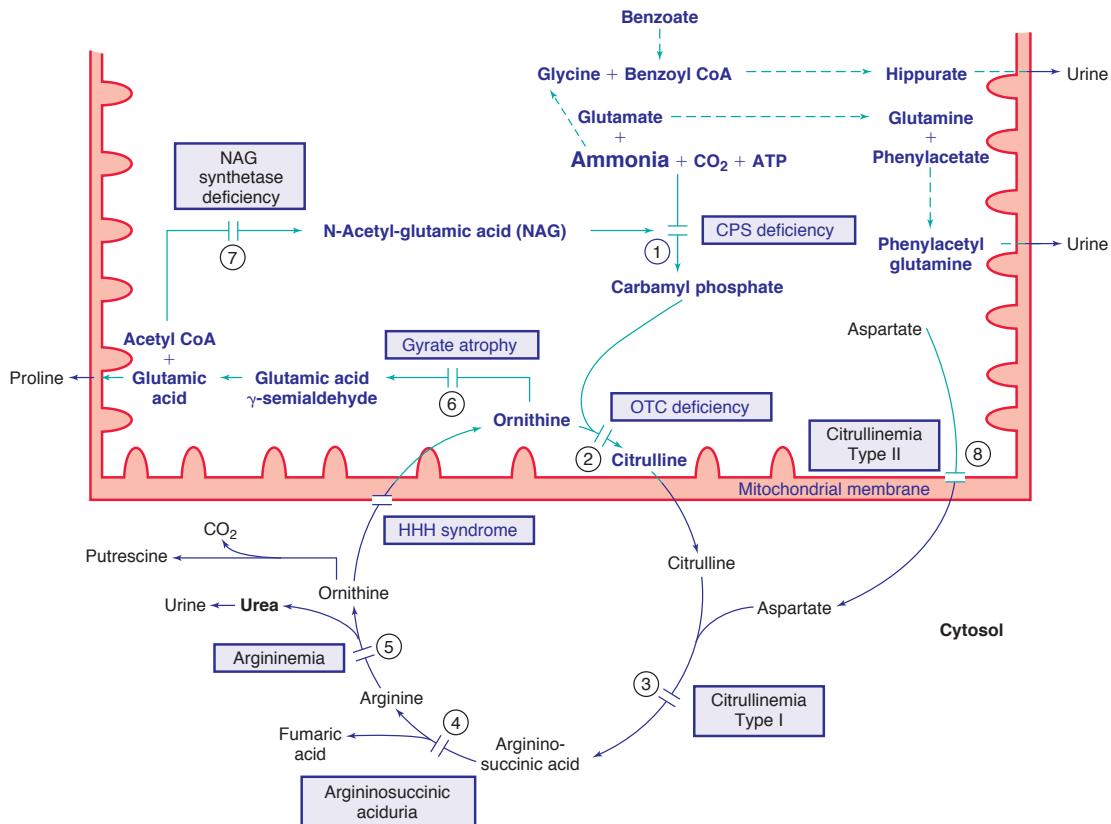
1. Methylmalonic aciduria
2. Propionic aciduria
3. Ketothiolase deficiency

1. MSUD\*
2. Isovaleric aciduria\*

**Figure 85-6** Clinical approach to infants with organic aciduria. Asterisks indicate disorders in which patients have a characteristic odor (see text and Table 85-2). MSUD, maple syrup urine disease.

# Metabolic Disorders

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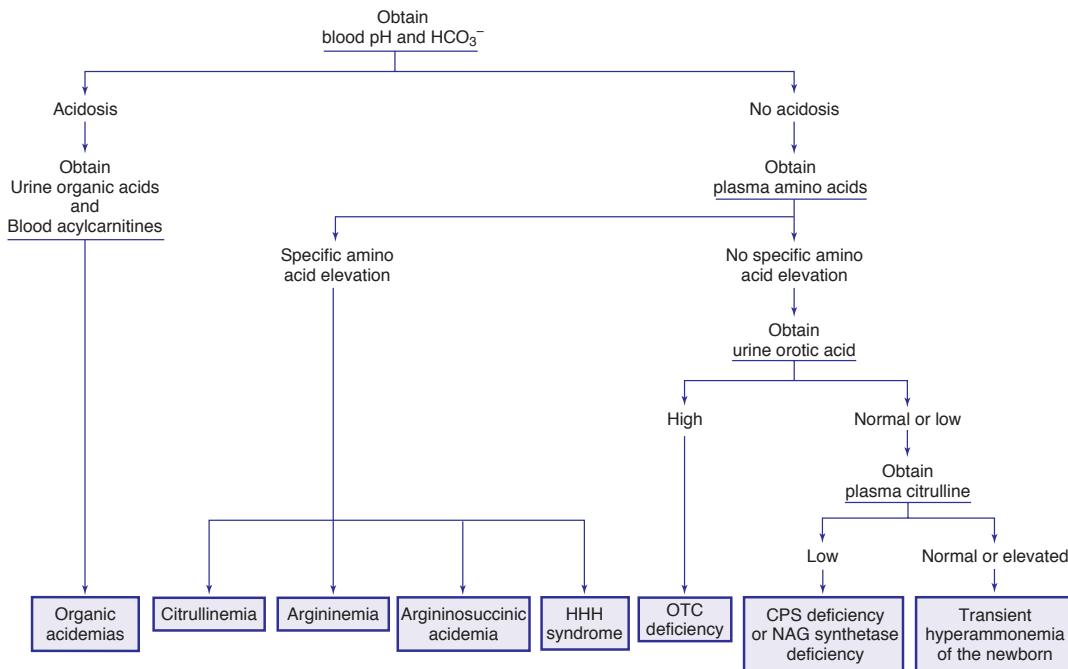
**Figure 85-12** Urea cycle: pathways for ammonia disposal and ornithine metabolism. Reactions occurring in the mitochondria are depicted in purple. Reactions shown with interrupted arrows are the alternate pathways for the disposal of ammonia. **Enzymes:** (1) Carbamyl phosphate synthetase (CPS), (2) ornithine transcarbamylase (OTC), (3) argininosuccinic acid synthetase (AS), (4) argininosuccinic acid lyase (AL), (5) arginase, (6) ornithine 5-aminotransferase, (7) N-acetylglutamate (NAG) synthetase, (8) citrin. HHH syndrome, hyperammonemia-hyperornithinemia-homocitrullinemia.

**Table 85-3** Inborn Errors of Metabolism Causing Hyperammonemia

Deficiencies of the urea cycle enzymes  
 Carbamyl phosphate synthetase  
 Ornithine transcarbamylase  
 Argininosuccinate synthetase  
 Argininosuccinate lyase  
 Arginase N-acetylglutamate synthetase  
 Organic acidemias  
 Propionic acidemia  
 Methylmalonic acidemia  
 Isovaleric acidemia  
 $\beta$ -Ketothiolase deficiency  
 Multiple carboxylase deficiencies  
 Medium-chain fatty acid acyl-coenzyme A dehydrogenase deficiency  
 Glutaric aciduria type I  
 3-Hydroxy-3-methylglutaric aciduria  
 Lysinuric protein intolerance  
 Hyperammonemia-hyperornithinemia-homocitrullinemia syndrome  
 Transient hyperammonemia of the newborn  
 Congenital hyperinsulinism with hyperammonemia

**Table 84-3** Inborn Errors of Amino Acid Metabolism Associated with Peculiar Odor

INBORN ERROR OF METABOLISM	URINE ODOR
Glutaric acidemia (type II)	Sweaty feet, acrid
Hawkinsuria	Swimming pool
3-Hydroxy-3-methylglutaric aciduria	Cat urine
Isovaleric acidemia	Sweaty feet, acrid
Maple syrup urine disease	Maple syrup
Hypermethioninemia	Boiled cabbage
Multiple carboxylase deficiency	Tomcat urine
Oasthouse urine disease	Hops-like
Phenylketonuria	Mousey or musty
Trimethylaminuria	Rotting fish
Tyrosinemia	Boiled cabbage, rancid butter



**Figure 85-13** Clinical approach to a newborn infant with symptomatic hyperammonemia. CPS, carbamyl phosphate synthetase; HHH syndrome, hyperammonemia-hyperornithinemia-homocitrullinemia; NAG, *N*-acetylglutamate; OTC, ornithine transcarbamylase.

**Table 85-4** Treatment of Acute Hyperammonemia in an Infant

- Provide adequate calories, fluid, and electrolytes intravenously (10% glucose,  $\text{NaCl}^*$  and intravenous lipids 1 g/kg/24 hr). Add minimal amounts of protein preferably as a mixture of essential amino acids (0.25 g/kg/24 hr) during the 1st 24 hr of therapy.
- Give priming doses of the following compounds:  
(To be added to 20 mL/kg of 10% glucose and infused within 1-2 hr)
  - Sodium benzoate 250 mg/kg<sup>†</sup>
  - Sodium phenylacetate 250 mg/kg<sup>†</sup>
  - Arginine hydrochloride 200-600 mg/kg as a 10% solution
- Continue infusion of sodium benzoate<sup>†</sup> (250-500 mg/kg/24 hr), sodium phenylacetate<sup>†</sup> (250-500 mg/kg/24 hr), and arginine (200-600 mg/kg/24 hr<sup>†</sup>) following the above priming doses. These compounds should be added to the daily intravenous fluid.
- Initiate peritoneal dialysis or hemodialysis if above treatment fails to produce an appreciable decrease in plasma ammonia.

**Table 86-2** Classification of Peroxisomal Disorders

**A: DISORDERS OF PEROXISOME IMPORT**

- Zellweger syndrome
- Neonatal adrenoleukodystrophy
- Infantile Refsum disease
- Rhizomelic chondrodyplasia punctata

**B: DEFECTS OF SINGLE PEROXISOMAL ENZYME**

- X-linked adrenoleukodystrophy
- Acyl-CoA oxidase deficiency
- Bifunctional enzyme deficiency
- Peroxisomal thiolase deficiency
- Classic Refsum disease
- 2-Methylacyl-CoA racemase deficiency
- DHAP acyltransferase deficiency
- Alkyl-DHAP synthase deficiency
- Mevalonic aciduria
- Glutaric aciduria type III
- Hyperoxaluria type I
- Acatalasemia

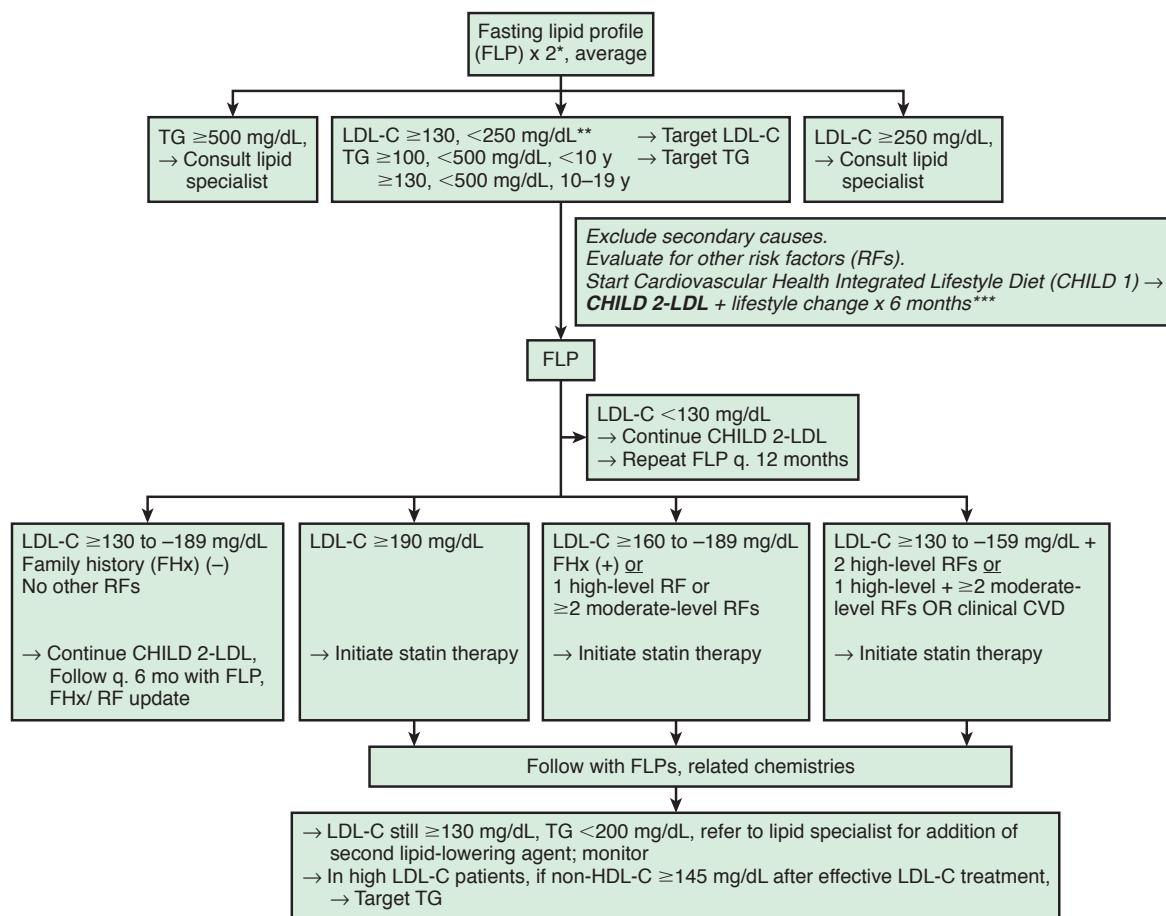
CoA, coenzyme A; DHAP, dihydroxyacetone phosphate.

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<b>Table 86-10</b>	Major Clinical Characteristics of Smith-Lemli-Opitz Syndrome: Frequent Anomalies (>50% of Patients)	<b>Table 86-11</b>	Characteristic Malformations of Internal Organs in Severely Affected Smith-Lemli-Opitz Patients
<b>CRANIOFACIAL</b>		<b>CENTRAL NERVOUS SYSTEM</b>	
Microcephaly		Frontal lobe hypoplasia	
Blepharoptosis		Enlarged ventricles	
Anteverted nares		Agenesis of corpus callosum	
Retromicrognathia		Cerebellar hypoplasia	
Low-set, posteriorly rotated ears		Holoprosencephaly	
Midline cleft palate			
Broad maxillary alveolar ridges		<b>CARDIOVASCULAR</b>	
Cataracts (<50%)		Atrioventricular canal	
<b>SKELETAL ANOMALIES</b>		Secundum atrial septal defect	
Syndactyly of toes II/III		Patent ductus arteriosus	
Postaxial polydactyly (<50%)		Membranous ventricular septal defect	
Equinovarus deformity (<50%)			
<b>GENITAL ANOMALIES</b>		<b>URINARY TRACT</b>	
Hypospadias		Renal hypoplasia or aplasia	
Cryptorchidism		Renal cortical cysts	
Sexual ambiguity (<50%)		Hydronephrosis	
<b>DEVELOPMENT</b>		Ureteral duplication	
Pre- and postnatal growth retardation			
Feeding problems		<b>GASTROINTESTINAL</b>	
Mental retardation		Hirschsprung disease	
Behavioral abnormalities		Pyloric stenosis	
		Refractory dysmotility	
		Cholestatic and noncholestatic progressive liver disease	
		<b>PULMONARY</b>	
		Pulmonary hypoplasia	
		Abnormal lobation	
		<b>ENDOCRINE</b>	
		Adrenal insufficiency	

<b>Table 86-13</b> Drugs Used for the Treatment of Hyperlipidemia			
<b>DRUG</b>	<b>MECHANISM OF ACTION</b>	<b>INDICATION</b>	<b>STARTING DOSE</b>
HMG-CoA reductase inhibitors (statins)	↓ Cholesterol and VLDL synthesis ↑ Hepatic LDL receptors	Elevated LDL	5-80 mg qhs
Bile acid sequestrants: Cholestyramine Colestipol	↑ Bile and excretion	Elevated LDL	4-32 g daily 5-40 g daily
Nicotinic acid	↓ Hepatic VLDL synthesis	Elevated LDL Elevated TG	100-2,000 mg tid
Fibric acid derivatives: Gemfibrozil	↑ LPL ↓ VLDL	Elevated TG	600 mg bid
Fish oils	↓ VLDL production	Elevated TG	3-10 g daily
Cholesterol absorption inhibitors: Ezetimibe	↓ Intestinal absorption cholesterol	Elevated LDL	10 mg daily

LDL, low-density lipoprotein; LPL, lipoprotein lipase; TG, triglyceride; VLDL, very-low-density lipoprotein.



**Figure 86-14** Algorithm of the evaluation, risk assessment, follow-up, and treatment of children based on low-density lipoprotein (LDL) cholesterol levels. FLP, fasting lipid profile; TG, triglycerides. (From Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary report. Pediatrics 128(Suppl 5):S213–S256, 2011, Fig. 9-1.)

**Table 86-14** Side Effects of Lipid-Lowering Drugs

DRUG AND SITE OR TYPE OF EFFECT	EFFECT
<b>STATINS</b>	
Skin	Rash
Nervous system	Loss of concentration, sleep disturbance, headache, peripheral neuropathy
Liver	Hepatitis, loss of appetite, weight loss, and increases in serum aminotransferases to 2-3 times the upper limit of the normal range
Gastrointestinal tract	Abdominal pain, nausea, diarrhea
Muscles	Muscle pain or weakness, myositis (usually with serum creatine kinase $> 1,000$ U/L), rhabdomyolysis with renal failure
Immune system	Lupus-like syndrome (lovastatin, simvastatin, or fluvastatin)
Protein binding	Diminished binding of warfarin (lovastatin, simvastatin, fluvastatin)
<b>BILE ACID-BINDING RESINS</b>	
Gastrointestinal tract	Abdominal fullness, nausea, gas, constipation, hemorrhoids, anal fissure, activation of diverticulitis, diminished absorption of vitamin D in children
Liver	Mild serum aminotransferase elevations, which can be exacerbated by concomitant treatment with a statin
Metabolic system	Increases in serum triglycerides of $\approx 10\%$ (greater increases in patients with hypertriglyceridemia)
Electrolytes	Hyperchlremic acidosis in children and patients with renal failure (cholestyramine)
Drug interactions	Binding of warfarin, digoxin, thiazide diuretics, thyroxine, statins
<b>NICOTINIC ACID</b>	
Skin	Flushing, dry skin, pruritus, ichthyosis, acanthosis nigricans
Eyes	Conjunctivitis, cystoid macular edema, retinal detachment
Respiratory tract	Nasal stuffiness
Heart	Supraventricular arrhythmias
Gastrointestinal tract	Heartburn, loose bowel movements or diarrhea
Liver	Mild increase in serum aminotransferases, hepatitis with nausea and fatigue
Muscles	Myositis
Metabolic system	Hyperglycemia (incidence: $\approx 5\%$ higher in patients with diabetes), increase of 10% in serum uric acid
<b>FIBRATES</b>	
Skin	Rash
Gastrointestinal tract	Stomach upset, abdominal pain (mainly gemfibrozil), cholesterol-saturated bile, increase of 1-2% in gallstone incidence
Genitourinary tract	Erectile dysfunction (mainly clofibrate)
Muscles	Myositis with impaired renal function
Plasma proteins	Interference with binding of warfarin, requiring reduction in the dose of warfarin by $\approx 30\%$
Liver	Increased serum aminotransferases

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**Table 86-15** Clinical Findings in Lysosomal Storage Diseases

NOMENCLATURE	ENZYME DEFECT	HYDROPS FETALIS	COARSE FACIAL FEATURES	DYSOSTOSIS MULTIPLEX	HEPATOSPLENOMEGLALY
<b>MUCOLIPIDOSES</b>					
Mucolipidosis II, I-cell disease	N-Acetylglucosaminylphosphotransferase	(+)	++	+	
Mucolipidosis III, Pseudo-Hurler	N-Acetylglucosaminylphosphotransferase	-	+	(+)	
Mucolipidosis IV	Unknown	-	-	+	
<b>SS</b>					
Fabry disease	$\alpha$ -Galactosidase	-	-	-	
Farber disease	Ceramidase	-	-	(+)	
Galactosialidosis	$\beta$ -Galactosidase and sialidase	(+)	++	++	
GM <sub>1</sub> gangliosidosis	$\beta$ -Galactosidase	(+)	++	+	
GM <sub>2</sub> gangliosidosis (Tay-Sachs disease, Sandhoff disease)	$\beta$ -Hexosaminidases A and B	-	-	(+)	
Gaucher type I	Glucocerebrosidase	-	-	++	
Gaucher type II	Glucocerebrosidase	(+)	-	++	
Gaucher type III	Glucocerebrosidase	(+)	-	+	
Niemann-Pick type A	Sphingomyelinase	(+)	-	++	
Niemann-Pick type B	Sphingomyelinase	-	-	++	
Metachromatic leukodystrophy	Arylsulfatase A	-	-	-	
Krabbe disease	$\beta$ -Galactocerebrosidase	-	-	-	
<b>LIPID STORAGE DISORDERS</b>					
Niemann-Pick type C	Intracellular cholesterol transport	-	-	(+)	
Wolman disease	Acid lipase	(+)	-	+	
Ceroid lipofuscinosis, infantile (Santavuori-Haltia)	Palmitoyl-protein thioesterase (CLN1)	-	-	-	
Ceroid lipofuscinosis, late infantile (Jansky-Bielschowsky)	Pepstatin-insensitive peptidase (CLN2); variants in Finland (CLN5), Turkey (CLN7), and Italy (CLN6)	-	-	-	
Ceroid lipofuscinosis, juvenile (Spielmeyer-Vogt)	CLN3, membrane protein	-	-	-	
Ceroid lipofuscinosis, adult (Kufs, Parry)	CLN4, probably heterogeneous	(+)	-	-	
<b>OLIGOSACCHARIDOSES</b>					
Aspartylglucosaminuria	Aspartylglucosaminidase	-	+	(+)	
Fucosidosis	$\alpha$ -Fucosidase	-	++	(+)	
$\alpha$ -Mannosidosis	$\alpha$ -Mannosidase	-	++	+	
$\beta$ -Mannosidosis	$\beta$ -Mannosidase	-	+	(+)	
Schindler disease	$\alpha$ -N-Acetylgalactosaminidase	-	-	-	
Sialidosis I	Sialidase	(+)	-	-	
Sialidosis II	Sialidase	(+)	++	+	

++, Prominent; +, often present; (+), inconstant or occurring later in the disease course; -, not present; GAG, glycosaminoglycans.

Modified from Hoffmann GF, Nyhan WL, Zschoke J, et al: Storage disorders in inherited metabolic diseases, Philadelphia, 2002, Lippincott Williams & Wilkins, pp. 346-351.

CARDIAC INVOLVEMENT CARDIAC FAILURE	MENTAL DETERIORATION	MYOCLONUS	SPASTICITY	PERIPHERAL NEUROPATHY	CHERRY-RED SPOT	CORNEAL CLOUDING	ANGIOKERATOMATA
++	++	-	-	-	-	(+)	-
-	(+)	-	-	-	-	+	-
-	(+)	-	-	-	-	-	-
+	-	-	-	-	-	+	++
++	+	-	-	+	(+)	-	-
+	++	(+)	+	-	+	+	+
(+)	++	-	(+)	-	(+)	+	+
-	++	+	+	-	++	-	-
-	-	-	-	-	-	-	-
-	++	+	+	-	-	-	-
-	+	(+)	(+)	-	-	-	-
-	+	(+)	-	(+)	(++)	-	-
-	-	-	-	(+)	(+)	-	-
-	++	-	+	++	(+)	-	-
-	++	-	+	++	(+)	-	-
-	+	-	-	-	(+)	-	-
(+)	-	-	-	-	(+)	-	-
-	+	+	+	-	-	-	-
-	+	+	+	-	-	-	-
-	+	-	(+)	-	-	-	-
-	+	-	-	-	-	-	-
(+)	+	-	-	-	-	(+)	(+)
+	++	+	+	-	-	-	(+)
-	++	-	(+)	-	-	++	(+)
-	+	-	+	+	-	-	(+)
-	+	+	+	-	-	-	-
-	-	++	+	+	++	(+)	-
+	++	(+)	-	-	++	-	+

## 708 Part XI ◆ Metabolic Disorders

<b>Table 86-16</b> Symptoms Encountered in Patients with Lysosomal Storage Disorders			
<b>SYSTEM</b>	<b>MANIFESTATIONS</b>	<b>SYSTEM</b>	<b>MANIFESTATIONS</b>
Neurologic	Hypotonia Floppy-infant syndrome Trismus Strabismus Opisthotonus Spasticity Seizures Peripheral neuropathy Developmental delay Irritability Extrapyramidal movement disorder Hydrocephalus	Facial	Bilateral epicanthal inferior orbital creases Palpebral edema Hypertelorism Coarse facies Low-set ears
Respiratory	Congenital lobar emphysema Recurrent respiratory infections Hoarseness	Gastrointestinal	Hepatosplenomegaly Neonatal cholestasis
Endocrine	Osteopenia Metabolic bone disease Secondary hyperparathyroidism Congenital adrenal hyperplasia	Bones and joints	Lytic bone lesions Joint contractures Dysostosis multiplex Hyperphosphatasemia Vertebral breaking Broadening of tubular bones Punctuate epiphysis Craniosynostosis Painful joint swelling
Cardiovascular	Cardiomegaly Congenital heart failure Arrhythmias Wolff-Parkinson-White syndrome Cardiomyopathy	Skin	Congenital ichthyosis Collodion infant Hypopigmentation Telangiectasias Extended Mongolian spots
Dysmorphology		Ocular	Corneal clouding Megalocornea Glaucoma Cherry-red spots Fundal hypopigmentation Bilateral cataracts
Head and neck	Macrocephaly Enlarged nuchal translucency Microstomia Micrognathia/microretrognathia Long philtrum	Hematologic	Anemia Thrombocytopenia
Limbs	Bilateral broad thumbs and toes Bilateral club feet	Hydrops fetalis	Nonimmune hydrops fetalis Congenital ascites
Oral	Macroglossia Molar hypoplasia Hypertrophic gums		

From Staretz-Chacham O, Lang TC, LaMarca ME, et al: Lysosomal storage disorders in the newborn, Pediatrics 123:1191–1207, 2009.

**Table 87-1** Features of the Disorders of Carbohydrate Metabolism

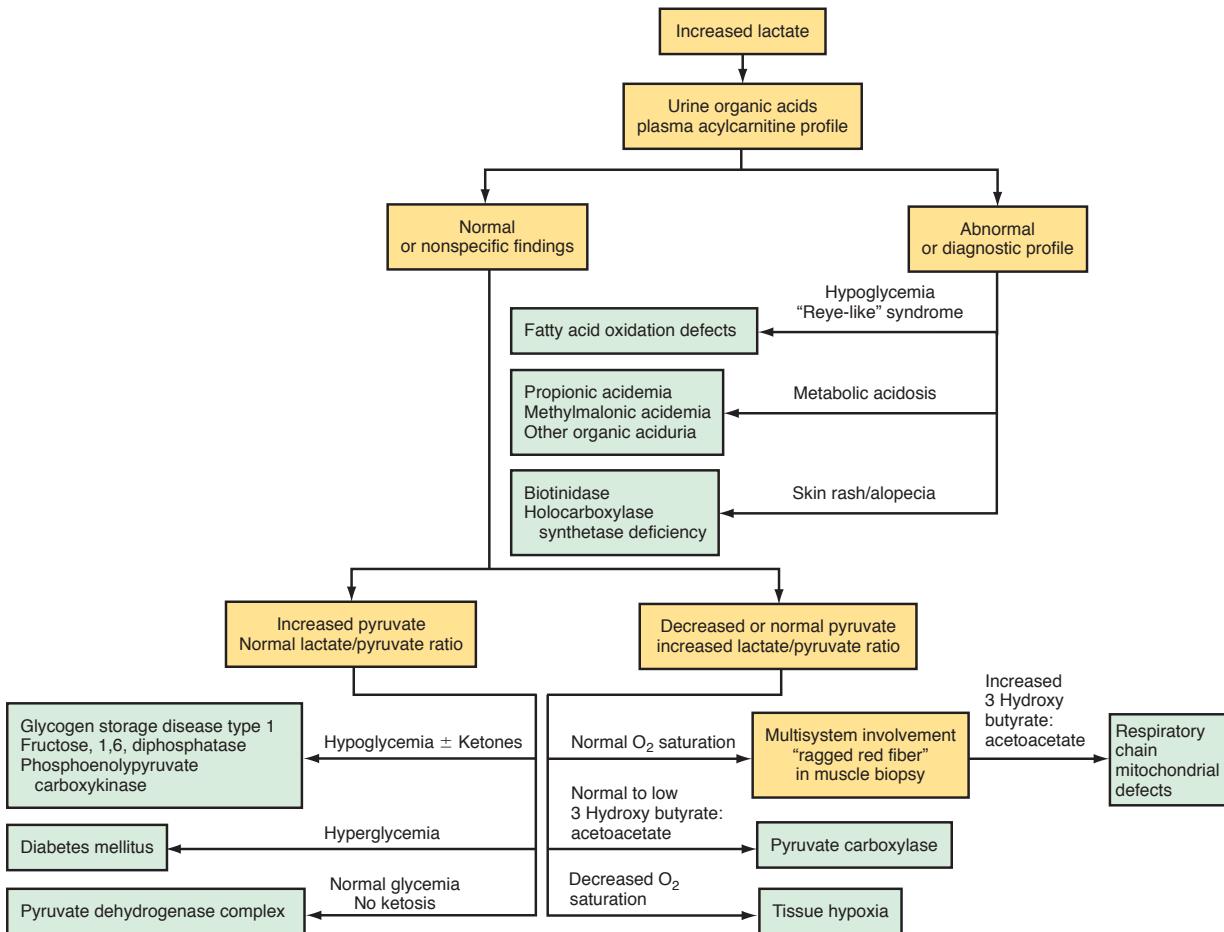
DISORDERS	BASIC DEFECTS	CLINICAL PRESENTATION	COMMENTS
<b>LIVER GLYCOGENOSSES</b>			
<i>Type/Common Name</i>			
Ia/Von Gierke	Glucose-6-phosphatase	Growth retardation, hepatomegaly, hypoglycemia; elevated blood lactate, cholesterol, triglyceride, and uric acid levels	Common, severe hypoglycemia
Ib	Glucose-6-phosphate translocase	Same as type Ia, with additional findings of neutropenia and impaired neutrophil function	10% of type Ia
IIIa/Cori or Forbes	Liver and muscle debrancher deficiency (amylo-1,6-glucosidase)	Childhood: hepatomegaly, growth retardation, muscle weakness, hypoglycemia, hyperlipidemia, elevated transaminase levels; liver symptoms can progress to liver failure later in life	Common, intermediate severity of hypoglycemia
IIIb	Liver debrancher deficiency; normal muscle enzyme activity	Liver symptoms same as in type IIIa; no muscle symptoms	15% of type III
IV/Andersen	Branching enzyme	Failure to thrive, hypotonia, hepatomegaly, splenomegaly, progressive cirrhosis (death usually before 5th yr), elevated transaminase levels	Rare neuromuscular variants exist
VI/Hers	Liver phosphorylase	Hepatomegaly, typically mild hypoglycemia, hyperlipidemia, and ketosis	Rare, typically benign glycogenosis; severe presentation also known
Phosphorylase kinase deficiency	Phosphorylase kinase	Hepatomegaly, mild hypoglycemia, hyperlipidemia, and ketosis	Common, typically a benign glycogenosis, severe progressive forms also present
Glycogen synthase deficiency	Glycogen synthase	Early morning drowsiness and fatigue, fasting hypoglycemia, and ketosis, no hepatomegaly	Decreased liver glycogen store
Fanconi-Bickel syndrome	Glucose transporter 2 (GLUT-2)	Failure to thrive, rickets, hepatorenomegaly, proximal renal tubular dysfunction, impaired glucose and galactose utilization	GLUT-2 expressed in liver, kidney, pancreas, and intestine
<b>MUSCLE GLYCOGENOSSES</b>			
<i>Type/Common Name</i>			
II/Pompe infantile	Acid $\alpha$ -glucosidase (acid maltase)	Cardiomegaly, hypotonia, hepatomegaly; onset: birth to 6 mo	Common, cardiorespiratory failure leading to death by age 1-2 yr; minimal to no residual enzyme activity
II/Late-onset Pompe (juvenile and adult) Danon disease	Acid $\alpha$ -glucosidase (acid maltase) Lysosome-associated membrane protein 2 (LAMP2)	Myopathy, variable cardiomyopathy, respiratory insufficiency; onset: childhood to adulthood Hypertrophic cardiomyopathy	Residual enzyme activity Rare, X-linked
PRKAG2 deficiency	Adenosine monophosphate (AMP)-activated protein kinase $\gamma$	Hypertrophic cardiomyopathy	Autosomal dominant
V/McArdle	Myophosphorylase	Exercise intolerance, muscle cramps, increased fatigability	Common, male predominance
VII/Tarui	Phosphofructokinase	Exercise intolerance, muscle cramps, hemolytic anemia, myoglobinuria	Prevalent in Japanese and Ashkenazi Jews
Phosphoglycerate kinase deficiency	Phosphoglycerate kinase	As with type V	Rare, X-linked
Phosphoglycerate mutase deficiency	M subunit of phosphoglycerate mutase	As with type V	Rare, majority of patients are African-American
Lactate dehydrogenase deficiency	M subunit of lactate dehydrogenase	As with type V	Rare
<b>GALACTOSE DISORDERS</b>			
Galactosemia with transferase deficiency	Galactose-1-phosphate uridylyltransferase	Vomiting, hepatomegaly, cataracts, aminoaciduria, failure to thrive	African-American patients tend to have milder symptoms
Galactokinase deficiency	Galactokinase	Cataracts	Benign
Generalized uridine diphosphate galactose-4-epimerase deficiency	Uridine diphosphate galactose-4-epimerase	Similar to transferase deficiency with additional findings of hypotonia and nerve deafness	A benign variant also exists
<b>FRUCTOSE DISORDERS</b>			
Essential fructosuria	Fructokinase Fructose-1-phosphate aldolase	Urine reducing substance Acute: vomiting, sweating, lethargy	Benign
Hereditary fructose intolerance		Chronic: failure to thrive, hepatic failure	Prognosis good with fructose restriction

Continued

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**Table 87-1** Features of the Disorders of Carbohydrate Metabolism—cont'd

DISORDERS	BASIC DEFECTS	CLINICAL PRESENTATION	COMMENTS
<b>DISORDERS OF GLUCONEOGENESIS</b>			
Fructose-1,6-diphosphatase deficiency	Fructose-1,6-diphosphatase	Episodic hypoglycemia, apnea, acidosis	Good prognosis, avoid fasting
Phosphoenolpyruvate carboxykinase deficiency	Phosphoenolpyruvate carboxykinase	Hypoglycemia, hepatomegaly, hypotonia, failure to thrive	Rare
<b>DISORDERS OF PYRUVATE METABOLISM</b>			
Pyruvate dehydrogenase complex defect	Pyruvate dehydrogenase	Severe fatal neonatal to mild late onset, lactic acidosis, psychomotor retardation, and failure to thrive	Most commonly caused by E <sub>1α</sub> subunit, defect X-linked
Pyruvate carboxylase deficiency	Pyruvate carboxylase	Same as above	Rare, autosomal recessive
Respiratory chain defects (oxidative phosphorylation disease)	Complexes I-V, many mitochondrial DNA mutations	Heterogeneous with multisystem involvement	Mitochondrial inheritance
<b>DISORDERS IN PENTOSE METABOLISM</b>			
Pentosuria	L-Xylulose reductase	Urine-reducing substance	Benign
Transaldolase deficiency	Transaldolase	Liver cirrhosis and failure, cardiomyopathy	Autosomal recessive
Ribose-5-phosphate isomerase deficiency	Ribose-5-phosphate isomerase	Progressive leukoencephalopathy and peripheral neuropathy	

**Figure 87-5** Algorithm of the differential diagnosis of lactic acidosis.

**Table 87-3** Modified Walker Criteria Applied to Children Referred for Evaluation of Mitochondrial Disease

	MAJOR CRITERIA	MINOR CRITERIA
Clinical	Clinically complete RC encephalomyopathy* or a mitochondrial cytopathy defined as fulfilling 3 criteria†	Symptoms compatible with an RC defect‡
Histology	>2% RRF in skeletal muscle	Smaller numbers of RRF, SSAM, or widespread electron microscopy abnormalities of mitochondria
Enzymology	Cytochrome c oxidase-negative fibers or residual activity of an RC complex <20% in a tissue; <30% in a cell line, or <30% in 2 or more tissues	Antibody-based demonstration of an RC defect or residual activity of an RC complex 20-30% in a tissue, 30-40% in a cell line, or 30-40% in 2 or more tissues
Functional	Fibroblast ATP synthesis rates >3 SD below mean	Fibroblast ATP synthesis rates 2-3 SD below mean, or fibroblasts unable to grow in galactose media
Molecular	Nuclear or mtDNA mutation of undisputed pathogenicity	Nuclear or mtDNA mutation of probable pathogenicity
Metabolic		One or more metabolic indicators of impaired metabolic function

\*Leigh disease, Alpers disease, lethal infantile mitochondrial disease, Pearson syndrome, Kearns-Sayre syndrome, MELAS (myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), MERRF (myoclonic epilepsy associated with ragged red fibers), NARP (neuropathy, ataxia and retinitis pigmentosa), MNGIE (mitochondrial neurogastrointestinal encephalomyopathy), and LHON (Leber hereditary optic neuropathy).

†(1) Unexplained combination of multisystemic symptoms that is essentially pathognomonic for an RC disorder, (2) a progressive clinical course with episodes of exacerbation or a family history strongly indicative of an mtDNA mutation, and (3) other possible metabolic or nonmetabolic disorders have been excluded by appropriate testing.

‡Added pediatric features: stillbirth associated with a paucity of intrauterine movement, neonatal death or collapse, movement disorder, severe failure to thrive, neonatal hypotonia, and neonatal hypertonia as minor clinical criteria.

ATP, adenosine triphosphate; mtDNA, mitochondrial DNA; RC, respiratory chain; RRF, ragged red fibers; SSAM, subsarcolemmal accumulation of mitochondria. From Scaglia F, Towbin JA, Craigen WJ, et al: Clinical spectrum, morbidity and mortality in 113 pediatric patients with mitochondrial disease, Pediatrics 114:925-931, 2004.

**Table 87-4 Clues to the Diagnosis of Mitochondrial Disease**

NEUROLOGIC
Cerebral stroke-like lesions in a nonvascular pattern
Basal ganglia disease
Encephalopathy: recurrent or with low/moderate dosing of valproate
Neurodegeneration
Epilepsia partialis continua
Myoclonus
Ataxia
MRI findings consistent with Leigh disease
Characteristic MRS peaks
Lactate peak at 1.3 ppm TE (time to echo) at 35 and 135
Succinate peak at 2.4 ppm
CARDIOVASCULAR
Hypertrophic cardiomyopathy with rhythm disturbance
Unexplained heart block in a child
Cardiomyopathy with lactic acidosis (>5 mM)
Dilated cardiomyopathy with muscle weakness
Wolff-Parkinson-White arrhythmia
OPHTHALMOLOGIC
Retinal degeneration with signs of night blindness, color vision deficits, decreased visual acuity, or pigmentary retinopathy
Ophthalmoplegia/paresis
Fluctuating, dysconjugate eye movements
Ptosis
Sudden- or insidious-onset optic neuropathy/atrophy
GASTROENTEROLOGIC
Unexplained or valproate-induced liver failure
Severe dysmotility
Pseudoobstructive episodes
OTHER
A newborn, infant, or young child with unexplained hypotonia, weakness, failure to thrive, and a metabolic acidosis (particularly lactic acidosis)
Exercise intolerance that is not in proportion to weakness
Hypersensitivity to general anesthesia
Episodes of acute rhabdomyolysis

From Haas RH, Parikh S, Falk MJ, et al: Mitochondrial disease: a practical approach for primary care physicians, Pediatrics 120:1326-1333, 2007, Table 1, p. 1327.

**Table 88-1** Recognition Pattern of Mucopolysaccharidoses

MANIFESTATIONS	Mucopolysaccharidosis Type						
	I-H	I-S	II	III	IV	VI	VII
Mental deficiency	+	-	±	+	-	-	±
Coarse facial features	+	(+)	+	+	-	+	±
Corneal clouding	+	+	-	-	(+)	+	±
Visceromegaly	+	(+)	+	(+)	-	+	+
Short stature	+	(+)	+	-	+	+	+
Joint contractures	+	+	+	-	-	+	+
Dysostosis multiplex	+	(+)	+	(+)	+	+	+
Leucocyte inclusions	+	(+)	+	+	-	+	+
Mucopolysacchariduria	+	+	+	+	+	+	+

I-H, Hurler disease; I-S, Scheie disease; II Hunter disease; III, Sanfilippo disease; IV, Morquio disease; VI, Maroteaux-Lamy disease; VII Sly disease.

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**Table 88-2** Mucopolysaccharidoses: Clinical, Molecular, and Biochemical Aspects

MPS TYPE	EPONYM	INHERITANCE	GENE CHROMOSOME	MAIN CLINICAL FEATURES	DEFECTIVE ENZYME	ASSAY	MIM NUMBER
I-H	Pfaundler-Hurler	AR	<i>IDUA</i> 4p16.3	Severe Hurler phenotype, mental deficiency, corneal clouding, death usually before age 14 yr; Hurler phenotype, mental retardation, corneal clouding, death usually before age 14 yr	α-L-iduronidase	L,F,Ac,CV	252800 607014
I-S	Scheie	AR	<i>IDUA</i> 4p16.4	Stiff joints, corneal clouding, aortic valve disease, normal intelligence, survive to adulthood	α-L-iduronidase	L,F,Ac,CV	607016
I-HS	Hurler-Scheie	AR	<i>IDUA</i> 4p16.4	Phenotype intermediate between I-H and I-S	α-L-iduronidase	L,F,Ac,Cv	607015
II	Hunter	XLR	<i>IDS</i> Xq27.3-28	Severe course similar to I-H but clear cornea. Mild course: less pronounced features, later manifestation, survival to adulthood with mild or without mental deficiency	Iduronate sulfate sulfatase	S,F,Af,Ac,Cv	309900
III-A	Sanfilippo A	AR	<i>SGSH</i> 17q25.3	Behavioral problems, sleeping disorder, aggression, progressive dementia, mild dysmorphism, coarse hair, clear corneas; survival to adulthood possible	Heparan-S-sulfamidase	L,F,Ac,Cv	252900 605270
II-IB	Sanfilippo B	AR	<i>NAGLU</i> 17q21		N-Acetyl- $\alpha$ -D-glucosaminidase	S,F,Ac,Cv	252920
III-C	Sanfilippo C	AR	<i>HGSNAT</i> 8p11.21		Acetyl-CoA: $\alpha$ -glucosaminide N-acetyltransferase	F,Ac	252930
III-D	Sanfilippo D	AR	<i>GNS</i> 12q14		N-Acetylglucosamine-6-sulfatase	F,Ac	252940 607664
IV-A	Morquio A	AR	<i>GALNS</i> 16q24.3	Short-trunk dwarfism, fine corneal opacities, characteristic bone dysplasia; final height below 125 cm	N-Acetyl-galactosamine-6-sulfatase	L,F,Ac	253000
IV-B	Morquio B	AR	<i>GLB1</i> 3p21.33	Same as IV-A, but milder; adult height over 120 cm	$\beta$ -Galactosidase	L,F,Ac,Cv	253010 230500
VI	Maroteaux-Lamy	AR	<i>ARSB</i> 5q11-q13	Hurler phenotype with marked corneal clouding but normal intelligence; mild, moderate and severe expression in different families	N-Acetyl-galactosamine-4-sulfatase (arylsulfatase B)	L,F,Ac	253200
VII	Sly	AR	<i>GUSB</i> 7q21.11	Varying from fetal hydrops to mild dysmorphism; dense inclusions in granulocytes	$\beta$ -Glucuronidase	S,F,Ac,Cv	253220
IX	Hyaluronidase deficiency	AR	<i>HYAL1</i> 3p21.3	Periarticular masses, no Hurler phenotype H	Hyaluronidase 1	S	601492

Ac, cultured amniotic cells; Af, amniotic fluid; Cv, chorionic villi; F, cultured fibroblasts; L, leukocytes; MIM, Mendelian Inheritance in Man Catalogue; S, serum.

**Table 88-3** Therapies Aimed at Proximate Causes of Mucopolysaccharidoses

MPS TYPE	STEM CELL TRANSPLANTATION (SCT)	ENZYME REPLACEMENT	REMARKS
I	Yes	Aldurazyme	Transplantation before age 2 yr. Enzyme replacement before and after transplantation
II	Questionable	Elaprase	Lack of neurologic improvement after stem cell transplantation
III	No	No	Experimental: Substrate reduction by flavanoids
IVA	No	Preclinical	Recombinant GALNS trial in course
VI	Yes	Naglazyme	Sustained improvement
VII	Questionable	?	Single SCT attempt without neurologic improvement

GALNS, galactosamine(N-acetyl)-6-sulfatase.

**Table 88-4** Symptomatic Management of Mucopolysaccharidoses

PROBLEM	PREDOMINANTLY IN	MANAGEMENT
<b>NEUROLOGIC</b>		
Hydrocephalus	MPS-I, -II, -VI, -VII	Funduscopic, CT scan
Chronic headaches	All	Ventriculoperitoneal shunting
Behavioral disturbance	MPS-III	Behavioral medication, sometimes CT scan, ventriculoperitoneal shunting
Disturbed sleep/wake circle	MPS-III	Melatonin
Seizures	MPS-I, -II, -III	Electroencephalogram, anticonvulsants
Odontoid hypoplasia	MPS-IV	Cervical MRI, upper cervical fusion
Spinal cord compression	All	Laminectomy, dural excision
<b>OPHTHALMOLOGIC</b>		
Corneal opacity	MPS-I, -VI, -VII	Corneal transplant
Glaucoma	MPS-I, -VI, -VII	Medication, surgery
Retinal degeneration	MPS-I, -II	Night light
<b>EARS, AIRWAYS</b>		
Recurrent otitis media	MPS-I, -II, -VI, -VII	Ventilating tubes
Impaired hearing	All except MPS-IV	Audiometry, hearing aids
Obstruction	All except MPS-III	Adenotomy, tonsillectomy, bronchodilator therapy, continuous positive airway pressure at night, laser excision of tracheal lesions, tracheotomy
<b>CARDIAC</b>		
Cardiac valve disease	MPS-I, -II, -VI, -VII	Endocarditis prevention, valve replacement
Coronary insufficiency	MPS-I, -II, -VI, -VII	Medical therapy
Arrhythmias	MPS-I, -II, -VI, -VII	Antiarrhythmic medication, pacemaker
<b>ORAL, GASTROINTESTINAL</b>		
Hypertrophic gums, poor teeth	MPS-I, -II, -VI, -VII	Dental care
Chronic diarrhea	MPS-II	Diet modification, loperamide
<b>MUSCULOSKELETAL</b>		
Joint stiffness	All except MPS-IV	Physical therapy
Weakness	All	Physical therapy, wheelchair
Gross long bone malalignment	All	Corrective osteotomies
Carpal tunnel syndrome	MPS-I, -II, -VI, -VII	Electromyography, surgical decompression
<b>ANESTHESIA</b>		
	All except MPS-III	Avoid atlantoaxial dislocation, use angulated video intubation laryngoscope and small endotracheal tubes

Table 91-1 | The Human Porphyrias: Mutations, Time of Presentation, and Tissue- and Symptom-Based Classifications

DISEASE (ABBREVIATION)	ENZYME (ABBREVIATION)	INHERITANCE	PRESENTATION	Classifications		
				HEPATIC	ERYTHROPOIETIC	ACUTE/NEUROLOGIC
X-Linked protoporphyrria (XLP)	δ-Aminolevulinate synthase 2 (ALAS2)	X-linked	Childhood	X	X*	X
δ-Aminolevulinic acid dehydratase porphyria (ADP)	δ-Aminolevulinic acid dehydratase (ALAD)	Autosomal recessive	Mostly post puberty	X	X*	X
Acute intermittent porphyria (AIP)	Porphobilinogen deaminase (PBGD)	Autosomal dominant	Post puberty	X	X	X
Homozygous AIP		Homozygous dominant	Childhood	X	X	X
Congenital erythropoietic porphyria (CEP)	Uroporphyrinogen III synthase (UROS)	Autosomal recessive	In utero or infancy	X	X	X
Porphyria cutanea tarda (PCT) type 1	Uroporphyrinogen decarboxylase (UROD)	Sporadic	Adults	X	X	X
PCT type 2 <sup>†</sup>		Autosomal dominant	Adults	X	X	X
PCT type 3		Unknown	Adults	X	X	X
Hepatoerythropoietic porphyria (HEP)		Homozygous dominant	Childhood	X	X*	X
Hereditary coproporphyria (HCP)	Coproporphyrinogen oxidase (CPOX)	Autosomal dominant	Post puberty	X	X	X
Homozygous HCP		Homozygous dominant	Childhood	X	X	X
Variegate porphyria (VP)	Protoporphyrinogen oxidase (PPOX)	Autosomal dominant	Post puberty	X	X	X
Homozygous VP		Homozygous dominant	Childhood	X	X	X
Erythropoietic protoporphyrria (EPP)	Ferrochelatase (FECH)	Autosomal recessive(most commonly heteroallelic with hypomorphic allele)	Childhood	X	X	X

\*ADP and HEP are considered primarily hepatic porphyrias, but substantial increases in erythrocyte zinc protoporphyrin suggest an erythropoietic component.

<sup>†</sup>PCT is a result of inhibition of hepatic UROD. Autosomal dominant inheritance of a partial deficiency of UROD is a predisposing factor in cases defined as familial (type 2) PCT.

**Table 91-2** The 3 Most Common Human Porphyrias and Their Major Features

	PRESENTING SYMPTOMS	EXACERBATING FACTORS	MOST IMPORTANT SCREENING TESTS	TREATMENT
Acute intermittent porphyria	Neurologic, adult onset	Drugs (mostly P450-inducers), progesterone, dietary restriction	Urinary porphobilinogen	Hemin, glucose
Porphyria cutanea tarda	Skin blistering and fragility (chronic), adult onset	Iron, alcohol, smoking, estrogens, hepatitis C, HIV, halogenated hydrocarbons	Plasma (or urine) porphyrins	Phlebotomy, low-dose hydroxychloroquine
Erythropoietic protoporphyrina	Skin pain and swelling (mostly acute), childhood onset		Erythrocyte (or plasma) porphyrins	Beta-carotene

**Table 91-3** Drugs Regarded as Unsafe and Safe in Acute Porphyrias

UNSAFE	SAFE
Barbiturates	Narcotic analgesics
Sulfonamide antibiotics*	Aspirin
Meprobamate* (also mebutamate,* tybutamate*)	Acetaminophen
Carisoprodol*	Phenothiazines
Glutethimide*	Penicillin and derivatives
Methyprylon	Streptomycin
Ethchlorvynol*	Glucocorticoids
Mephenytoin	Bromides
Phenytoin*	Insulin
Succinimides	Atropine
Carbamazepine*	Cimetidine
Clonazepam†	Ranitidine†
Primidone*	Acetaminophen (paracetamol)
Valproic acid*	Acetazolamide
Pyrazolones (aminopyrine, antipyrine)	Allopurinol
Griseofulvin*	Amiloride
Ergots	Bethanidine
Metoclopramide*‡	Bumetanide
Rifampin*	Cimetidine
Pyrazinamide*‡	Coumarins
Diclofenac*‡	Fluoxetine
Progesterone and synthetic progestins*	Gabapentin
Danazol*	Gentamicin
Alcohol	Guanethidine
Angiotensin-converting enzyme inhibitors (especially enalapril)*‡	Ofloxacin
Calcium channel blockers (especially nifedipine)*‡	Propranolol
Ketoconazole	Succinylcholine Tetracycline

**Table 92-1** Manifestations of Hypoglycemia in Childhood

FEATURES ASSOCIATED WITH ACTIVATION OF AUTONOMIC NERVOUS SYSTEM AND EPINEPHRINE RELEASE*	
Anxiety†	
Perspiration†	
Palpitation (tachycardia)†	
Pallor†	
Tremulousness†	
Weakness	
Hunger	
Nausea	
Emesis	
FEATURES ASSOCIATED WITH CEREBRAL GLUCOPENIA	
Headache†	
Mental confusion†	
Visual disturbances (↓ acuity, diplopia)†	
Organic personality changes†	
Inability to concentrate†	
Dysarthria	
Staring	
Paresthesias	
Dizziness	
Amnesia	
Ataxia, incoordination	
Refusal to feed†	
Somnolence, lethargy†	
Seizures†	
Coma	
Stroke, hemiplegia, aphasia	
Decerebrate or decorticate posture	

\*Some of these features will be attenuated if the patient is receiving  $\beta$ -adrenergic blocking agents.

†Common.

‡Most common manifestations in the newborn.

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**Table 92-2** Classification of Hypoglycemia in Infants and Children

<b>NEONATAL TRANSITIONAL (ADAPTIVE) HYPOGLYCEMIA</b>	<b>Lipolysis Disorders</b>
<i>Associated with Inadequate Substrate or Immature Enzyme Function in Otherwise Normal Neonates</i>	<b>Fatty Acid Oxidation Disorders</b>
Prematurity	Carnitine transporter deficiency (primary carnitine deficiency)
Small for gestational age	Carnitine palmitoyltransferase-1 deficiency
Normal newborn	Carnitine translocase deficiency
<b>Transient Neonatal Hyperinsulinism</b>	Carnitine palmitoyltransferase-2 deficiency
Infant of diabetic mother	Secondary carnitine deficiencies
Small for gestational age	Very-long-, long-, medium-, short-chain acyl-CoA dehydrogenase deficiency
Discordant twin	
Birth asphyxia	
Infant of toxemic mother	
<b>NEONATAL, INFANTILE, OR CHILDHOOD PERSISTENT HYPOGLYCEMIAS</b>	<b>OTHER ETIOLOGIES</b>
<b>Hyperinsulinism</b>	<b>Substrate-Limited</b>
Recessive K <sub>ATP</sub> channel HI	Ketotic hypoglycemia
Recessive HADH (hydroxyl acyl-CoA dehydrogenase) mutation HI	Poisoning—drugs
Recessive UCP2 (mitochondrial uncoupling protein 2) mutation HI	Salicylates
Focal K <sub>ATP</sub> channel HI	Alcohol
Dominant K <sub>ATP</sub> channel HI	Oral hypoglycemic agents
Atypical congenital hyperinsulinemia (no mutations in ABCC8 or KCN11 genes)	Insulin
Dominant glucokinase HI	Propranolol
Dominant glutamate dehydrogenase HI (hyperinsulinism/hyperammonemia syndrome)	Pentamidine
Dominant mutations in HNF-4A and HNF-1A (hepatic nuclear factors 4α and 1α) HI with monogenic diabetes of youth later in life	Quinine
Dominant mutation in SLC16A1 (the pyruvate transporter)—exercise-induced hypoglycemia	Disopyramide
Acquired islet adenoma	Ackee fruit (unripe)—hypoglycin
Beckwith-Wiedemann syndrome	Vacor (rat poison)
Insulin administration (Munchausen syndrome by proxy)	Trimethoprim-sulfamethoxazole (with renal failure)
Oral sulfonylurea drugs	<b>Liver Disease</b>
Congenital disorders of glycosylation	Reye syndrome
<b>Counterregulatory Hormone Deficiency</b>	Hepatitis
Panhypopituitarism	Cirrhosis
Isolated growth hormone deficiency	Hepatoma
Adrenocorticotrophic hormone deficiency	
Addison disease	
Epinephrine deficiency	
<b>Glycogenolysis and Gluconeogenesis Disorders</b>	<b>AMINO ACID AND ORGANIC ACID DISORDERS</b>
Glucose-6-phosphatase deficiency (GSD 1a)	Maple syrup urine disease
Glucose-6-phosphate translocase deficiency (GSD 1b)	Propionic acidemia
Amylo-1,6-glucosidase (debranching enzyme) deficiency (GSD 3)	Methylmalonic acidemia
Liver phosphorylase deficiency (GSD 6)	Tyrosinosis
Phosphorylase kinase deficiency (GSD 9)	Glutaric aciduria
Glycogen synthetase deficiency (GSD 0)	3-Hydroxy-3-methylglutaric aciduria
Fructose-1,6-diphosphatase deficiency	
Pyruvate carboxylase deficiency	
Galactosemia	
Hereditary fructose intolerance	
	<b>SYSTEMIC DISORDERS</b>
	Sepsis
	Carcinoma/sarcoma (secreting—insulin-like growth factor II)
	Heart failure
	Malnutrition
	Malabsorption
	Antiinsulin receptor antibodies
	Antiinsulin antibodies
	Neonatal hyperviscosity
	Renal failure
	Diarrhea
	Burns
	Shock
	Postsurgical
	Pseudohypoglycemia (leukocytosis, polycythemia)
	Excessive insulin therapy of insulin-dependent diabetes mellitus
	Factitious
	Nissen fundoplication (dumping syndrome)
	Falciparum malaria

GSD, glycogen storage disease; HI, hyperinsulinemia; K<sub>ATP</sub>, regulated potassium channel.

**Table 92-3** Hypoglycemia in Infants and Children: Clinical and Laboratory Features

GROUP	AGE AT DIAGNOSIS (mo)	GLUCOSE* (mg/dL)	INSULIN ( $\mu$ U/mL)	FASTING TIME TO HYPOGLYCEMIA (hr)
<b>HYPERINSULINEMIA (N = 12)</b>				
Mean	7.4	23.1	22.4	2.1 <sup>†</sup>
SEM	2.0	2.7	3.2	0.6
<b>NONHYPERINSULINEMIA (N = 16)</b>				
Mean	41.8	36.1	5.8	18.2
SEM	7.3	2.4	0.9	2.9

\*In hypoglycemia caused by hyperinsulinism β OH butyrate and FFA are low compared with normal at same duration of fasting.

<sup>†</sup>Milder forms of hyperinsulinism may require up to 18 hr of fasting to provoke hypoglycemia.

SEM, standard error of mean.

Adapted from Antunes JD, Geffner ME, Lippe BM, et al: Childhood hypoglycemia: differentiating hyperinsulinemic from nonhyperinsulinemic causes, J Pediatr 116:105-108, 1990.

**Table 92-4** Correlation of Clinical Features with Molecular Defects in Persistent Hyperinsulinemic Hypoglycemia in Infancy

TYPE	MACROSOMIA	HYPOGLYCEMIA/ HYPERINSULINEMIA	FAMILY HISTORY	MOLECULAR DEFECTS	BIOMOLECULAR, OR MOLECULAR FEATURES	RESPONSE TO MEDICAL MANAGEMENT	RECOMMENDED SURGICAL APPROACH	
							ASSOCIATED CLINICAL, BIOCHEMICAL, OR MOLECULAR FEATURES	
Sporadic	Present at birth	Moderate/severe in first days to weeks of life	Negative	? SUR1/K <sub>R</sub> 6.2	Loss of heterozygosity in microadenomatous tissue	Generally poor; may respond better to somatostatin than to diazoxide	Partial pancreatectomy if frozen section shows β-cell crowding with small nuclei—suggests microadenoma	Excellent if focal adenoma is removed, thereby curing hypoglycemia and retaining sufficient pancreas to avoid diabetes
							Subtotal >25% pancreatectomy if frozen section shows giant nuclei in β-cells—suggests diffuse hyperplasia	Guarded if subtotal (>95%) pancreatectomy is performed because diabetes develops in, and hypoglycemia persists in
Autosomal recessive	Present at birth	Severe in first days to weeks of life	Positive	SUR/K <sub>R</sub> 6.2	Consanguinity a feature in some populations	Poor	Subtotal pancreatectomy	Guarded
Autosomal dominant	Unusual	Moderate onset usually post 6 mo of age	Positive	Glucokinase (activating) Some cases gene unknown	None	Very good to excellent	Surgery usually not required Partial pancreatectomy only if medical management fails	Excellent
Autosomal dominant	Unusual	Moderate onset usually post 6 mo of age	Positive	Glutamate dehydrogenase (activating)	Modest hyperammonemia	Very good to excellent	Surgery usually not required	Excellent
Beckwith-Wiedemann syndrome	Present at birth	Moderate, spontaneously resolves post 6 mo of age	Negative	Duplicating/ imprinting in chromosome 11p15.1	Macroglossia, omphalocele, hemihypertrophy	Good	Not recommended	Excellent for hypoglycemia; guarded for possible development of embryonal tumors (Wilms hepatoblastoma)
Congenital disorders of glycosylation	Not usual	Moderate/onset post 3 mo of age	Negative	Phosphomannose isomerase deficiency	Hepatomegaly, vomiting, intractable diarrhea	Good with mannose supplement	Not recommended	Fair

**Table 92-5** Analysis of Critical Blood Sample During Hypoglycemia and 30 Minutes After Glucagon\*

SUBSTRATES
Glucose
Free fatty acids
Ketones
Lactate
Uric acid
Ammonia

HORMONES
Insulin
Cortisol
Growth hormone
Thyroxine, thyroid-stimulating hormone
Insulin-like growth factor binding protein-1†

\*Glucagon 50 µg/kg with maximum of 1 mg IV or IM.

†Measure once only before or after glucagon administration. Rise in glucose of ≥40 mg/dL after glucagon given at the time of hypoglycemia strongly suggests a hyperinsulinemic state with adequate hepatic glycogen stores and intact glycogenolytic enzymes. If ammonia is elevated to 100–200 µM, consider activating mutation of glutamate dehydrogenase.

**Table 92-6** Criteria for Diagnosing Hyperinsulinism Based on "Critical" Samples (Drawn at a Time of Fasting Hypoglycemia: Plasma Glucose <50 mg/dL)

- Hyperinsulinemia (plasma insulin >2 µU/mL)\*
- Hypofatty acidaemia (plasma free fatty acids <1.5 mmol/L)
- Hypoketonemia (plasma β-hydroxybutyrate: <2.0 mmol/L)
- Inappropriate glycemic response to glucagon, 1 mg IV (change in glucose >40 mg/dL)

\*Depends on sensitivity of insulin assay.

**Table 92-7** Diagnosis of Acute Hypoglycemia in Infants and Children

#### ACUTE SYMPTOMS PRESENT

- Obtain blood sample before and 30 min after glucagon administration.
- Obtain urine as soon as possible. Examine for ketones; if not present and hypoglycemia confirmed, suspect hyperinsulinemia or fatty acid oxidation defect; if present, suspect ketotic, hormone deficiency, inborn error of glycogen metabolism, or defective gluconeogenesis.
- Measure glucose in the original blood sample. If hypoglycemia is confirmed, proceed with substrate-hormone measurement as in Table 92-5.
- If glycemic increment after glucagon exceeds 40 mg/dL above basal, suspect hyperinsulinemia.
- If insulin level at time of confirmed hypoglycemia is >5 µU/mL, suspect endogenous hyperinsulinemia; if >100 µU/mL, suspect factitious hyperinsulinemia (exogenous insulin injection). Admit to hospital for supervised fast.
- If cortisol is <10 µg/dL or growth hormone is <5 ng/mL, or both, suspect adrenal insufficiency or pituitary disease, or both. Admit to hospital for hormonal testing and neuroimaging.

#### HISTORY SUGGESTIVE: ACUTE SYMPTOMS NOT PRESENT

- Careful history for relation of symptoms to time and type of food intake, bearing in mind age of patient. Exclude possibility of alcohol or drug ingestion. Assess possibility of insulin injection, salt craving, growth velocity, intracranial pathology.
- Careful examination for hepatomegaly (glycogen storage disease; defect in gluconeogenesis); pigmentation (adrenal failure); stature and neurologic status (pituitary disease).
- Admit to hospital for provocative testing:
  - 24 hr fast under careful observation; when symptoms provoked, proceed with steps 1–4 as when acute symptoms present.
  - Pituitary–adrenal function using arginine-insulin stimulation test if indicated.
- Consider molecular diagnostic test before liver biopsy for histologic and enzyme determinations.
- Oral glucose tolerance test (1.75 g/kg; max 75 g) if reactive hypoglycemia suspected (dumping syndrome, etc.).

**Table 93-2** Levels of In-Hospital Perinatal Care

#### MATERNAL

##### BASIC

Monitor and care for low-risk patients

Triage for high risk for transfer

Detection and care of unanticipated labor problems

Emergency cesarean delivery within 30 min

Blood bank, anesthesia, radiology, ultrasound, and laboratory support

Care of postpartum problems

Obstetrician, nurse, midwife staff

##### SPECIAL CARE

*Basic services plus:*

Care of high-risk pregnancies

Triage, transfer of high-risk pregnancies (<32 wk, intrauterine growth retardation, preeclampsia, severe maternal medical illness)

##### SUBSPECIALTY CARE

*Basic plus specialty care plus:*

Experienced perinatologist (24-hr coverage)

Evaluation of high-risk therapies

Care for severe maternal medical or obstetric illnesses

High-risk fetal care (Rh disease, nonimmune hydrops, life-threatening anomalies)

Outcomes research

Community education

#### NEONATE

Resuscitation

Stabilization

Well neonatal care

Nursery care

Visitation

General pediatrician staff (capable of neonatal resuscitation)

*Basic services plus:*

Care of high-risk neonate with short-term problems

Stabilization before transfer (<1,500 g, <32 wk, critically ill)

Accept convalescing back (reverse) transfers

*Basic plus specialty care plus:*

Experienced neonatologist (24-hr coverage)

Inborn plus transferred patients

Evaluation of high-risk therapies

All pediatric medical, radiologic, and surgical subspecialties

Neonatal intensive care unit with operating room capabilities

High-risk follow-up

Outcomes research

Community education

From American Academy of Pediatrics, American College of Obstetricians and Gynecologists: Guidelines for perinatal care, ed 5, Elk Grove Village, IL, 2002, American Academy of Pediatrics.

Table 92-8 | Clinical Manifestations and Differential Diagnosis in Childhood Hypoglycemia

Condition	Hypoglycemia	Serum				Effect of 24-36 hr Fast on Plasma				Glycemic Response to Glucagon		Glycemic Response to Infusion of Alanine or Glycerol	
		URIC ACID	LIPIDS	GLUCOSE	INSULIN	KETONES	ALANINE	LACTATE	FED	FASTED	ALANINE	GLYCEROL	
Normal	0	0	0	Normal	↓	↓	↑	↓	Normal	↑	↓	Not indicated	
Hyperinsulinemia	Recurrent severe	0	0	Normal or ↑	↓↓	↑↑	↓↓	Normal	Normal	↑	↑	Not indicated	
Ketotic hypoglycemia	Severe with missed meals	Ketonuria +++	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	↓↓	Not indicated	
Fatty acid oxidation disorder	Severe with missed meals	Absent	0 to + Abnormal liver function test results	Abnormal ↑	Contraindicated	↑	↑	↓↓	↑	↓	↑	Not indicated	
Hypopituitarism	Moderate with missed meals	Ketonuria ++	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	↓↓	↑	
Adrenal insufficiency	Severe with missed meals	Ketonuria 0 ++	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	↓↓	↑	
Enzyme deficiencies	Severe-constant	Ketonuria +++	↑↑	↑↑	↓↓	↓	↑↑	↑↑	↑↑	0	0↓↓	0	
Glucose-6-phosphatase debrancher	Moderate with fasting	++	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	0↓↓	↑	
Phosphorylase	Mild-moderate	Ketonuria + ++	Normal	Normal	↓	↓	↑↑	↓↓	Normal	0↑	0↓↓	↑	
Fructose-1,6-diphosphatase	Severe with fasting	Ketonuria +++	↑↑	↑↑	↓↓	↓	↑↑	↑↑	↑↑	↑	0↓↓	↓	
Galactosemia	After milk or milk products	0 Ketones; (s) +	Normal	Normal	↓	↑	↓	Normal	↑	0↓↓	↑	↑	
Fructose intolerance	After fructose +	0 Ketones; (s) +++	Normal	Normal	↓	↑	↓	Normal	↑	0↓↓	↑	↑	

Details of each condition are discussed in the text.  
0, absence; ↑ or ↓ indicates respectively small increase or decrease; ↑↑ or ↓↓ indicates respectively large increase or decrease.

# *The Newborn Infant*

**Table 93-3** Morbidities and Sequelae of Perinatal and Neonatal Illness

MORBIDITIES	EXAMPLES
<b>CENTRAL NERVOUS SYSTEM</b>	
Spastic diplegic-quadriplegic cerebral palsy	Hypoxic-ischemic encephalopathy, periventricular leukomalacia, undetermined antenatal factors
Choreoathetotic cerebral palsy	Bilirubin encephalopathy (kernicterus)
Microcephaly	Hypoxic-ischemic encephalopathy, intrauterine infection (rubella, CMV)
Communicating hydrocephalus	Intraventricular hemorrhage, meningitis
Seizures	Hypoxic-ischemic encephalopathy, hypoglycemia
Encephalopathy	Congenital infections (rubella, CMV, HIV, toxoplasmosis)
Educational failure and/or mental retardation	Immaturity, hypoxia, hypoglycemia, cerebral palsy, intraventricular hemorrhage, low socioeconomic status
<b>SENSATION—PERIPHERAL NERVES</b>	
Reduced visual acuity (blindness)	Retinopathy of prematurity
Strabismus	Undetermined, prematurity
Hearing impairment (deafness)	Drug toxicity (furosemide, aminoglycosides), bilirubin encephalopathy, hypoxia ± hyperventilation
Poor speech	Immaturity, chronic illness, hypoxia, prolonged endotracheal intubation, hearing deficit
Paralysis—paresis	Birth trauma—brachial plexus, phrenic nerve, spinal cord
<b>RESPIRATORY</b>	
BPD	Oxygen toxicity, barotrauma
Subglottic stenosis	Endotracheal tube injury
Sudden infant death syndrome	Prematurity, BPD, infant of illicit drug user
Choanal stenosis, nasal septum destruction	Nasotracheal intubation
	Growth failure
<b>CARDIOVASCULAR</b>	
Cyanosis	Precorrective palliative care of congenital cyanotic heart disease, cor pulmonale from BPD, reactive airway
Heart failure	Precorrective palliative care of complex congenital heart disease, BPD, ventricular septal defect
<b>GASTROINTESTINAL</b>	
Short-gut syndrome	Necrotizing enterocolitis, gastroschisis, malrotation-volvulus, cystic fibrosis, intestinal atresia
Cholestatic liver disease (cirrhosis, hepatic failure)	Hyperalimentation toxicity, sepsis, short-gut syndrome
Failure to thrive	Short-gut syndrome, cholestasis, BPD, cerebral palsy, severe congenital heart disease
Inguinal hernia	Unknown
<b>MISCELLANEOUS</b>	
Cutaneous scars	Chest tube or intravenous catheter placement, hyperalimentation, subcutaneous infiltration, fetal puncture, intrauterine varicella, cutis aplasia
Absence of radial artery pulse	Frequent arterial puncture
Hypertension	Renal thrombi, repair of coarctation of aorta

BPD, bronchopulmonary dysplasia; CMV, cytomegalovirus.

**Table 93-4** Incidence of Adverse Outcome According to Completed Week of Gestation at Delivery for Infants Born by Caesarean Section

OUTCOME	WK 37 (N = 934)	WK 38 (N = 3909)	WK 39 (N = 6512)	WK 40 (N = 1385)	WK 41 (N = 1385)	WK 42 (N = 113)
Respiratory distress syndrome	3.7	1.9	0.9	0.9	0.8	1.8
Transient tachypnea of the newborn	4.8	3.9	2.7	2.5	4.8	6.2
Admission to the neonatal intensive care unit	12.8	8.1	5.9	4.8	7.9	14.2
Suspected sepsis	6.6	3.9	2.4	2.6	3.6	10.6
Treated hypoglycemia	2.4	0.9	0.7	0.8	1.6	1.8
Ventilation	1.9	0.9	0.4	0.4	0.4	

From Tita AT, Landon MB, Spong CY, et al: Timing of elective repeat cesarean delivery at term and neonatal outcomes, *N Engl J Med* 360:111–120, 2009.

<b>Table 93-1</b>	Major Causes of Perinatal and Neonatal Mortality
<b>FETAL</b>	
Placental insufficiency	
Intrauterine infection	
Severe congenital malformations (anomalies)	
Umbilical cord accident	
Abruption placentae	
Hydrops fetalis	
<b>PRETERM</b>	
Severe immaturity	
Respiratory distress syndrome	
Intraventricular hemorrhage	
Congenital anomalies	
Infection	
Necrotizing enterocolitis	
Bronchopulmonary dysplasia (BPD)	
<b>FULL TERM</b>	
Congenital anomalies	
Birth asphyxia	
Trauma	
Infection	
Meconium aspiration pneumonia	
Persistent pulmonary hypertension (PPHN)	

<b>Table 94-3</b>	Factors Affecting the Apgar Score*
<b>FALSE-POSITIVE (NO FETAL ACIDOSIS OR HYPOXIA; LOW APGAR SCORE)</b>	
Prematurity	
Analgesics, narcotics, sedatives	
Magnesium sulfate	
Acute cerebral trauma	
Precipitous delivery	
Congenital myopathy	
Congenital neuropathy	
Spinal cord trauma	
Central nervous system anomaly	
Lung anomaly (diaphragmatic hernia)	
Airway obstruction (choanal atresia)	
Congenital pneumonia and sepsis	
Previous episodes of fetal asphyxia (recovered)	
Hemorrhage-hypovolemia	
<b>FALSE-NEGATIVE (ACIDOSIS; NORMAL APGAR SCORE)</b>	
Maternal acidosis	
High fetal catecholamine levels	
Some full-term infants	

\*Regardless of the etiology, a low Apgar score because of fetal asphyxia, immaturity, central nervous system depression, or airway obstruction identifies an infant needing immediate resuscitation.

<b>Table 93-2</b>	Levels of In-Hospital Perinatal Care
<b>MATERNAL</b>	
<b>BASIC</b>	
Monitor and care for low-risk patients	
Triage for high risk for transfer	
Detection and care of unanticipated labor problems	
Emergency cesarean delivery within 30 min	
Blood bank, anesthesia, radiology, ultrasound, and laboratory support	
Care of postpartum problems	
Obstetrician, nurse, midwife staff	
<b>SPECIAL CARE</b>	
<i>Basic services plus:</i>	
Care of high-risk pregnancies	
Triage, transfer of high-risk pregnancies (<32 wk, intrauterine growth retardation, preeclampsia, severe maternal medical illness)	
<b>SUBSPECIALTY CARE</b>	
<i>Basic plus specialty care plus:</i>	
Experienced perinatologist (24-hr coverage)	
Evaluation of high-risk therapies	
Care for severe maternal medical or obstetric illnesses	
High-risk fetal care (Rh disease, nonimmune hydrops, life-threatening anomalies)	
Outcomes research	
Community education	
<b>NEONATE</b>	
Resuscitation	
Stabilization	
Well neonatal care	
Nursery care	
Visitation	
General pediatrician staff (capable of neonatal resuscitation)	
<i>Basic services plus:</i>	
Care of high-risk neonate with short-term problems	
Stabilization before transfer (<1,500 g, <32 wk, critically ill)	
Accept convalescing back (reverse) transfers	
<i>Basic plus specialty care plus:</i>	
Experienced neonatologist (24-hr coverage)	
Inborn plus transferred patients	
Evaluation of high-risk therapies	
All pediatric medical, radiologic, and surgical subspecialties	
Neonatal intensive care unit with operating room capabilities	
High-risk follow-up	
Outcomes research	
Community education	

From American Academy of Pediatrics, American College of Obstetricians and Gynecologists: Guidelines for perinatal care, ed 5, Elk Grove Village, IL, 2002, American Academy of Pediatrics.

<b>Table 94-5</b>	Criteria for Discharge from the Normal Newborn Nursery*
Uncomplicated antepartum, intrapartum, postpartum courses	
Vaginal delivery	
Singleton at 38-42 wk; appropriate for gestational age	
Normal vital signs including respiratory rate <60 breaths/min; axillary temperature 36.1-37°C (97.0-98.6°F) in open crib	
Physical examination reveals no abnormalities requiring continued hospitalization	
Urination; stool x 1	
At least 2 uneventful, successful feedings	
No excessive bleeding 2 hr after circumcision	
No jaundice within 24 hr of birth; if jaundice, appropriate management and follow-up are in place	
Evidence of parental knowledge, ability, and confidence to care for the baby at home:	
Feeding	
Cord, skin, genital care	
Recognition of illness (jaundice, poor feeding, lethargy, fever, etc.)	
Infant safety (car seat, supine sleep position, etc.)	
Availability of family and physician support (physician follow-up)	
Laboratory evaluation:	
Syphilis	
Hepatitis B surface antigen and vaccination or appointment for vaccination	
Coombs test and blood type if clinically indicated	
Expanded metabolic screening: phenylketonuria, thyroid, galactosemia, sickle cell	
Hearing screening	
No social risks:	
Substance abuse	
History of child abuse	
Domestic violence	
Mental illness	
Teen mother	
Homelessness	
Barriers to follow-up	
Source of continuing medical care is identified	

\*It is not likely that all these criteria will be met before 48 hr of age.

Adapted from American Academy of Pediatrics, American College of Obstetricians and Gynecologists: Guidelines for perinatal care, ed 7, Elk Grove Village, IL, 2012, American Academy of Pediatrics.

<b>Table 94-6</b>	Ten Steps to Successful Breastfeeding
Every facility providing maternity services and care for newborn infants should accomplish the following:	
1. Have a written breastfeeding policy that is routinely communicated to all healthcare staff.	
2. Train all healthcare staff in the skills necessary to implement this policy.	
3. Inform all pregnant women about the benefits and management of breastfeeding.	
4. Help mothers initiate breastfeeding within a half hour of birth.	
5. Show mothers how to breastfeed and how to maintain lactation even if they should be separated from their infants.	
6. Give newborn infants no food or drink other than breast milk unless medically indicated.	
7. Practice rooming-in (allow mothers and infants to remain together) 24 hr a day.	
8. Encourage breastfeeding on demand.	
9. Give no artificial teats or pacifiers (also called dummies or soothers) to breastfeeding infants.	
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.	

From Protecting, promoting and supporting breastfeeding: the special role of maternity services. A joint WHO/UNICEF statement. Geneva, 1989, World Health Organization.

<b>Table 94-7</b>	Drugs and Breastfeeding
<b>CONTRAINdICATED</b>	Metoclopramide
Amphetamines	Metronidazole
Antineoplastic agents	Meperidine
Bromocriptine	Oxycodone
Chloramphenicol	Phenobarbital*
Clozapine	Primidone
Cocaine	Psychotropic drugs
Cyclophosphamide	Reserpine
Diethylstilbestrol	Salicylazosulfapyridine (sulfasalazine)
Doxorubicin	
Ecstasy	
Ergots	
Gold salts	
Heroin	
Immunosuppressants	
Iodides	
Kava	
Lithium	
Methimazole	
Methamphetamine	
Phencyclidine (PCP)	
Radiopharmaceuticals	
Thiouracil	
Yohimbe	
<b>PROBABLY SAFE</b>	
Acetaminophen	
Acyclovir	
Aldomet	
Anesthetics	
Antibiotics (not chloramphenicol)	
Antiepileptics	
Antihistamines*	
Antithyroid (not methimazole)	
Bishydroxycoumarin (dicumarol)	
Chlorpromazine*	
Cyclosporine	
Depo-Provera	
Digoxin	
Dilantin (phenytoin)	
Diuretics	
Fluoxetine	
Furosemide	
Haloperidol*	
Hydralazine	
Indomethacin, other nonsteroidal antiinflammatory drugs	
Low-molecular-weight heparins	
Metformin	
Methadone*	
Morphine	
Muscle relaxants	
Paroxetine	
Prednisone	
Propranolol	
Propylthiouracil	
Sedatives*	
Sertraline	
Theophylline	
Vitamins	
Warfarin	
<b>AVOID OR GIVE WITH CAUTION</b>	
Alcohol	
Amiodarone	
Anthraquinones (laxatives)	
Aspirin (salicylates)	
Atropine	
β-Adrenergic blocking agents	
Benzodiazepines	
Birth control pills	
Bromides	
Buprenorphine/naltrexone	
Bupropion	
Calciferol	
Cascara	
Ciprofloxacin	
Codeine	
Dicumarol	
Dihydrotachysterol	
Domperidone	
Estrogens	
Hydrocodone	
Marijuana	

\*Watch for sedation.

**Table 94-8** Summary of Infectious Agents Detected in Milk and Newborn Disease

INFECTIOUS AGENT	DETECTED IN BREAST MILK?	BREAST MILK REPORTED AS CAUSE OF NEWBORN DISEASE?	MATERNAL INFECTION CONTRAINDICATION TO BREASTFEEDING?
<b>BACTERIA</b>			
Mastitis/Staphylococcus aureus	Yes	No	No, unless breast abscess present
Mycobacterium tuberculosis:			
Active disease	Yes	No	Yes, because of aerosol spread, or tuberculosis mastitis
Purified protein derivative skin test result positive, chest radiograph findings negative	No	No	No
Escherichia coli, other Gram-negative rods	Yes, stored	Yes, stored	—
Group B streptococci	Yes	Yes	No*
Listeria monocytogenes	Yes	Yes	No*
Coxiella burnetii	Yes	Yes	No*
Syphilis	No	No	No†

Continued

**Table 94-8** Summary of Infectious Agents Detected in Milk and Newborn Disease—cont'd

INFECTIOUS AGENT	DETECTED IN BREAST MILK?	BREAST MILK REPORTED AS CAUSE OF NEWBORN DISEASE?	MATERNAL INFECTION CONTRAINDICATION TO BREASTFEEDING?
<b>VIRUSES</b>			
HIV	Yes	Yes	Yes, developed countries
Cytomegalovirus:			
Term infant	Yes	Yes	No
Preterm infant	Yes	Yes	Evaluate on an individual basis
Hepatitis B virus	Yes, surface antigen	No	No, developed countries‡
Hepatitis C virus	Yes	No	No§
Hepatitis E virus	Yes	No	No
Human T-cell leukemia virus (HTLV)-1	Yes	Yes	Yes, developed countries
HTLV-2	Yes	?	Yes, developed countries
Herpes simplex virus	Yes	No/?yes	No, unless breast vesicles present
Rubella			
Wild type	Yes	Yes, rare	No
Vaccine	Yes	No	No
Varicella-zoster virus	Yes	No	No, cover active lesions¶
Epstein-Barr virus	Yes	No	No
Human herpesvirus (HHV)-6	No	No	No
HHV-7	Yes	No	No
West Nile virus	Possible	Possible	Unknown
<b>PARASITES</b>			
Toxoplasma gondii	Yes	Yes, 1 case	No

\*Provided that the mother and child are taking appropriate antibiotics.

†Treat mother and child if active disease.

‡Immunize and immune globulin at birth.

§Provided that the mother is HIV-seronegative. Mothers should be counseled that breast milk transmission of hepatitis C virus has not been documented, but is theoretically possible.

¶Provide appropriate antiviricella therapy or prophylaxis to newborn.

Modified from Jones CA: Maternal transmission of infectious pathogens in breast milk, J Paediatr Child Health 37:576–582, 2001.

**Table 94-2** Apgar Evaluation of Newborn Infants\*

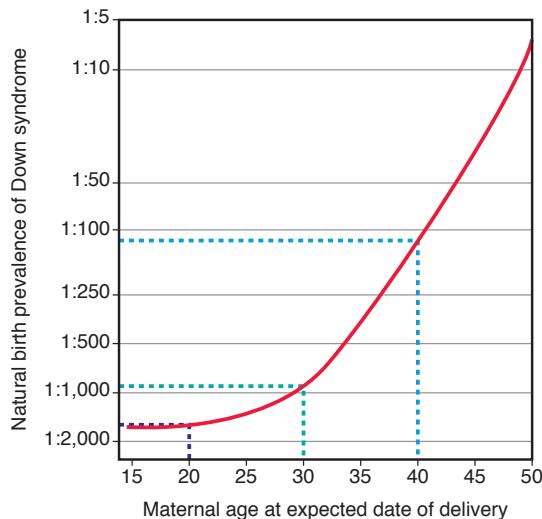
SIGN	0	1	2
Heart rate	Absent	Below 100	Over 100
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Response to catheter in nostril (tested after oropharynx is clear)	No response	Grimace	Cough or sneeze
Color	Blue, pale	Body pink, extremities blue	Completely pink

\*Sixty sec after complete birth of the infant (disregarding the cord and placenta), the 5 objective signs listed here are evaluated, and each is given a score of 0, 1, or 2. A total score of 10 indicates an infant in the best possible condition. An infant with a score of 0–3 requires immediate resuscitation.

Modified from Apgar V: A proposal for a new method of evaluation of the newborn infant, Curr Res Anesth Analg 32:260–267, 1953.

**Table 95-1** Factors Associated with High-Risk Pregnancy

ECONOMIC	
Poverty	
Unemployment	
Uninsured, underinsured health insurance	
Poor access to prenatal care	
CULTURAL-BEHAVIORAL	
Low educational status	
Poor healthcare attitudes	
No care or inadequate prenatal care	
Cigarette, alcohol, illicit drug use	
Age <20 or >40 yr	
Unmarried	
Short interpregnancy interval	
Lack of support group (husband, family, religion)	
Stress (physical, psychologic)	
Black race	
BIOLOGIC-GENETIC	
Previous low birthweight or preterm infant	
Low weight for height	
Poor weight gain during pregnancy	
Short stature	
Poor nutrition	
Consanguinity	
Intergenerational effects	
Low maternal birthweight	
Hereditary diseases (inborn error of metabolism)	
REPRODUCTIVE	
Previous cesarean section	
Previous infertility	
Conception by reproductive technology	
Prolonged gestation	
Prolonged labor	
Previous infant with cerebral palsy, mental retardation, birth trauma, congenital anomalies	
Abnormal lie (breech)	
Multiple gestations	
Premature rupture of membranes	
Infection (systemic, amniotic, extra-amniotic, cervical)	
Preeclampsia or eclampsia	
Uterine bleeding (abruptio placentae, placenta previa)	
Parity (0 or >5 previous deliveries)	
Uterine or cervical anomalies	
Fetal disease	
Abnormal fetal growth	
Idiopathic premature labor	
Iatrogenic prematurity	
High or low levels of maternal serum $\alpha$ -fetoprotein	
MEDICAL	
Diabetes mellitus	
Hypertension	
Congenital heart disease	
Autoimmune disease	
Sickle cell anemia	
Intercurrent surgery or trauma	
Sexually transmitted infection	
Maternal hypercoagulable states	
Exposure to prescription medications	
TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) infection	



**Figure 95-1** Natural birth prevalence of Down syndrome according to maternal age.

**Table 95-4** Conditions Associated with Disorders of Amniotic Fluid Volume

OLIGOHYDRAMNIOS	
Amniotic fluid leak/rupture of membranes	
Intrauterine growth restriction	
Fetal anomalies	
Twin-twin transfusion (donor)	
Renal agenesis (Potter syndrome)	
Urethral atresia	
Prune-belly syndrome	
Pulmonary hypoplasia	
Amnion nodosum	
Indomethacin	
Angiotensin-converting enzyme inhibitors or receptor antagonists	
Intestinal pseudoobstruction	
POLYHYDRAMNIOS	
Congenital anomalies:	
Anencephaly	
Hydrocephaly	
Tracheoesophageal fistula	
Duodenal atresia	
Spina bifida	
Cleft lip or palate	
Cystic adenomatoid lung malformation	
Diaphragmatic hernia	
Syndromes:	
Achondroplasia	
Klippel-Feil	
Trisomy 18	
Trisomy 21	
TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex)	
Hydrops fetalis	
Multiple congenital anomalies	
Other:	
Diabetes mellitus	
Twin-twin transfusion (recipient)	
Fetal anemia	
Fetal heart failure	
Polyuric renal disease	
Neuromuscular diseases	
Nonimmune hydrops	
Chylothorax	
Teratoma	
Idiopathic	

## 804 Part XII ◆ The Fetus and the Neonatal Infant

**Table 95-2** Maternal Conditions Affecting the Fetus or Neonate

DISORDER	EFFECT(S)	MECHANISM(S)
Autoantibody against folate receptors	Neural tube defects	Blockage of cellular uptake of folate
Cervical neoplasia	Preterm premature rupture of membranes	Associated with loop electrosurgical excision procedure or cone therapy
Cholestasis	Preterm delivery, intrauterine fetal demise	Unknown, possibly hepatitis E
Cyanotic heart disease	Intrauterine growth restriction	Low fetal oxygen delivery
Diabetes mellitus:		
Mild	Large for gestational age, hypoglycemia	Fetal hyperglycemia—produces hyperinsulinemia; insulin promotes growth
Severe	Growth restriction	Vascular disease, placental insufficiency
Drug addiction	Intrauterine growth restriction, neonatal withdrawal	Direct drug effect plus poor diet
Endemic goiter	Hypothyroidism	Iodine deficiency
Graves disease	Transient neonatal thyrotoxicosis	Placental immunoglobulin passage of thyroid-stimulating antibody
Herpes gestationis (noninfectious)	Bullous rash, intrauterine fetal demise	Autoantibody similar to that in bullous pemphigoid
Hyperparathyroidism	Neonatal hypocalcemia	Maternal calcium crosses to fetus and suppresses fetal parathyroid gland
Hypertension	Intrauterine growth restriction, intrauterine fetal demise	Placental insufficiency, fetal hypoxia
Idiopathic thrombocytopenic purpura	Thrombocytopenia	Nonspecific maternal platelet antibodies cross placenta
Isoimmune neutropenia or thrombocytopenia	Neutropenia or thrombocytopenia	Specific antifetus neutrophil or platelet antibody crosses placenta after sensitization of mother
Malignant melanoma	Placental or fetal tumor	Metastasis
Myasthenia gravis	Transient neonatal myasthenia	Immunoglobulin to acetylcholine receptor crosses placenta
Myotonic dystrophy	Neonatal myotonic dystrophy, congenital contractures, respiratory insufficiency	Genetic anticipation
Obesity	Macrosomia, hypoglycemia	Unknown
Phenylketonuria	Microcephaly, retardation	Elevated fetal phenylalanine values
Poor nutrition	Intrauterine growth restriction, adult insulin resistance	Reduced fetal nutrients, nutritional programming
Preeclampsia, eclampsia	Intrauterine growth restriction, thrombocytopenia, neutropenia, fetal demise	Uteroplacental insufficiency, fetal hypoxia, vasoconstriction
Renal transplantation	Intrauterine growth restriction	Uteroplacental insufficiency
Rhesus or other blood group sensitization	Fetal anemia, hypoalbuminemia, hydrops, neonatal jaundice	Antibody crosses placenta and is directed to fetal cells with antigen
Sickle cell anemia	Preterm birth, intrauterine growth restriction, stillbirth	Maternal sickling producing fetal hypoxia
Systemic lupus erythematosus	Congenital heart block, rash, anemia, thrombocytopenia, neutropenia	Antibody directed to fetal heart, red and white blood cells, and platelets

**Table 95-3** Maternal Infections Affecting the Fetus or Newborn

INFECTION	MODE(S) OF TRANSMISSION	OUTCOME
<b>BACTERIA</b>		
Group B streptococcus	Ascending cervical	Sepsis, pneumonia
<i>Escherichia coli</i>	Ascending cervical	Sepsis, pneumonia
<i>Listeria monocytogenes</i>	Transplacental	Sepsis, pneumonia
<i>Ureaplasma urealyticum</i>	Ascending cervical	Pneumonia, meningitis
<i>Mycoplasma hominis</i>	Ascending cervical	Pneumonia
<i>Chlamydia trachomatis</i>	Vaginal passage	Conjunctivitis, pneumonia
Syphilis	Transplacental, vaginal passage	Congenital syphilis
<i>Borrelia burgdorferi</i>	Transplacental	Prematurity, fetal demise
<i>Neisseria gonorrhoeae</i>	Vaginal passage	Ophthalmia (conjunctivitis), sepsis, meningitis
<i>Mycobacterium tuberculosis</i>	Transplacental	Prematurity, fetal demise, congenital tuberculosis
Granulocytic ehrlichiosis	Transplacental	Sepsis
<b>VIRUS</b>		
Rubella	Transplacental	Congenital rubella
Cytomegalovirus	Transplacental, breast milk (rare)	Congenital cytomegalovirus or asymptomatic
HIV	Transplacental, vaginal passage, breast milk	Congenital acquired immunodeficiency syndrome
Hepatitis B	Vaginal passage, transplacental, breast milk	Neonatal hepatitis, chronic hepatitis B surface antigen carrier state
Hepatitis C	Transplacental	Uncommon, but neonatal hepatitis, chronic carrier state possible
Lymphocytic choriomeningitis	Transplacental	Fetal, neonatal death; hydrocephalus, chorioretinitis
Herpes simplex type 2 or 1	Transplacental	Congenital herpes simplex virus
Varicella-zoster	Vaginal passage, ascending Transplacental: Early Late	Neonatal encephalitis, disseminated viremia
Parvovirus	Transplacental	Congenital anomalies
Coxsackie B	Fecal-oral	Neonatal varicella
Poliomyelitis	Transplacental	Fetal anemia, hydrops
Epstein-Barr	Transplacental	Myocarditis, meningitis, hepatitis
Rubeola	Transplacental	Congenital poliomyelitis
West Nile	Transplacental	Anomalies(?)
Dengue virus	Transplacental	Abortion, fetal measles
Chorioretinitis, focal cerebral necrosis		Chorioretinitis, focal cerebral necrosis
Thrombocytopenia, lymphocytosis		Thrombocytopenia, lymphocytosis
<b>PARASITES</b>		
Toxoplasmosis	Transplacental	Congenital toxoplasmosis or asymptomatic
Malaria	Transplacental	Abortion, prematurity, intrauterine growth restriction
Trypanosomiasis	Transplacental	Congenital Chagas disease
Hookworm	None	Maternal anemia, low birthweight
<b>FUNGI</b>		
<i>Candida</i>	Ascending, cervical	Sepsis, pneumonia, rash
<b>PRION</b>		
Creutzfeldt-Jakob disease	Transplacental, colostrum	Hypothetical route, no long-term data

**Table 97-1** Factors That Define an Infant as Being High Risk

<b>DEMOGRAPHIC SOCIAL FACTORS</b>	Multiple gestation Preeclampsia Premature rupture of membranes Short interpregnancy time Poly-/oligohydramnios Acute medical or surgical illness Inadequate prenatal care Familial or acquired hypercoagulable states Abnormal fetal ultrasonographic findings Treatment of infertility
<b>PAST MEDICAL HISTORY</b>	
Genetic disorders Diabetes mellitus Hypertension Asymptomatic bacteriuria Rheumatologic illness (systemic lupus erythematosus) Immune-mediated diseases (immunoglobulin G crossing placenta) Long-term medication (see Tables 96-5 and 96-6 in Chapter 96)	Premature labor (<37 wk) Postdates pregnancy (≥42 wk) Fetal distress Immature leathin:sphingomyelin ratio; absence of phosphatidylglycerol Breech presentation Meconium-stained fluid Nuchal cord Cesarean section Forceps delivery Apgar score <4 at 1 min
<b>PREVIOUS PREGNANCY</b>	
Intrauterine fetal demise Neonatal death Prematurity Intrauterine growth restriction Congenital malformation Incompetent cervix Blood group sensitization, neonatal jaundice Neonatal thrombocytopenia Hydrops Inborn errors of metabolism	Respiratory distress, cyanosis Congenital malformation Pallor, plethora, petechiae
<b>PRESENT PREGNANCY</b>	
Vaginal bleeding (abruptio placentae, placenta previa) Sexually transmitted infections (colonization: herpes simplex, group B streptococcus, chlamydia, syphilis, hepatitis B, HIV)	Birthweight <2,500 or >4,000 g Birth <37 or ≥42 wk of gestation Small or large for gestational age

**Table 96-1** Fetal Diagnosis and Assessment

METHOD	COMMENT(S) AND INDICATION(S)
<b>IMAGING</b>	
Ultrasound (real-time)	Biometry (growth), anomaly (morphology) detection Biophysical profile Amniotic fluid volume, hydrops Velocimetry (blood flow velocity)
Ultrasound (Doppler)	Detection of increased vascular resistance secondary to fetal hypoxia
Embryoscopy	Early diagnosis of limb anomaly
Fetoscopy	Detection of facial, limb, cutaneous anomalies
MRI	Defining of lesions before fetal surgery
<b>FLUID ANALYSIS</b>	
Amniocentesis	Fetal maturity (L:S ratio), karyotype (cytogenetics), biochemical enzyme analysis, molecular genetic DNA diagnosis, bilirubin, or $\alpha$ -fetoprotein determination Bacterial culture, pathogen antigen, or genome detection
Cordocentesis (percutaneous umbilical blood sampling)	Detection of blood type, anemia, hemoglobinopathies, thrombocytopenia, acidosis, hypoxia, polycythemia, immunoglobulin M antibody response to infection Rapid karyotyping and molecular DNA genetic diagnosis Fetal therapy (see Table 96-5)
<b>FETAL TISSUE ANALYSIS</b>	
Chorionic villus biopsy	Karyotype, molecular DNA genetic analysis, enzyme assays
Skin biopsy	Hereditary skin disease*
Liver biopsy	Enzyme assay*
Circulating fetal DNA or cells in maternal blood or plasma	Molecular DNA genetic analysis including microarray analysis, chromosome number, specific gene testing, or genetic sequencing
<b>MATERNAL SERUM <math>\alpha</math>-FETOPROTEIN CONCENTRATION</b>	
Elevated	Twins, neural tube defects (anencephaly, spina bifida), intestinal atresia, hepatitis, nephrosis, fetal demise, incorrect gestational age
Reduced	Trisomies, aneuploidy
<b>MATERNAL CERVIX</b>	
Fetal fibronectin	Indicates risk of preterm birth
Bacterial culture	Identifies risk of fetal infection (group B streptococcus, <i>Neisseria gonorrhoeae</i> )
Fluid	Determination of premature rupture of membranes
<b>ANTEPARTUM BIOPHYSICAL MONITORING</b>	
Nonstress test	Fetal distress; hypoxia
Contraction stress test	Fetal distress; hypoxia
Biophysical profile and modified biophysical profile	Fetal distress; hypoxia
Intrapartum fetal heart rate monitoring	See Fig. 96-4

\*DNA genetic analysis on chorionic villus samples, amniocytes from amniocentesis, or fetal cells recovered from the maternal circulation may obviate the need for direct fetal tissue biopsy if the gene or genetic marker is available (e.g., the gene for Duchenne muscular dystrophy).

L:S, lecithin:sphingomyelin ratio.

**Table 96-2** Biophysical Profile Scoring: Technique and Interpretation

BIOPHYSICAL VARIABLE	NORMAL SCORE (2)	ABNORMAL SCORE (0)
Fetal breathing movements (FBMs)	At least 1 episode of FBM of at least 30 sec duration in 30 min observation	Absence of FBM or no episode $\geq$ 30 sec in 30 min
Gross body movement	At least 3 discrete body/limb movements in 30 min (episodes of active continuous movement considered a single movement)	2 or fewer episodes of body/limb movements in 30 min
Fetal tone	At least 1 episode of active extension with return to flexion of fetal limb(s) or trunk Opening and closing of hand considered evidence of normal tone	Either slow extension with return to partial flexion or movement of limb in full extension or absence of fetal movement with the hand held in complete or partial deflection
Reactive fetal heart rate (FHR)	At least 2 episodes of FHR acceleration of $\geq$ 15 beats/min and at least 15 sec in duration associated with fetal movement in 30 min	Less than 2 episodes of acceleration of FHR or acceleration of <15 beats/min in 30 min
Qualitative amniotic fluid (AF) volume*	At least 1 pocket of AF that measures at least 2 cm in 2 perpendicular planes	Either no AF pockets or a pocket <2 cm in 2 perpendicular planes

\*Modification of the criteria for reduced amniotic fluid from less than 1 cm to less than 2 cm would seem reasonable. Ultrasound is used for biophysical assessment of the fetus.

From Creasy RK, Resnik R, Iams JD, editors: Maternal-fetal medicine: principles and practice, ed 5, Philadelphia, 2004, Saunders.

**Table 96-3** Characteristics of Decelerations of the Fetal Heart Rate**LATE DECELERATION**

- Visually apparent, usually symmetric gradual decrease and return of the fetal heart rate (FHR) associated with a uterine contraction.
- A gradual FHR decrease is defined as duration of  $\geq 30$  sec from the onset to the nadir of the FHR.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The deceleration is delayed in timing, with the nadir of the deceleration occurring after the peak of the contraction.
- In most cases, the onset, nadir, and recovery of the deceleration occur after the beginning, peak, and ending of the contraction, respectively.

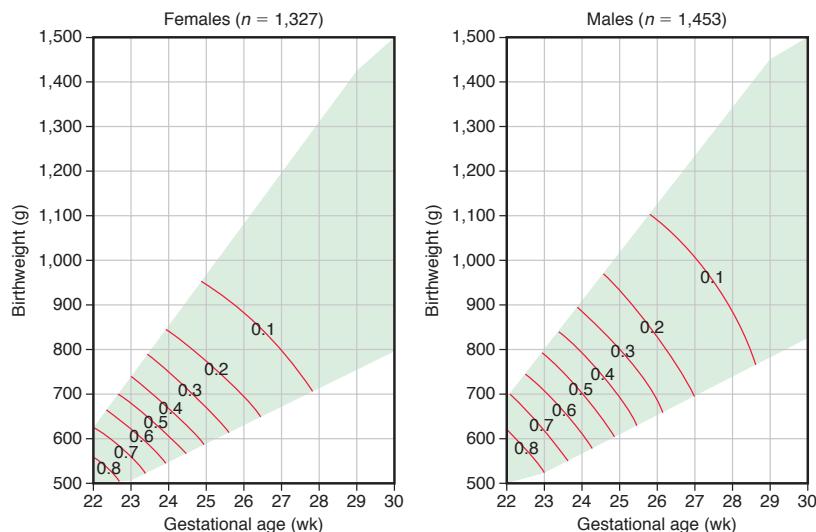
**EARLY DECELERATION**

- Visually apparent, usually symmetric gradual decrease and return of the FHR associated with a uterine contraction.
- A gradual FHR decrease is defined as duration of  $\geq 30$  sec from the onset to the FHR nadir.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The nadir of the deceleration occurs at the same time as the peak of the contraction.
- In most cases, the onset, nadir, and recovery of the deceleration are coincident with the beginning, peak, and ending of the contraction, respectively.

**VARIABLE DECELERATION**

- Visually apparent, abrupt decrease in FHR.
- An abrupt FHR decrease is defined as duration  $< 30$  sec from the onset of the deceleration to the beginning of the FHR nadir of the deceleration.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The decrease in FHR is  $\geq 15$  beats/min, lasting  $\geq 15$  sec, and  $< 2$  min in duration.
- When variable decelerations are associated with uterine contractions, their onset, depth, and duration commonly vary with successive uterine contractions.

From Macones GA, Hankins GDV, Spong CY, et al: The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines, *Obstet Gynecol* 112:661–666, 2008.



**Figure 97-1** Estimated mortality risk by birthweight and gestational age based on singleton infants in National Institute of Child Health and Human Development (NICHD) Neonatal Research Network centers between January 1, 1995, and December 31, 1996. (From Lemons JA, Bauer CR, Oh W, et al: Very low birthweight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996, *Pediatrics* 107:E1, 2001; available at [www.pediatrics.org/cgi/content/full/107/1/e1](http://www.pediatrics.org/cgi/content/full/107/1/e1).)

**Table 96-4** Three-Tier Fetal Heart Rate Interpretation System**CATEGORY I**

Category I fetal heart rate (FHR) tracings include all of the following:

- Baseline rate: 110–160 beats per minute (beats/min)
- Baseline FHR variability: moderate
- Late or variable decelerations: absent
- Early decelerations: present or absent
- Accelerations: present or absent

**CATEGORY II**

Category II FHR tracings include all FHR tracings not categorized as category I or category III. Category II tracings may represent an appreciable fraction of those encountered in clinical care.

Examples of category II FHR tracings include any of the following:

- Baseline rate
  - Bradycardia not accompanied by absence of baseline variability
  - Tachycardia
- Baseline FHR variability
  - Minimal baseline variability
  - Absence of baseline variability not accompanied by recurrent decelerations
  - Marked baseline variability
- Accelerations
  - Absence of induced accelerations after fetal stimulation
  - Periodic or episodic decelerations
  - Recurrent variable decelerations accompanied by minimal or moderate baseline variability
  - Prolonged deceleration,  $\geq 2$  min but  $< 10$  min
  - Recurrent late decelerations with moderate baseline variability
  - Variable decelerations with other characteristics, such as slow return to baseline, "overshoots," and "shoulders"

**CATEGORY III**

Category III FHR tracings include either:

- Absence of baseline FHR variability and any of the following:
  - Recurrent late decelerations
  - Recurrent variable decelerations
  - Bradycardia
  - Sinusoidal pattern

**Table 96-5** Agents Acting on Pregnant Women That May Adversely Affect the Structure or Function of the Fetus and Newborn

DRUG	EFFECT ON FETUS
Accutane (isotretinoin)	Facial-ear anomalies, heart disease, CNS anomalies
Alcohol	Congenital cardiac, CNS, limb anomalies; IUGR; developmental delay; attention deficits; autism
Aminopterin	Abortion, malformations
Amphetamines	Congenital heart disease, IUGR, withdrawal
Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists	Oligohydramnios, IUGR, renal failure, Potter-like syndrome
Azathioprine	Abortion
Busulfan (Myleran)	Stunted growth; corneal opacities; cleft palate; hypoplasia of ovaries, thyroid, and parathyroids
Carbamazepine	Spina bifida, possible neurodevelopmental delay
Carbimazole	Scalp defects, choanal atresia, esophageal atresia, developmental delay
Carbon monoxide	Cerebral atrophy, microcephaly, seizures
Chloroquine	Deafness
Chorionic villus sampling	Probably no effect, possibly limb reduction
Cigarette smoking	LBW for gestational age
Cocaine/crack	Microcephaly, LBW, IUGR, behavioral disturbances
Cyclophosphamide	Multiple malformations
Danazol	Virilization
17 $\alpha$ -Ethinyl testosterone (Progesterone)	Masculinization of female fetus
Hyperthermia	Spina bifida
Infliximab	Possible increased risk of live vaccine associated disease in infant; neutropenia
Lithium	Ebstein anomaly, macrosomia
Lopinavir-ritonavir	Transient adrenal dysfunction
6-Mercaptopurine	Abortion
Methyl mercury	Minamata disease, microcephaly, deafness, blindness, mental retardation
Methyltestosterone	Masculinization of female fetus
Misoprostol	Arthrogryposis, cranial neuropathies (Möbius syndrome), equinovarus
Mycophenolate mofetil	Craniofacial, limb, cardiovascular, CNS anomalies
Norethindrone	Masculinization of female fetus
Penicillamine	Cutis laxa syndrome
Phenytoin	Congenital anomalies, IUGR, neuroblastoma, bleeding (vitamin K deficiency)
Polychlorinated biphenyls	Skin discoloration—thickening, desquamation, LBW, acne, developmental delay
Prednisone	Oral clefts

**Table 96-5** Agents Acting on Pregnant Women That May Adversely Affect the Structure or Function of the Fetus and Newborn—cont'd

DRUG	EFFECT ON FETUS
Progesterone	Masculinization of female fetus
Quinine	Abortion, thrombocytopenia, deafness
Selective serotonin reuptake inhibitors	Small increased risk of congenital anomalies, persistent pulmonary hypertension of newborn
Statins	IUGR, limb deficiencies, VACTERL
Stilbestrol (diethylstilbestrol [DES])	Vaginal adenocarcinoma in adolescence
Streptomycin	Deafness
Tetracycline	Retarded skeletal growth, pigmentation of teeth, hypoplasia of enamel, cataract, limb malformations
Thalidomide	Phocomelia, deafness, other malformations
Toluene (solvent abuse)	Craniofacial abnormalities, prematurity, withdrawal symptoms, hypertonia
Topiramate	Cleft lip
Trimethadione and paramethadione	Abortion, multiple malformations, mental retardation
Valproate	CNS (spina bifida), facial and cardiac anomalies, limb defects, impaired neurologic function, autism spectrum disorder
Vitamin D	Supravalvular aortic stenosis, hypercalcemia
Warfarin (Coumadin)	Fetal bleeding and death, hypoplastic nasal structures

**Table 96-6** Agents Acting on Pregnant Women That May Adversely Affect the Newborn Infant\*

Acebutolol—IUGR, hypotension, bradycardia
Acetazolamide—metabolic acidosis
Amiodarone—bradycardia, hypothyroidism
Anesthetic agents (volatile)—CNS depression
Adrenal corticosteroids—adrenocortical failure (rare)
Ammonium chloride—acidosis (clinically inapparent)
Aspirin—neonatal bleeding, prolonged gestation
Atenolol—IUGR, hypoglycemia
Baclofen—withdrawal
Blue cohosh herbal tea—neonatal heart failure
Bromides—rash, CNS depression, IUGR
Captopril, enalapril—transient anuric renal failure, oligohydramnios
Caudal-paracervical anesthesia with mepivacaine (accidental introduction of anesthetic into scalp of baby)—bradypnea, apnea, bradycardia, convulsions
Cholinergic agents (edrophonium, pyridostigmine)—transient muscle weakness
CNS depressants (narcotics, barbiturates, benzodiazepines) during labor—CNS depression, hypotonia
Cephalothin—positive direct Coombs test reaction
Dexamethasone—periventricular leukomalacia
Fluoxetine and other SSRIs—transient neonatal withdrawal, hypertonicity, minor anomalies, preterm birth, prolonged QT interval
Haloperidol—withdrawal
Hexamethonium bromide—paralytic ileus
Ibuprofen—oligohydramnios, pulmonary hypertension
Imipramine—withdrawal
Indomethacin—oliguria, oligohydramnios, intestinal perforation, pulmonary hypertension
Intravenous fluids during labor (e.g., salt-free solutions)—electrolyte disturbances, hyponatremia, hypoglycemia
Iodide (radioactive)—goiter
Iodides—goiter
Lead—reduced intellectual function
Magnesium sulfate—respiratory depression, meconium plug, hypotonia
Methimazole—goiter, hypothyroidism
Morphine and its derivatives (addiction)—withdrawal symptoms (poor feeding, vomiting, diarrhea, restlessness, yawning and stretching, dyspnea and cyanosis, fever and sweating, pallor, tremors, convulsions)
Naphthalene—hemolytic anemia (in G6PD-deficient infants)
Nitrofurantoin—hemolytic anemia (in G6PD-deficient infants)
Oxytocin—hyperbilirubinemia, hyponatremia
Phenobarbital—bleeding diathesis (vitamin K deficiency), possible long-term reduction in IQ, sedation
Primaquine—hemolytic anemia (in G6PD-deficient infants)
Propranolol—hypoglycemia, bradycardia, apnea

Continued

**Table 96-6** Agents Acting on Pregnant Women That May Adversely Affect the Newborn Infant—cont'd

Propylthiouracil—goiter, hypothyroidism
Pyridoxine—seizures
Reserpine—drowsiness, nasal congestion, poor temperature stability
Sulfonamides—interfere with protein binding of bilirubin; kernicterus at low levels of serum bilirubin, hemolysis with G6PD deficiency
Sulfonylurea agents—refractory hypoglycemia
Sympathomimetic (tocolytic β-agonist) agents—tachycardia
Thiazides—neonatal thrombocytopenia (rare)
Tumor necrosis factor blocking agents—neutropenia
Valproate—developmental delay
Zolpidem (Ambien)—low birthweight

\*See also Table 96-5.

CNS, central nervous system; G6PD, glucose-6-phosphate dehydrogenase; IUGR, intrauterine growth restriction; SSRI, selective serotonin reuptake inhibitor.

**Table 99-5** HIE in Term Infants

SIGNS	STAGE 1	STAGE 2	STAGE 3
Level of consciousness	Hyperalert	Lethargic	Stuporous, coma
Muscle tone	Normal	Hypotonic	Flaccid
Posture	Normal	Flexion	Decerebrate
Tendon reflexes/clonus	Hyperactive	Hyperactive	Absent
Myoclonus	Present	Present	Absent
Moro reflex	Strong	Weak	Absent
Pupils	Mydriasis	Miosis	Unequal, poor light reflex
Seizures	None	Common	Decerebration
Electroencephalographic findings	Normal	Low voltage changing to seizure activity	Burst suppression to isoelectric
Duration	<24 hr if progresses; otherwise, may remain normal	24 hr-14 days	Days to weeks
Outcome	Good	Variable	Death, severe deficits

## 816 Part XII ◆ The Fetus and the Neonatal Infant

**Table 96-7** Significance of Fetal Ultrasonographic Anatomic Findings

PRENATAL OBSERVATION	DEFINITION	DIFFERENTIAL DIAGNOSIS	SIGNIFICANCE	POSTNATAL EVALUATION
Dilated cerebral ventricles	Ventriculomegaly ≥10 mm	Hydrocephalus Hydranencephalus Dandy-Walker cyst Agenesis of corpus callosum	Transient isolated ventriculomegaly is common and usually benign Persistent or progressive ventriculomegaly more worrisome Identify associated cranial and extracranial anomalies Bilateral ventriculomegaly increases risk of developmental delay Unilateral ventriculomegaly may be normal variant	Serial head US or CT Evaluate for extracranial anomalies
Choroid plexus cysts	Size ~10 mm: unilateral or bilateral 1-3% incidence	Abnormal karyotype (trisomy 18, 21) Aneuploidy risk 1:100 if isolated. ↑ Risk (1:3) with other anomalies. Risk ↑ if large, complex, or bilateral cysts or advanced maternal age	Often isolated, benign; resolves by 24-28 wk Fetus should be examined for other organ anomalies; then amniocentesis should be performed for karyotype	Head US or CT Examine for extracranial anomalies; karyotype if indicated
Nuchal pad thickening	≥6 mm at 15-20 wk	Cystic hygroma trisomy 21, 18 Turner syndrome (XO) Nonchromosomal syndromes Normal (~25%)	≈50% of affected fetuses have chromosome abnormalities Amniocentesis for karyotype needed	Evaluate for multiple organ malformations; karyotype if indicated
Dilated renal pelvis	Pyelectasis ≥5 to 10 mm 0.6-1% incidence	Uteropelvic junction obstruction Vesicoureteral reflux Posterior ureteral valves Entopic ureterocele Large-volume nonobstruction	Often "physiologic" and transient Reflux is common If dilation is >10 mm or associated with caliectasis, pathologic cause should be considered If large bladder present, posterior urethral valves and megacystis-megaduodenum syndrome should be considered	Repeat ultrasonography on day 5 and at 1 mo; voiding cystourethrogram, prophylactic antibiotics
Echogenic bowel	0.6% incidence	CF, meconium peritonitis, trisomy 21 or 18, other chromosomal abnormalities cytomegalovirus, toxoplasmosis, GI obstruction	Often normal (65%) 10% of affected fetuses have CF; 1.5% have aneuploidy	Sweat chloride and DNA testing Karyotype Surgery for obstruction Evaluation for TORCH (toxoplasmosis, other agents, rubella, CMV, herpes simplex) syndrome
Stomach appearance	Small or absent or with double bubble	Upper GI obstruction (esophageal atresia) Double bubble signifies duodenal atresia Abnormal karyotype Polyhydramnios Stomach in chest signifies diaphragmatic hernia	Must also consider neurologic disorders that reduce swallowing Over 30% with double bubble have trisomy 21	Chromosomes, kidney, ureter, and bladder radiograph if indicated, upper GI series, neurologic evaluation

**Table 99-2** Multiorgan Systemic Effects of Asphyxia

SYSTEM	EFFECT(S)
CNS	HIE, infarction, intracranial hemorrhage, seizures, cerebral edema, hypotonia, hypertension
Cardiovascular	Myocardial ischemia, poor contractility, cardiac stunning, tricuspid insufficiency, hypotension
Pulmonary	Pulmonary hypertension, pulmonary hemorrhage, RDS
Renal	Acute tubular or cortical necrosis
Adrenal	Adrenal hemorrhage
Gastrointestinal	Perforation, ulceration with hemorrhage, necrosis
Metabolic	Inappropriate secretion of antidiuretic hormone, hyponatremia, hypoglycemia, hypocalcemia, myoglobinuria
Integument	Subcutaneous fat necrosis
Hematology	Disseminated intravascular coagulation

**Table 96-8** Fetal Therapy

DISORDER	POSSIBLE TREATMENT
<b>HEMATOLOGIC</b>	
Anemia with hydrops (erythroblastosis fetalis)	Umbilical vein packed red blood cell transfusion
Thalassemia	Fetal stem cell transplantation
Isoimmune thrombocytopenia	Umbilical vein platelet transfusion, maternal IVIG
Autoimmune thrombocytopenia (ITP)	Maternal steroids and IVIG
Chronic granulomatous disease	Fetal stem cell transplantation
<b>METABOLIC-ENDOCRINE</b>	
Maternal phenylketonuria (PKU)	Phenylalanine restriction
Fetal galactosemia	Galactose-free diet (?)
Multiple carboxylase deficiency	Biotin if responsive
Methylmalonic acidemia	Vitamin B <sub>12</sub> if responsive
21-Hydroxylase deficiency	Dexamethasone
Maternal diabetes mellitus	Tight insulin control during pregnancy, labor, and delivery
Fetal goiter	Maternal hyperthyroidism—maternal propylthiouracil
Bartter syndrome	Fetal hypothyroidism— intra-amniotic thyroxine
Neonatal iron storage disease (alloimmune)	Maternal indomethacin may prevent nephrocalcinosis and postnatal sodium losses Maternal IVIG
<b>FETAL DISTRESS</b>	
Hypoxia	Maternal oxygen, position
Intrauterine growth restriction	Maternal oxygen, position, improve macronutrients and micronutrients if deficient
Oligohydramnios, premature rupture of membranes with variable deceleration	Amnioinfusion (antenpartum and intrapartum)
Polyhydramnios	Amnioreduction (serial), indomethacin (if from increased urine output) if indicated
Supraventricular tachycardia	Maternal digoxin,* flecainide, procainamide, amiodarone, quinidine
Lupus anticoagulant	Maternal aspirin, prednisone
Meconium-stained fluid	Amnioinfusion
Congenital heart block	Dexamethasone, pacemaker (with hydrops)
Premature labor	Magnesium sulfate, antibiotics sympathomimetics, indomethacin
<b>RESPIRATORY</b>	
Pulmonary immaturity	Betamethasone
Bilateral chylothorax—pleural effusions	Thoracentesis, pleuroamniotic shunt
<b>CONGENITAL ABNORMALITIES<sup>†</sup></b>	
Neural tube defects	Folate, vitamins (prevention); fetal surgery <sup>‡</sup>
Posterior urethral valves, urethral atresia (lower urinary tract obstruction)	Percutaneous vesicoamniotic shunt
Cystic adenomatoid malformation (with hydrops)	Pleuroamniotic shunt or resection <sup>‡</sup>
Fetal neck masses	Secure an airway with EXIT procedure <sup>‡</sup>
<b>INFECTIOUS DISEASE</b>	
Group B streptococcus colonization	Ampicillin, penicillin
Chorioamnionitis	Antibiotics
Toxoplasmosis	Spiramycin, pyrimethamine, sulfadiazine, and folic acid
Syphilis	Penicillin
Tuberculosis	Antituberculosis drugs
Lyme disease	Penicillin, ceftriaxone
Parvovirus	Intrauterine red blood cell transfusion for hydrops, severe anemia
Chlamydia trachomatis	Erythromycin
HIV-AIDS	Maternal and neonatal antiretroviral therapy (see Chapter 276)
Cytomegalovirus	Ganciclovir by umbilical vein

Continued

**Table 96-8** Fetal Therapy

DISORDER	POSSIBLE TREATMENT
<b>OTHER</b>	
Nonimmune hydrops (anemia)	Umbilical vein packed red blood cell transfusion
Narcotic abstinence (withdrawal)	Maternal low-dose methadone
Severe combined immunodeficiency disease	Fetal stem cell transplantation
Sacrococcygeal teratoma (with hydrops)	In utero resection or catheter directed vessel obliteration
Twin-twin transfusion syndrome	Repeated amniocentesis, yttrium-aluminum-garnet (YAG) laser photocoagulation of shared vessels
Twin reversed arterial perfusion (TRAP) syndrome	Digoxin, indomethacin, cord occlusion
Multifetal gestation	Selective reduction
Neonatal hemochromatosis	Maternal IVIG

\*Drug of choice (may require percutaneous umbilical cord sampling and umbilical vein administration if hydrops is present). Most drug therapy is given to the mother, with subsequent placental passage to the fetus.

<sup>†</sup>Detailed fetal ultrasonography is needed to detect other anomalies; karyotype is also indicated.

<sup>‡</sup>EXIT permits surgery and other procedures.

EXIT, ex utero intrapartum treatment; IVIG, intravenous immunoglobulin; (?), possible but not proved efficacy.

**Table 97-3** Identifiable Causes of Preterm Birth

FETAL
Fetal distress
Multiple gestation
Erythroblastosis
Nonimmune hydrops
PLACENTAL
Placental dysfunction
Placenta previa
Abruption placentae
UTERINE
Bicornuate uterus
Incompetent cervix (premature dilation)
MATERNAL
Preeclampsia
Chronic medical illness (cyanotic heart disease, renal disease)
Infection ( <i>Listeria monocytogenes</i> , group B streptococcus, urinary tract infection, bacterial vaginosis, chorioamnionitis)
Drug abuse (cocaine)
OTHER
Premature rupture of membranes
Polyhydramnios
Iatrogenic
Trauma

**Table 97-4** Factors Often Associated with Intrauterine Growth Restriction

FETAL
Chromosomal disorders
Chronic fetal infections (cytomegalic inclusion disease, congenital rubella, syphilis)
Congenital anomalies—syndrome complexes
Irradiation
Multiple gestation
Pancreatic hypoplasia
Insulin deficiency (production or action of insulin)
Insulin-like growth factor type I deficiency
PLACENTAL
Decreased placental weight, cellularity, or both
Decrease in surface area
Villous placentitis (bacterial, viral, parasitic)
Infarction
Tumor (chorioangioma, hydatidiform mole)
Placental separation
Twin transfusion syndrome
MATERNAL
Toxemia
Hypertension or renal disease, or both
Hypoxemia (high altitude, cyanotic cardiac or pulmonary disease)
Malnutrition (micronutrient or macronutrient deficiencies)
Chronic illness
Sickle cell anemia
Drugs (narcotics, alcohol, cigarettes, cocaine, antimetabolites)

**Table 98-3** Common Life-Threatening Congenital Anomalies

NAME	MANIFESTATIONS
Choanal atresia	Respiratory distress in delivery room, nasogastric tube cannot be passed through nares Suspect CHARGE (coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies) syndrome
Pierre Robin syndrome Stickler syndrome	Micrognathia, cleft palate, airway obstruction
Diaphragmatic hernia	Scaphoid abdomen, bowel sounds present in chest, respiratory distress
Tracheoesophageal fistula	Polyhydramnios, aspiration pneumonia, excessive salivation, nasogastric tube cannot be placed in stomach Suspect VATER (vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia) syndrome
Intestinal obstruction: volvulus, duodenal atresia, ileal atresia	Polyhydramnios, bile-stained emesis, abdominal distention Suspect trisomy 21, cystic fibrosis, cocaine
Gastroschisis, omphalocele	Polyhydramnios, intestinal obstruction
Renal agenesis, Potter syndrome	Oligohydramnios, anuria, pulmonary hypoplasia, pneumothorax
Neural tube defects: anencephalus, meningomyelocele	Polyhydramnios, elevated $\alpha$ -fetoprotein, decreased fetal activity
Ductus-dependent congenital heart disease	Cyanosis, hypotension, murmur

**Table 98-2** Pain in the Neonate: General Considerations

- Pain in newborns is often unrecognized and/or undertreated.
- If a procedure is painful in adults, it should be considered painful in newborns.
- Healthcare institutions should develop and implement patient care policies to assess, prevent, and manage pain in neonates.
- Pharmacologic agents with known pharmacokinetic and pharmacodynamic properties and demonstrated efficacy in neonates should be used. Agents known to compromise cardiorespiratory function should be administered only by persons experienced in neonatal airway management and in settings with the capacity for continuous monitoring.
- Educational programs to increase the skills of healthcare professionals in the assessment and management of stress and pain in neonates should be provided.
- Further research is needed to develop and validate neonatal pain assessment tools that are useful in the clinical setting; to determine optimal behavioral and pharmacologic interventions; and to study long-term effects of pain and pain management.

Adapted from Prevention and management of pain and stress in the neonate: American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on Anesthesiology. Section on Surgery. Canadian Paediatric Society. Fetus and Newborn Committee, Pediatrics 105:454–461, 2000; and Anand KJS; International Evidence-Based Group for Neonatal Pain: Consensus statement for the prevention and management of pain in the newborn, Arch Pediatr Adolesc Med 155:173–180, 2001.

**Table 97-5** Problems of Infants Small for Gestational Age or with Intrauterine Growth Retardation\*

PROBLEM	PATHOGENESIS
Intrauterine fetal demise	Hypoxia, acidosis, infection, lethal anomaly
Perinatal asphyxia	↓ Uteroplacental perfusion during labor ± chronic fetal hypoxia–acidosis; meconium aspiration syndrome
Hypoglycemia	↓ Tissue glycogen stores, ↓ gluconeogenesis, hyperinsulinism, ↑ glucose needs of hypoxia, hypothermia, large brain
Polycythemia–hyperviscosity	Fetal hypoxia with ↑ erythropoietin production
Reduced oxygen consumption/hypothermia	Hypoxia, hypoglycemia, starvation effect, poor subcutaneous fat stores
Dysmorphology	Syndrome anomalies, chromosomal–genetic disorders, oligohydramnios-induced deformation, TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) infection

\*Other problems include pulmonary hemorrhage and those common to the gestational age-related risks of prematurity if born at less than 37 wk.  
↓, Decreased; ↑, increased.

**Table 97-6** Neonatal Problems Associated with Premature Infants

#### RESPIRATORY

Respiratory distress syndrome (hyaline membrane disease)\*  
Bronchopulmonary dysplasia  
Pneumothorax, pneumomediastinum; interstitial emphysema  
Congenital pneumonia  
Apnea\*

#### CARDIOVASCULAR

Patent ductus arteriosus\*  
Hypotension  
Bradycardia (with apnea)\*

#### HEMATOLOGIC

Anemia (early or late onset)

#### GASTROINTESTINAL

Poor gastrointestinal function—poor motility\*  
Necrotizing enterocolitis  
Hyperbilirubinemia—direct and indirect\*  
Spontaneous gastrointestinal isolated perforation

#### METABOLIC-ENDOCRINE

Hypocalcemia\*  
Hypoglycemia\*  
Hyperglycemia\*  
Late metabolic acidosis  
Hypothermia\*  
Euthyroid but low thyroxine status  
Osteopenia

#### CENTRAL NERVOUS SYSTEM

Intraventricular hemorrhage\*  
Periventricular leukomalacia  
Seizures  
Retinopathy of prematurity  
Deafness  
Hypotonia\*

#### RENAL

Hyponatremia\*  
Hypernatremia\*  
Hyperkalemia\*  
Renal tubular acidosis  
Renal glycosuria  
Edema

#### OTHER

Infections\* (congenital, perinatal, nosocomial: bacterial, viral, fungal, protozoal)

\*Common.

#### Neuromuscular maturity

	-1	0	1	2	3	4	5
Posture							
Square window (wrist)							
Arm recoil							
Popliteal angle							
Scarf sign							
Heel to ear							

**Figure 97-6** Neuromuscular criteria for maturity. The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants. (From Ballard JL, Khoury JC, Wedig K, et al: New Ballard score, expanded to include extremely premature infants, *J Pediatr* 119:417–423, 1991.)

#### Physical maturity

	-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 on ant. 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola—no bud	Stripped 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	Slightly 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, labia flat	Prominent clitoris, small labia minora	Prominent clitoris, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

#### Physical criteria for maturity

The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants.

#### Maturity Rating

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

**Figure 97-7** Maturity rating. The physical and neurologic scores are added to calculate gestational age.

**Table 97-7** Potential Adverse Reactions to Drugs Administered to Premature Infants

DRUG	REACTION(S)
Oxygen	Retinopathy of prematurity, bronchopulmonary dysplasia
Sulfisoxazole	Kernicterus
Chloramphenicol	Gray baby syndrome—shock, bone marrow suppression
Vitamin K analogs	Jaundice
Novobiocin	Jaundice
Hexachlorophene	Encephalopathy
Benzyl alcohol	Acidosis, collapse, intraventricular bleeding
Intravenous vitamin E	Ascites, shock
Phenolic detergents	Jaundice
NaHCO <sub>3</sub>	Intraventricular hemorrhage
Amphotericin	Anuric renal failure, hypokalemia, hypomagnesemia
Reserpine	Nasal stuffiness
Indomethacin	Oliguria, hyponatremia, intestinal perforation
Cisapride	Prolonged QTc interval
Tetracycline	Enamel hypoplasia
Tolazoline	Hypotension, gastrointestinal bleeding
Calcium salts	Subcutaneous necrosis
Aminoglycosides	Deafness, renal toxicity
Enteric gentamicin	Resistant bacteria
Prostaglandins	Seizures, diarrhea, apnea, hyperostosis, pyloric stenosis
Phenobarbital	Altered state, drowsiness
Morphine	Hypotension, urine retention, withdrawal
Pancuronium	Edema, hypovolemia, hypotension, tachycardia, vecuronium contractions, prolonged hypotonia
Iodine antiseptics	Hypothyroidism, goiter
Fentanyl	Seizures, chest wall rigidity, withdrawal
Dexamethasone	Gastrointestinal bleeding, hypertension, infection, hyperglycemia, cardiomyopathy, reduced growth
Eurosemide	Deafness, hyponatremia, hypokalemia, hypochloremia, nephrocalcinosis, biliary stones
Heparin (not low-dose prophylactic use)	Bleeding, intraventricular hemorrhage, thrombocytopenia
Erythromycin	Pyloric stenosis

**Table 97-8** Sequelae of Low Birthweight

IMMEDIATE	LATE
Hypoxia, ischemia	Mental retardation, spastic diplegia, microcephaly, seizures, poor school performance
Intraventricular hemorrhage	Mental retardation, spasticity, seizures, hydrocephalus
Sensorineural injury	Hearing, visual impairment, retinopathy of prematurity, strabismus, myopia
Respiratory failure	Bronchopulmonary dysplasia, cor pulmonale, bronchospasm, malnutrition, subglottic stenosis
Necrotizing enterocolitis	Short-bowel syndrome, malabsorption, malnutrition, infectious diarrhea
Cholestatic liver disease	Cirrhosis, hepatic failure, malnutrition
Nutrient deficiency	Osteopenia, fractures, anemia, growth failure
Social stress	Child abuse or neglect, failure to thrive, divorce
Other	Sudden infant death syndrome, infections, inguinal hernia, cutaneous scars (chest tube, patent ductus arteriosus ligation, intravenous infiltration), gastroesophageal reflux, hypertension, craniosynostosis, cholelithiasis, nephrocalcinosis, cutaneous hemangiomas

**Table 101-1** Potential Causes of Neonatal Apnea and Bradycardia

Central nervous system	Intraventricular hemorrhage, drugs, seizures, hypoxic injury, herniation, neuromuscular disorders, Leigh syndrome, brainstem infarction or anomalies (e.g., olivopontocerebellar atrophy), spinal cord injury after general anesthesia
Respiratory	Pneumonia, obstructive airway lesions, upper airway collapse, atelectasis, extreme prematurity, laryngeal reflex, phrenic nerve paralysis, pneumothorax, hypoxia
Infectious	Sepsis, meningitis (bacterial, fungal, viral), respiratory syncytial virus, pertussis
Gastrointestinal	Oral feeding, bowel movement, necrotizing enterocolitis, intestinal perforation
Metabolic	↓ Glucose, ↓ calcium, ↓/↑ sodium, ↑ ammonia, ↑ organic acids, ↑ ambient temperature, hypothermia
Cardiovascular	Hypotension, hypertension, heart failure, anemia, hypovolemia, vagal tone
Other	Immaturity of respiratory center, sleep state

**Table 98-1**

## Differential Diagnosis of Cyanosis in the Newborn

**CENTRAL OR PERIPHERAL NERVOUS SYSTEM****HYPVENTILATION**

- Birth asphyxia
- Intracranial hypertension, hemorrhage
- Oversedation (direct or through maternal route)
- Diaphragm palsy
- Neuromuscular diseases
- Seizures

**RESPIRATORY DISEASE****Airway**

- Choanal atresia/stenosis
- Pierre Robin syndrome
- Intrinsic airway obstruction (laryngeal/bronchial/tracheal stenosis)
- Extrinsic airway obstruction (bronchogenic cyst, duplication cyst, vascular compression)

**Lung**

- Respiratory distress syndrome
- Transient tachypnea
- Meconium aspiration
- Pneumonia (sepsis)
- Pneumothorax
- Congenital diaphragmatic hernia
- Pulmonary hypoplasia

**CARDIAC RIGHT-TO-LEFT SHUNT***Abnormal connections (pulmonary blood flow normal or increased)*

- Transposition of great vessels
- Total anomalous pulmonary venous return
- Truncus arteriosus
- Hypoplastic left heart syndrome
- Single ventricle or tricuspid atresia with large ventricular septal defect but without pulmonic stenosis
- Obstructed pulmonary blood flow (pulmonary blood flow decreased)**
- Pulmonic atresia with intact ventricular septum
- Tetralogy of Fallot
- Critical pulmonic stenosis with patent foramen ovale or atrial septal defect
- Tricuspid atresia
- Single ventricle with pulmonic stenosis
- Ebstein malformation of the tricuspid valve
- Persistent fetal circulation (persistent pulmonary hypertension of newborn)

**METHEMOGLOBINEMIA**

- Congenital (hemoglobin M, methemoglobin reductase deficiency)
- Acquired (nitrates, nitrites)
- Inadequate ambient O<sub>2</sub> or less O<sub>2</sub> delivered than expected (rare)
- Disconnection of O<sub>2</sub> supply to nasal cannula, head hood
- Connection of air, rather than O<sub>2</sub>, to a mechanical ventilator

**SPURIOUS/ARTIFACTUAL**

- Oximeter artifact (poor contact between probe and skin, poor pulse searching)
- Arterial blood gas artifact (contamination with venous blood)

**OTHER**

- Hypoglycemia
- Adrenogenital syndrome
- Polycythemia

**BLOOD LOSS****Table 97-9**

## Readiness for Discharge of High-Risk Infants Criteria

Resolution of acute life-threatening illnesses

Ongoing follow-up for chronic but stable problems:

Bronchopulmonary dysplasia

Intraventricular hemorrhage

Necrotizing enterocolitis after surgery or recovery

Ventricular septal defect, other cardiac lesions

Anemia

Retinopathy of prematurity

Hearing problems

Apnea

Cholestasis

Stable temperature regulation

Gain of weight with oral feedings:

Breastfeeding

Bottle-feeding

Gastric tube

Free of significant apnea; home monitoring for apnea if needed

Appropriate immunizations and planning for respiratory syncytial virus prophylaxis if indicated

Hearing screenings

Ophthalmologic examination if <27 wk of gestation or <1,250 g at birth

Mother's knowledge, skill, confidence documented in:

Administration of medications (diuretics, methylxanthines, aerosols, etc.)

Use of oxygen, apnea monitors, oximeters

Nutritional support:

Timing

Volume

Mixing concentrated formulas

Recognition of illness and deterioration

Basic cardiopulmonary resuscitation

Infant safety (see Table 97-1)

Scheduling of referrals:

Primary care provider

Neonatal follow-up clinic

Occupational therapy/physical therapy

Imaging (head ultrasound)

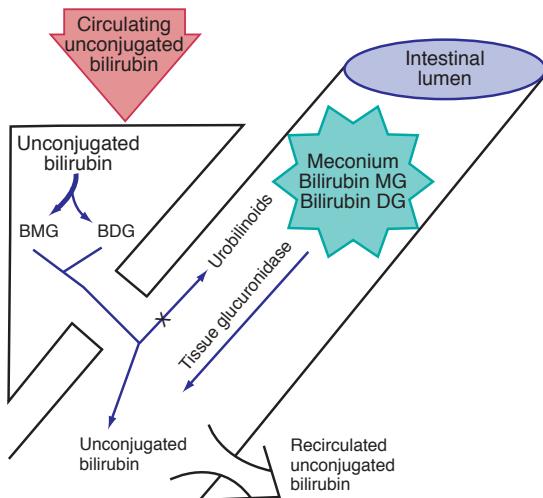
Assessment of and solution to social risks (see Table 97-1)

Adapted from American Academy of Pediatrics, American College of Obstetricians: Guidelines for perinatal care, ed 7, Elk Grove Village, IL, 2013, American Academy of Pediatrics.

**Table 101-1**

## Potential Causes of Neonatal Apnea and Bradycardia

Central nervous system	Intraventricular hemorrhage, drugs, seizures, hypoxic injury, herniation, neuromuscular disorders, Leigh syndrome, brainstem infarction or anomalies (e.g., olivopontocerebellar atrophy), spinal cord injury after general anesthesia
Respiratory	Pneumonia, obstructive airway lesions, upper airway collapse, atelectasis, extreme prematurity, laryngeal reflex, phrenic nerve paralysis, pneumothorax, hypoxia
Infectious	Sepsis, meningitis (bacterial, fungal, viral), respiratory syncytial virus, pertussis
Gastrointestinal	Oral feeding, bowel movement, necrotizing enterocolitis, intestinal perforation
Metabolic	↓ Glucose, ↓ calcium, ↓/↑ sodium, ↑ ammonia, ↑ organic acids, ↑ ambient temperature, hypothermia
Cardiovascular	Hypotension, hypertension, heart failure, anemia, hypovolemia, vagal tone
Other	Immaturity of respiratory center, sleep state



**Figure 102-6** The neonatal production rate of bilirubin is 6–8 mg/kg/24 hr (in contrast to 3–4 mg/kg/24 hr in adults). Water-insoluble bilirubin is bound to albumin. At the plasma-hepatocyte interface, a liver membrane carrier (bilirubin translocase) transports bilirubin to a cytosolic binding protein (ligandin or Y protein, now known to be glutathione S-transferase), which prevents back-absorption to plasma. Bilirubin is converted to bilirubin monoglucuronide (BMG). Neonates excrete more BMG than adults do. In the fetus, conjugated lipid-insoluble BMG and bilirubin diglucuronide (BDG) must be deconjugated by tissue  $\beta$ -glucuronidases to facilitate placental transfer of lipid-soluble unconjugated bilirubin across the placental lipid membranes. After birth, intestinal or milk-containing glucuronyltransferases contribute to the enterohepatic recirculation of bilirubin and possibly to the development of hyperbilirubinemia.

**Table 102-2**

Risk Factors for Development of Severe Hyperbilirubinemia in Infants  $\geq 35$  Wk of Gestation (in Approximate Order of Importance)

#### MAJOR RISK FACTORS

- Predischarge TSB or TcB level in the high-risk zone (see Fig. 102-8)
- Jaundice observed in the 1st 24 hr
- Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (glucose-6-phosphate dehydrogenase deficiency), elevated end-tidal CO concentration
- Gestational age 35–36 wk
- Previous sibling received phototherapy
- Cephalohematoma or significant bruising
- Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
- East Asian race\*

#### MINOR RISK FACTORS

- Predischarge TSB or TcB level in the high intermediate-risk zone
- Gestational age 37–38 wk
- Jaundice observed before discharge
- Previous sibling with jaundice
- Macrosomic infant of a diabetic mother
- Maternal age  $\geq 25$  yr
- Male gender

#### DECREASED RISK (THESE FACTORS ARE ASSOCIATED WITH DECREASED RISK OF SIGNIFICANT JAUNDICE, LISTED IN ORDER OF DECREASING IMPORTANCE)

- TSB or TcB level in the low-risk zone (see Fig. 102-8)
- Gestational age  $\geq 41$  wk
- Exclusive bottle-feeding
- Black race
- Discharge from hospital after 72 hr

\*Race as defined by mother's description.

TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

From AAP Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, Pediatrics 114:297–316, 2004.

**Table 102-3**

Laboratory Evaluation of the Jaundiced Infant  $\geq 35$  Wk of Gestation

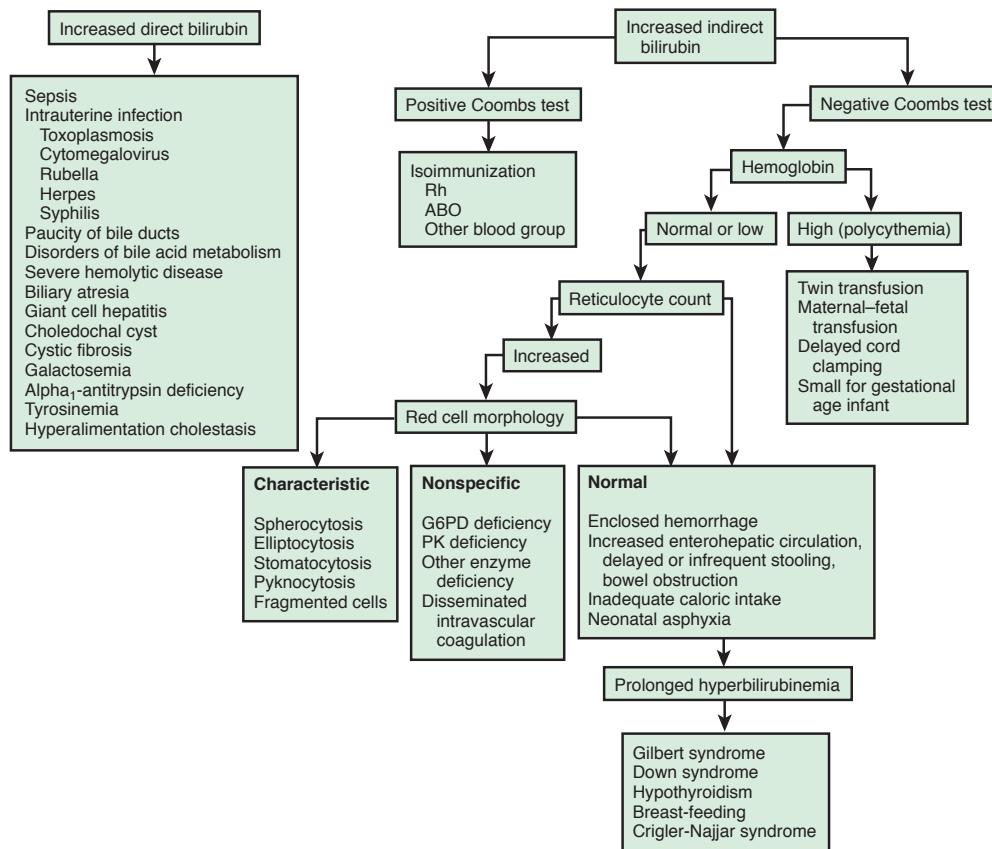
#### INDICATIONS

#### ASSESSMENTS

Jaundice in 1st 24 hr	Measure TcB and/or TSB
Jaundice appears excessive for infant's age	Measure TcB and/or TSB
Infant receiving phototherapy or TSB rising rapidly (i.e., crossing percentiles [see Fig. 102-8]) and unexplained by history and physical examination	Blood type and Coombs test, if not obtained with cord blood Complete blood count and smear Measure direct or conjugated bilirubin It is an option to perform reticulocyte count, G6PD, and ETCO <sub>c</sub> , if available Repeat TSB in 4–24 hr depending on infant's age and TSB level
TSB concentration approaching exchange levels or not responding to phototherapy	Perform reticulocyte count, G6PD, albumin, ETCO if available
Elevated direct (or conjugated) bilirubin level	Do urinalysis and urine culture Evaluate for sepsis if indicated by history and physical examination
Jaundice present at or beyond age 3 wk, or sick infant	Total and direct (or conjugated) bilirubin level If direct bilirubin elevated, evaluate for causes of cholestasis Check results of newborn thyroid and galactosemia screen, and evaluate infant for signs or symptoms of hypothyroidism

ETCO<sub>c</sub>, end tidal carbon monoxide concentration; G6PD, glucose-6-phosphate dehydrogenase; TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

From AAP Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, Pediatrics 114:297–316, 2004.



**Figure 102-7** Schematic approach to the diagnosis of neonatal jaundice. G6PD, glucose-6-phosphate dehydrogenase; PK, pyruvate kinase. (From Oski FA: Differential diagnosis of jaundice. In Taeusch HW, Ballard RA, Avery MA, editors: Schaffer and Avery's diseases of the newborn, ed 6, Philadelphia, 1991, WB Saunders.)

**Table 101-2** Definition of BPD: Diagnostic Criteria\*

	GESTATIONAL AGE	
	<32 Wk	≥32 Wk
Time point of assessment	36 wk postmenstrual age or discharge home, whichever comes first Treatment with >21% oxygen for at least 28 days plus	>28 days but <56 days postnatal age or discharge home, whichever comes first Treatment with >21% oxygen for at least 28 days plus
Mild BPD	Breathing room air at 36 wk postmenstrual age or discharge home, whichever comes first	Breathing room air by 56 days postnatal age or discharge home, whichever comes first
Moderate BPD	Need <sup>†</sup> for <30% oxygen at 36 wk postmenstrual age or discharge home, whichever comes first	Need <sup>†</sup> for <30% oxygen at 56 days postnatal age or discharge home, whichever comes first
Severe BPD	Need <sup>†</sup> for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 36 wk postmenstrual age or discharge home, whichever comes first	Need <sup>†</sup> for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 days postnatal age or discharge home, whichever comes first

\*BPD usually develops in neonates being treated with oxygen and PPV for respiratory failure, most commonly respiratory distress syndrome. Persistence of the clinical features of respiratory disease (tachypnea, retractions, crackles) is considered common to the broad description of BPD and has not been included in the diagnostic criteria describing the severity of BPD. Infants treated with >21% oxygen and/or PPV for nonrespiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless parenchymal lung disease also develops and they have clinical features of respiratory distress. A day of treatment with >21% oxygen means that the infant received >21% oxygen for more than 12 hr on that day. Treatment with >21% oxygen and/or PPV at 36 wk postmenstrual age or at 56 days postnatal age or discharge should not reflect an "acute" event, but should rather reflect the infant's usual daily therapy for several days preceding and after 36 wk postmenstrual age, 56 days postnatal age, or discharge.

<sup>†</sup>A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range.

BPD, bronchopulmonary dysplasia; NCPAP, nasal continuous positive airway pressure; PPV, positive-pressure ventilation.

From Jobe AH, Bancalari E: Bronchopulmonary dysplasia, Am J Respir Crit Care Med 163:1723-1729, 2001.

**Table 102-4** Diagnostic Features of the Various Types of Neonatal Jaundice

DIAGNOSIS	NATURE OF VAN DEN BERGH REACTION	JAUNDICE		PEAK BILIRUBIN CONCENTRATION		BILIRUBIN RATE OF ACCUMULATION (mg/dL/day)	REMARKS
		Appears	Disappears	mg/dL	Age in Days		
"Physiologic jaundice": Full-term Premature	Indirect Indirect	2-3 days 3-4 days	4-5 days 7-9 days	10-12 15	2-3 6-8	<5	Usually relates to degree of maturity
Hyperbilirubinemia caused by metabolic factors: Full-term	Indirect	2-3 days	Variable	>12	1st wk	<5	Metabolic factors: hypoxia, respiratory distress, lack of carbohydrate
Premature	Indirect	3-4 days	Variable	>15	1st wk	<5	Hormonal influences: cretinism, hormones, Gilbert syndrome Genetic factors: Crigler-Najjar syndrome, Gilbert syndrome Drugs: vitamin K, novobiocin
Hemolytic states and hematoma	Indirect	May appear in 1st 24 hr	Variable	Unlimited	Variable	Usually >5	Erythroblastosis: Rh, ABO, Kell congenital hemolytic states: spherocytic, nonspherocytic Infantile pyknocytosis Drug: vitamin K Enclosed hemorrhage—hematoma
Mixed hemolytic and hepatotoxic factors	Indirect and direct	May appear in 1st 24 hr	Variable	Unlimited	Variable	Usually >5	Infection: bacterial sepsis, pyelonephritis, hepatitis, toxoplasmosis, cytomegalic inclusion disease, rubella, syphilis Drug: vitamin K
Hepatocellular damage	Indirect and direct	Usually 2-3 days; may appear by 2nd wk	Variable	Unlimited	Variable	Variable, can be >5	Biliary atresia; paucity of bile ducts, familial cholestasis, galactosemia; hepatitis and infection

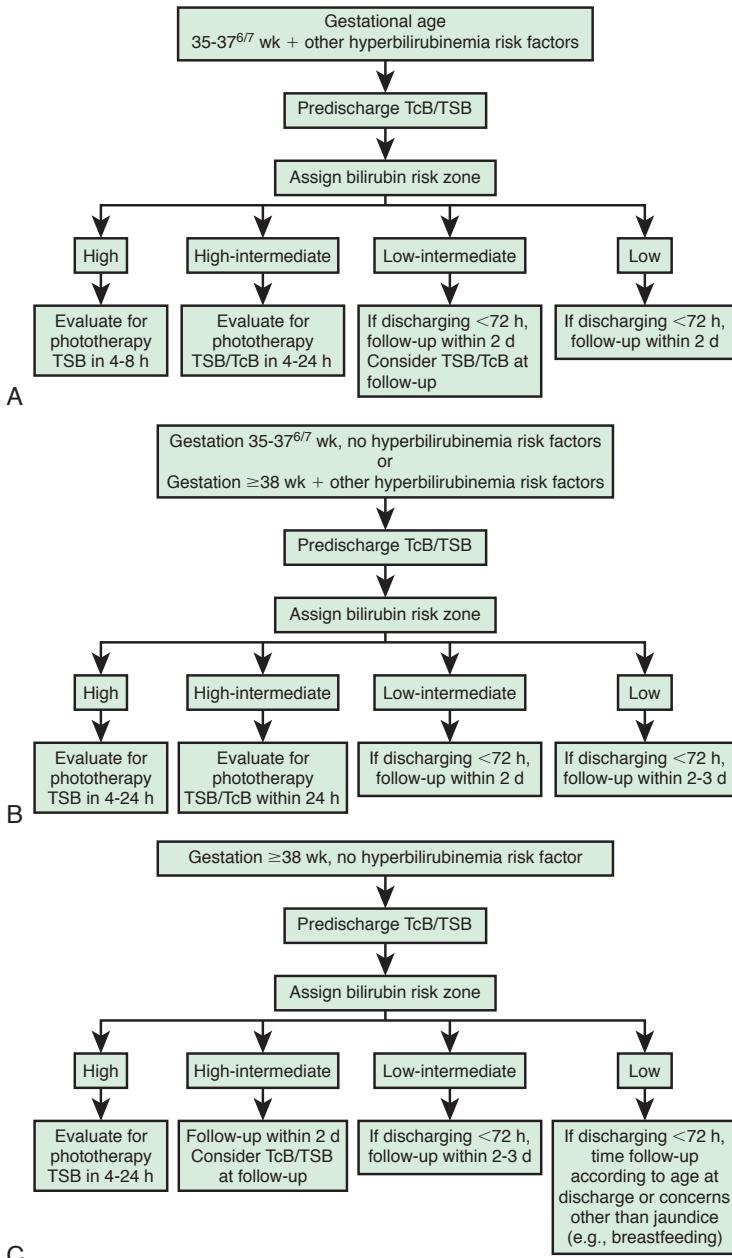
**Table 103-2** Transfusion Protocol

HEMATOCRIT (%)	HEMOGLOBIN (g/dL)	RESPIRATORY SUPPORT AND/OR SYMPTOMS	TRANSFUSION VOLUME
≤35	≤11	Infants requiring moderate or significant mechanical ventilation (mean arterial pressure >8 cm H <sub>2</sub> O and FIO <sub>2</sub> >0.4)	15 mL/kg PRBCs* over 2-4 hr
≤30	≤10	Infants requiring minimal respiratory support (any mechanical ventilation or endotracheal/nasal continuous positive airway pressure >6 cm H <sub>2</sub> O and FIO <sub>2</sub> ≤0.4)	15 mL/kg PRBCs over 2-4 hr
≤25	≤8	Infants not requiring mechanical ventilation but who are receiving supplemental O <sub>2</sub> or CPAP with an FIO <sub>2</sub> ≤0.4 and in whom 1 or more of the following is present: <ul style="list-style-type: none"> <li>• ≤24 hr of tachycardia (heart rate &gt;180 beats/min) or tachypnea (respiratory rate &gt;80 breaths/min)</li> <li>• An increased oxygen requirement from the previous 48 hr, defined as a ≥4-fold increase in nasal canula flow (i.e., from 0.25 to 1 L/min) or an increase in nasal CPAP ≥20% from the previous 48 hr (i.e., 5-6 cm H<sub>2</sub>O)</li> <li>• Weight gain &lt;10 g/kg/day over the previous 4 days while infant is receiving ≥100 kcal/kg/day</li> <li>• An increase in episodes of apnea and bradycardia (&gt;9 episodes in a 24-hr period or ≥2 episodes in 24 hr requiring bag and mask ventilation) while infant is receiving therapeutic doses of methylxanthines</li> <li>• Undergoing surgery</li> </ul>	20 mL/kg PRBCs over 2-4 hr (divide into 2 10-mL/kg volumes if infant is fluid sensitive)
≤20	≤7	Asymptomatic and an absolute reticulocyte count <100,000 cells/µL	20 mL/kg PRBCs over 2-4 hr (2 10-mL/kg volumes)

\*RBCs should be irradiated prior to transfusion.

CPAP, continuous positive airway pressure; FIO<sub>2</sub>, fractional inspired oxygen; PRBCs, packed red blood cells.

From Ohls RK, Ehrenkranz RA, Wright LL, et al: Effects of early erythropoietin therapy on the transfusion requirements of preterm infants below 1250 grams birth weight: a multicenter, randomized, controlled trial, Pediatrics 108:934-942, 2001.



**Figure 102-10** Algorithm providing recommendations for management and follow-up according to predischarge bilirubin measurements, gestation, and risk factors for subsequent hyperbilirubinemia. TcB, transcutaneous bilirubin; TSB, total serum bilirubin. (From Maisels MJ, Bhutani VK, Bogen D, et al: Hyperbilirubinemia in the newborn infant ≥35 weeks' gestation: an update with clarifications, Pediatrics 124:1193-1198, 2009.)

**Table 102-7**

Example of a Clinical Pathway for Management of the Newborn Infant Readmitted for Phototherapy or Exchange Transfusion

#### TREATMENT

Use intensive phototherapy and/or exchange transfusion as indicated in Figs. 102-11 and 102-12

#### LABORATORY TESTS

TSB and direct bilirubin levels

Blood type (ABO, Rh)

Direct antibody test (Coombs)

Serum albumin

Complete blood cell count with differential and smear for red cell morphology

Reticulocyte count

End-tidal CO concentration (if available)

Glucose-6-phosphate dehydrogenase if suggested by ethnic or geographic origin or if poor response to phototherapy

Urine for reducing substances

If history and/or presentation suggest sepsis, perform blood culture, urine culture, and cerebrospinal fluid for protein, glucose, cell count, and culture

#### INTERVENTIONS

If TSB ≥25 mg/dL (428 μmol/L) or ≥20 mg/dL (342 μmol/L) in a sick infant or infant <38 wk gestation, obtain a type and crossmatch, and request blood in case an exchange transfusion is necessary

In infants with isoimmune hemolytic disease and TSB level rising in spite of intensive phototherapy or within 2-3 mg/dL (34-51 μmol/L) of exchange level (see Fig. 102-12), administer intravenous immunoglobulin 0.5-1 g/kg over 2 hr and repeat in 12 hr if necessary

If infant's weight loss from birth is >12% or there is clinical or biochemical evidence of dehydration, recommend formula or expressed breast milk. If oral intake is in question, give intravenous fluids

#### FOR INFANTS RECEIVING INTENSIVE PHOTOTHERAPY:

Breastfeed or bottle-feed (formula or expressed breast milk) every 2-3 hr

If TSB ≥25 mg/dL (428 μmol/L), repeat TSB within 2-3 hr

If TSB 20-25 mg/dL (342-428 μmol/L), repeat within 3-4 hr. If TSB <20 mg/dL (342 μmol/L), repeat in 4-6 hr. If TSB continues to fall, repeat in 8-12 hr

If TSB is not decreasing or is moving closer to level for exchange transfusion or the TSB/albumin ratio exceeds levels shown in Fig. 102-12, consider exchange transfusion (see Fig. 102-12 for exchange transfusion recommendations)

When TSB is <13-14 mg/dL (239 μmol/L), discontinue phototherapy

Depending on the cause of the hyperbilirubinemia, it is an option to measure TSB 24 hr after discharge to check for rebound

<b>Table 103-1</b> Normal Red Blood Cell Values from 18 Wk of Gestation to 14 Wk of Life				
AGE	HEMOGLOBIN (g/dL)	HEMATOCRIT (%)	MCV ( $\mu^3$ )	RETICULOCYTES (%)
<b>GESTATIONAL (WK)</b>				
18-20*	11.5 ± 0.8	36 ± 3	134 ± 8.8	N/A
21-22*	12.3 ± 0.9	39 ± 3	130 ± 6.2	N/A
23-25*	12.4 ± 0.8	39 ± 2	126 ± 6.2	N/A
26-27	19.0 ± 2.5	62 ± 8	132 ± 14.4	9.6 ± 3.2
28-29	19.3 ± 1.8	60 ± 7	131 ± 13.5	7.5 ± 2.5
30-31	19.1 ± 2.2	60 ± 8	127 ± 12.7	5.8 ± 2.0
32-33	18.5 ± 2.0	60 ± 8	123 ± 15.7	5.0 ± 1.9
34-35	19.6 ± 2.1	61 ± 7	122 ± 10.0	3.9 ± 1.6
36-37	19.2 ± 1.7	64 ± 7	121 ± 12.5	4.2 ± 1.8
38-40	19.3 ± 2.2	61 ± 7	119 ± 9.4	3.2 ± 1.4
<b>POSTNATAL (DAYS)</b>				
1	19.0 ± 2.2	61 ± 7	119 ± 9.4	3.2 ± 1.4
2	19.0 ± 1.9	60 ± 6	115 ± 7.0	3.2 ± 1.3
3	18.7 ± 3.4	62 ± 9	116 ± 5.3	2.8 ± 1.7
4	18.6 ± 2.1	57 ± 8	114 ± 7.5	1.8 ± 1.1
5	17.6 ± 1.1	57 ± 7	114 ± 8.9	1.2 ± 0.2
6	17.4 ± 2.2	54 ± 7	113 ± 10.0	0.6 ± 0.2
7	17.9 ± 2.5	56 ± 9	118 ± 11.2	0.5 ± 0.4
<b>POSTNATAL (WK)</b>				
1-2	17.3 ± 2.3	54 ± 8	112 ± 19.0	0.5 ± 0.3
2-3	15.6 ± 2.6	46 ± 7	111 ± 8.2	0.8 ± 0.6
3-4	14.2 ± 2.1	43 ± 6	105 ± 7.5	0.6 ± 0.3
4-5	12.7 ± 1.6	36 ± 5	101 ± 8.1	0.9 ± 0.8
5-6	11.9 ± 1.5	36 ± 6	102 ± 10.2	1.0 ± 0.7
6-7	12.0 ± 1.5	36 ± 5	105 ± 12.0	1.2 ± 0.7
7-8	11.1 ± 1.1	33 ± 4	100 ± 13.0	1.5 ± 0.7
8-9	10.7 ± 0.9	31 ± 3	93 ± 12.0	1.8 ± 1.0
9-10	11.2 ± 0.9	32 ± 3	91 ± 9.3	1.2 ± 0.6
10-11	11.4 ± 0.9	34 ± 2	91 ± 7.7	1.2 ± 0.7
11-12	11.3 ± 0.9	33 ± 3	88 ± 7.9	0.7 ± 0.3
12-14	11.9	37	86.8	0.9

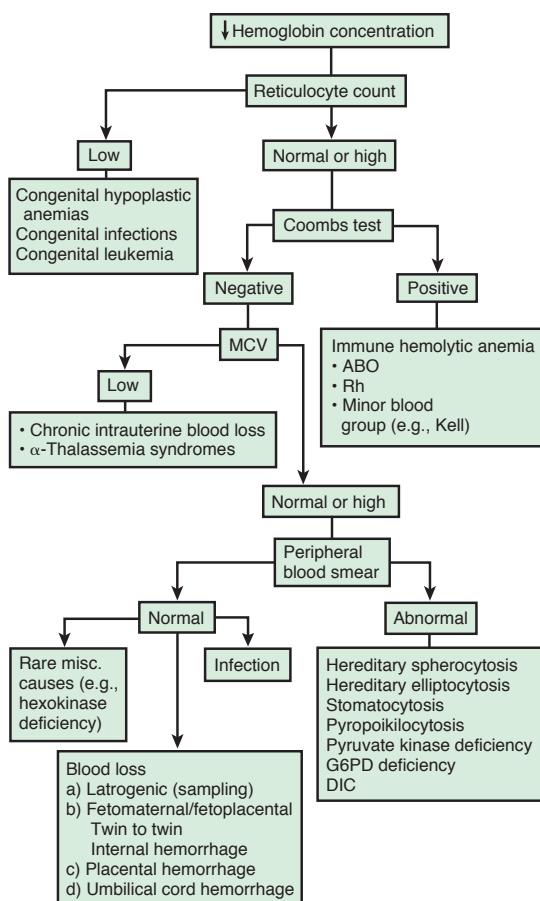
\*Based on samples collected in utero. Results expressed as mean value ± 1 standard deviation from the mean except for postnatal weeks 12-14 in which only the mean value is given.

From Bizzarro MJ, Colson E, Ehrenkranz RA: Differential diagnosis and management of anemia in the newborn, *Pediatr Clin North Am* 51:1087-1107, 2004.

<b>Table 103-3</b> Etiology of Hydrops Fetalis*			
CATEGORY	DISORDER(S)	CATEGORY	DISORDER(S)
Anemia	Immune (Rh, Kell) hemolysis α-Thalassemia Red blood cell enzyme deficiencies (glucose-6-phosphate dehydrogenase) Fetomaternal hemorrhage Donor in twin-to-twin transfusion Diamond-Blackfan syndrome	Teratomas	Choriocarcinoma Sacrococcygeal teratoma
Cardiac dysrhythmias	Supraventricular tachycardia Atrial flutter Congenital heart block	Tumors and storage diseases	Neuroblastoma Hepatoblastoma Gaucher disease Niemann-Pick disease Mucolipidosis GM <sub>1</sub> gangliosidosis Mucopolysaccharidosis
Structural heart lesions	Premature closure of foramen ovale Tricuspid insufficiency Hypoplastic left heart Endocardial cushion defect Cardiomyopathy Endocardial fibroelastosis Tuberous sclerosis with cardiac rhabdomyoma Pericardial teratoma	Chromosome abnormalities	Trisomy 13, 15, 16, 18, 21 XX/XY, 45XO Partial duplication of chromosomes 11, 15, 17, 18 Partial deletion of chromosomes 13, 18 Triploidy Tetraploidy
Vascular	Chorioangioma of placenta, chorionic vessels, or umbilical vessels Umbilical artery aneurysm Angiomyxoma of umbilical cord True knot of umbilical cord Hepatic hemangioma Cerebral arteriovenous malformation (aneurysm of vein of Galen) Angioosteohypertrophy (Klippel-Trénaunay syndrome) Thrombosis of renal or umbilical vein or inferior vena cava Recipient in twin-to-twin transfusion	Bone diseases	Osteogenesis imperfecta Asphyxiating thoracic dystrophy Skeletal dysplasias
Lymphatic	Lymphangiectasia Cystic hygroma Chylothorax, chylous ascites Noonan syndrome Multiple pterygium syndrome	Congenital infections	Cytomegalovirus Parvovirus Rubella Toxoplasmosis Syphilis Leptospirosis Chagas disease
Central nervous system	Absent corpus callosum Encephalocele Intracranial hemorrhage Holoprosencephaly	Others	Bowel obstruction with perforation and meconium peritonitis, volvulus Hepatic fibrosis Beckwith-Wiedemann syndrome Prune-belly syndrome Congenital nephrosis Infant of a diabetic mother Myotonic dystrophy Neu-Laxova syndrome Maternal therapy with indomethacin Fetal akinesia
Thoracic lesions	Cystic adenomatoid malformation of lung Mediastinal teratoma Diaphragmatic hernia Sequestered lung	Idiopathic	Multiple congenital anomaly syndromes

\*The incidence of nonimmune (nonhemolytic) hydrops fetalis is 1/2,000-1/3,500 live births.

Modified from Phibbs R. In Polin R, Fox W, editors: *Fetal and neonatal physiology*, ed 2, Philadelphia, 1998, WB Saunders.



**Figure 103-2** Diagnostic approach to anemia in newborn infants. DIC, disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase; MCV, mean corpuscular volume.

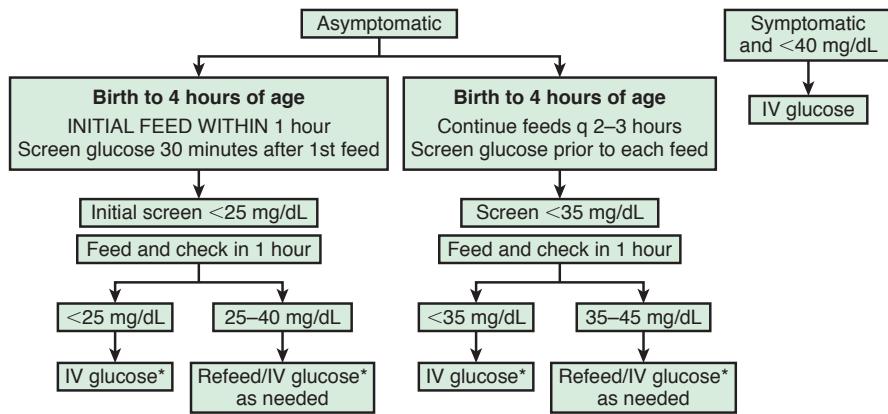
<b>Table 106-1</b>   Neurobehavioral Scale	
DOMAIN	ITEMS
Physiologic	Labored breathing Nasal flaring
Autonomic	Sweating Spit-up Hiccoughing Sneezing Nasal stuffiness Yawning
Central nervous system	Abnormal sucking Choreiform movements Athetoid postures and movements Tremors Cogwheel movements Startles Hypertonia Back arching Fisting Cortical thumb Myoclonic jerks Generalized seizures Abnormal posture
Skin	Pallor Mottling Lividity Overall cyanosis Circumoral cyanosis Periocular cyanosis
Visual	Gaze aversion during orientation Pull-down during orientation Fuss/cry during orientation Obligatory following during orientation End-point nystagmus during orientation Sustained spontaneous nystagmus Visual locking Hyperalertness Setting sun sign Roving eye movements Strabismus Tight blinking Other abnormal eye signs
Gastrointestinal	Gagging/choking Loose stools, watery stools Excessive gas, bowel sounds
State	High-pitched cry Monotone-pitch cry Weak cry No cry Extreme irritability Abrupt state changes Inability to achieve quiet awake state (state 4)

**Table 106-2** Pharmacologic Therapy for Neonatal Abstinence Syndrome

DRUG	INITIAL DOSING	DOSING INCREASES	RESCUE DOSING	ADD ADJUVANT THERAPY	WEANING SCHEDULE
Morphine	0.1 mg kg <sup>-1</sup> dose <sup>-1</sup> orally every 4 hr	Increase by 20–30% every 12 hr until scores <8 × 24 hr	Repeat previous dose between scheduled dose intervals	At morphine dose of 1.25 mg kg <sup>-1</sup> dose <sup>-1</sup> , add phenobarbital or clonidine	Decrease by 10% every 24 hr, while scores <8. Discontinue when 0.15 kg <sup>-1</sup> dose <sup>-1</sup>
Methadone	0.1 mg kg <sup>-1</sup> dose <sup>-1</sup> orally every 12 hr	Calculate entire methadone dose for previous 24 hr and divide by two for BID dosing	Additional dosing of 0.025 mg kg <sup>-1</sup> dose <sup>-1</sup> every 4 hr while scoring >8. Max dose 0.5 mg kg <sup>-1</sup> dose <sup>-1</sup>	When max dosing has been reached	Decrease by 10% every 1–2 wk. Discontinue when 0.05 mg kg <sup>-1</sup> dose <sup>-1</sup>
Buprenorphine	15.9 µg kg <sup>-1</sup> dose <sup>-1</sup> divided in 3 doses, orally	Increase by 25%	Max dose 60 µg kg <sup>-1</sup> dose <sup>-1</sup>		After 3 days of stabilization, decrease by 10% while scores <8. Discontinue when dose is 10% of initial dose
Phenobarbital	20 mg/kg loading	Maintenance dose 5 mg/kg		Adjuvant	
Clonidine	0.5 to 1.5 µg/kg orally	Increase by over 1 to 2 days to target dose 3 to 5 µg kg <sup>-1</sup> day <sup>-1</sup> , divided every 4–6 hr		Adjuvant	No taper required

**Screening and Management of Postnatal Glucose Homeostasis in Late Preterm and Term SGA, IDM/LGA Infants**

[(LPT) Infants 34–36<sup>67</sup> weeks and SGA (screen 0–24 hrs); IDM and LGA ≥34 weeks (screen 0–12 hrs)]



\*Glucose dose = 200 mg/kg (dextrose 10% at 2 mL/kg) and/or IV infusion at 5–8 mg/kg per min (80–100 mL/kg per d). Achieve plasma glucose level of 40–50 mg/dL.

Symptoms of hypoglycemia include: Irritability, tremors, jitteriness, exaggerated Moro reflex, high-pitched cry, seizures, lethargy, floppiness, cyanosis, apnea, poor feeding.

**Figure 107-3** Screening for and management of postnatal glucose homeostasis in late-preterm (LPT 34–36 wk) and term small-for-gestational age (SGA) infants and infants who were born to mothers with diabetes (IDM)/large-for-gestational age (LGA) infants. LPT and SGA, screen 0–24 hr; IDM and LGA ≥34 wk, screen 0–12 hr. IV indicates intravenous.

**Table 108-1** Mechanisms, Terminology, and Definitions of Dysmorphology

TERMINOLOGY	DEFINITION	EXAMPLE
Malformation sequence	Single, local tissue morphogenesis abnormality that produces a chain of subsequent defects	DiGeorge sequence of primary fourth branchial arch and 3rd and 4th pharyngeal pouch defects that lead to aplasia or hypoplasia of the thymus and parathyroid glands, aortic arch anomalies, and micrognathia
Deformation sequence	Mechanical (uterine) forces that alter structure of intrinsically normal tissue	Oligohydramnios produces deformations by in utero compression of limbs (dislocated hips, equinovarus foot deformity), crumpled ears, dislocated nose, or small thorax
Disruption sequence	In utero tissue destruction after a period of normal morphogenesis	Amniotic membrane rupture sequence, leading to amputation of fingers/toes, tissue fibrosis, and destructive tissue bands
Dysplasia sequence	Poor organization of cells into tissues or organs	Neurocutaneous melanosis sequence with poor migration of melanocyte precursor cells from the neural crest to the periphery, manifesting as melanocytic hamartosis of skin, meninges, and so forth
Malformation syndrome	Appearance of multiple malformations in unrelated tissues without an understandable unifying cause; with enhanced genetic investigation, a single etiology may become identified	Trisomy 21 Teratogens

**Table 109-8** Definitions of Systemic Inflammatory Respiratory Response Syndrome and Sepsis in Pediatric Patients

**SIRS:** The systemic inflammatory response to a variety of clinical insults, manifested by 2 or more of the following conditions:  
 Temperature instability <35°C (95°F) or >38.5°C (101.3°F)  
 Respiratory dysfunction:  
 Tachypnea >2 SD above the mean for age  
 Hypoxemia ( $\text{PaO}_2$  <70 mm Hg on room air)  
 Cardiac dysfunction:  
 Tachycardia >2 SD above the mean for age  
 Delayed capillary refill >3 sec  
 Hypotension >2 SD below the mean for age  
 Perfusion abnormalities:  
 Oliguria (urine output <0.5 mL/kg/hr)  
 Lactic acidosis (elevated plasma lactate and/or arterial pH <7.25)  
 Altered mental status  
**Sepsis:** The systemic inflammatory response to an infectious process

**Table 108-2**

Examples of Malformations with Distinct Causes, Clinical Features, and Pathogenesis			
DISORDER	CAUSE/INHERITANCE	CLINICAL FEATURES	PATHOGENESIS
Spondylocostal dysostosis syndromes	Mendelian autosomal recessive	Abnormal vertebral segmentation Neural tube defects	<i>DLL3</i> mutations; mutations can also be present in other genes
Rubinstein-Taybi syndrome	Mendelian autosomal recessive	Mental retardation Broad thumbs, toes Hypoplastic maxillae Prominent nose Congenital heart disease	<i>CBP</i> mutations or haploinsufficiency
X-linked lissencephaly	Mendelian X-linked	Male: Severe mental retardation Seizures Female: Variable	<i>DCX</i> mutation
Aniridia	Autosomal semidominant	Reduced or absent iris	<i>PAX6</i> mutations
Waardenburg syndrome	Autosomal semidominant	Deafness White forelock Wide-spaced eyes Pale eye pigment	<i>PAX3</i> mutations <i>MITF</i> mutations
Holoprosencephaly	Loss of function or heterozygosity	Microcephaly Cyclopia Single central incisor	<i>SHH</i> mutations
Velocardiofacial syndrome	Microdeletion 22q11.2	Conotruncal congenital heart disease Cleft palate T-cell defects Facial anomalies	<i>TBX1</i> haploinsufficiency/mutations; haploinsufficiency for other genes in the deleted interval
Down syndrome	Chromosomal	Mental retardation  Characteristic dysmorphic features Congenital heart disease Increased risk of leukemia Alzheimer disease	50% increase of estimated 250 genes on chromosome 21  Trisomy 21
Neural tube defects	Multifactorial	Meningomyelocele	Defects in folate sensitive enzymes or folic acid uptake
Fetal alcohol syndrome	Teratogenic	Microcephaly Developmental delay Facial abnormalities Behavioral abnormalities	Ethanol toxicity to developing brain
Retinoic acid embryopathy	Teratogenic	Microtia Congenital heart disease	Isotretinoin effects on neural crest and branchial arch development

**Table 108-4**

Childhood Diseases and Syndromes Associated with Motile and Sensory Ciliopathies		
PEDIATRIC CILIOPATHY	CLINICAL MANIFESTATIONS	GENE(S)
<b>MOTOR</b>		
Primary ciliary dyskinesia	Chronic bronchitis, rhinosinusitis, otitis media, laterality defects, infertility, CHD	<i>DNAI1</i> , <i>DNAH5</i> , <i>DNAH11</i> , <i>DNAI2</i> , <i>KTU</i> , <i>TXNDC3</i> , <i>LRRK50</i> , <i>RSPH9</i> , <i>RSPH4A</i> , <i>CCDC40</i> , <i>CCDC39</i>
<b>SENSORY</b>		
Autosomal recessive polycystic kidney disease	RFD, CHF	<i>PKHD1</i>
Nephronophthisis	RFD, interstitial nephritis, CHF, RP	<i>NPHP1-8</i> , <i>ALMS1</i> , <i>CEP290</i>
Barde-Biedl syndrome	Obesity, polydactyly, ID, RP, renal anomalies, anosmia, CHD	<i>BBS1-12</i> , <i>MKS1</i> , <i>MKS3</i> , <i>CEP290</i>
Meckel-Gruber syndrome	RFD, polydactyly, ID, CNS anomalies, CHD, cleft lip, cleft palate	<i>MKS1-6</i> , <i>CC2D2A</i> , <i>CEP290</i> , <i>TMEM216</i>
Joubert syndrome	CNS anomalies, ID, ataxia, RP, polydactyly, cleft lip, cleft palate	<i>NPHP1</i> , <i>JBTS1</i> , <i>JBTS3</i> , <i>JBTS4</i> , <i>CORS2</i> , <i>AHI1</i> , <i>CEP290</i> , <i>TMEM216</i>
Alstrom syndrome	Obesity, RP, DM, hypothyroidism, hypogonadism, skeletal dysplasia, cardiomyopathy, pulmonary fibrosis	<i>ALMS1</i>
Orofaciodigital syndrome type 1	Polydactyly, syndactyly, cleft lip, cleft palate, CNS anomalies, ID, RFD	<i>OFD1</i>
Ellis van Creveld syndrome	Chondrodyostrophy, polydactyly, ectodermal dysplasia, CHD	<i>EVC</i> , <i>EVC2</i>
Jeune asphyxiating thoracic dystrophy	Narrow thorax, RFD, RP, dwarfism, polydactyly	<i>IFT80</i>
Sensenbrenner syndrome	Dolichocephaly, ectodermal dysplasia, dental dysplasia, narrow thorax, RFD, CHD	<i>IFT122</i> , <i>IFT43</i> , <i>WDR35</i>
Short rib-polydactyly syndromes	Narrow thorax, short limb dwarfism, polydactyly, renal dysplasia	<i>WDR35</i> , <i>DYNC2H1</i> , <i>NEK1</i>

CHD, congenital heart disease; CHF, congenital hepatic fibrosis; CNS, central nervous system; DM, diabetes mellitus; ID, intellectual disabilities; RFD, renal fibrocystic disease; RP, retinitis pigmentosa.

From Ferkol TW, Leigh MW: Ciliopathies: the central role of cilia in a spectrum of pediatric disorders. J Pediatr 160:366-371, 2012.

**Table 108-3** Causes of Congenital Malformations

MONOGENIC (7.5% of major anomalies)	
X-linked hydrocephalus	
Achondroplasia	
Ectodermal dysplasia	
Apert syndrome	
Treacher Collins syndrome	
CHROMOSOMAL (6% of major anomalies)	
Trisomy 21, 18, 13	
XO, XYY	
Deletions 4p-, 5p-, 7q-, 13q-, 18p-, 18q-, 22q-	
Prader-Willi syndrome (50% of affected patients have deletion of chromosome 15)	
MATERNAL INFECTION (2% of major anomalies)	
Intrauterine infections (e.g., herpes simplex virus, cytomegalovirus, varicella-zoster virus, rubella virus, and toxoplasmosis)	
MATERNAL ILLNESS (3.5% of major anomalies)	
Diabetes mellitus	
Phenylketonuria	
Hyperthermia	
UTERINE ENVIRONMENT (% unknown)	
Deformation	
Uterine pressure, oligohydramnios: clubfoot, torticollis, congenital hip dislocation, pulmonary hypoplasia, 7th nerve palsy	
Disruption	
Amniotic bands, congenital amputations, gastroschisis, porencephaly, intestinal atresia	
Twinning	
ENVIRONMENTAL AGENTS (% unknown)	
Polychlorinated biphenyls	
Herbicides	
Mercury	
Alcohol	
MEDICATIONS (% unknown)	
Thalidomide	
Diethylstilbestrol	
Phenytoin	
Warfarin	
Cytotoxic drugs	
Paroxetine	
Angiotensin-converting enzyme inhibitors	
Isotherapy (vitamin A)	
D-Penicillamine	
Valproic acid	
UNKNOWN ETIOLOGIES	
Polygenic	
Associated with infertility (spontaneous or with treatment)	
Anencephaly/spina bifida	
Cleft lip/palate	
Pyloric stenosis	
Congenital heart disease	
SPORADIC SYNDROME COMPLEXES	
VATER (vertebral defects, anal atresia, tracheoesophageal fistula with esophageal atresia, and radial and renal anomalies) syndrome	
Pierre Robin syndrome	
Prune-belly syndrome	
NUTRITIONAL	
Low folic acid-neural tube defects	

**Table 109-4** Clinical Manifestations of Transplacental Infections

MANIFESTATION	PATHOGEN
Intrauterine growth restriction	CMV, <i>Plasmodium</i> , rubella, toxoplasmosis, <i>Treponema pallidum</i> , <i>Trypanosoma cruzi</i> , VZV
Congenital anatomic defects:	
Cataracts	Rubella
Cardiac defects	Rubella
Hydrocephalus	HSV, lymphocytic choriomeningitis virus, rubella, toxoplasmosis
Intracranial calcification	CMV, HIV, toxoplasmosis, <i>T. cruzi</i>
Limb hypoplasia	VZV
Microcephaly	CMV, HSV, rubella, toxoplasmosis
Microphthalmos	CMV, rubella, toxoplasmosis
Neonatal organ involvement:	
Anemia	CMV, parvovirus, <i>Plasmodium</i> , rubella, toxoplasmosis, <i>T. cruzi</i> , <i>T. pallidum</i>
Carditis	Coxackieviruses, rubella, <i>T. cruzi</i>
Encephalitis	CMV, enteroviruses, HSV, rubella, toxoplasmosis, <i>T. cruzi</i> , <i>T. pallidum</i>
Hepatitis	CMV, enteroviruses, HSV
Hepatosplenomegaly	CMV, enteroviruses, HIV, HSV, <i>Plasmodium</i> , rubella, <i>T. cruzi</i> , <i>T. pallidum</i>
Hydrops	Parvovirus, <i>T. pallidum</i> , toxoplasmosis
Lymphadenopathy	CMV, HIV, rubella, toxoplasmosis, <i>T. pallidum</i>
Osteitis	Rubella, <i>T. pallidum</i>
Petechiae, purpura	CMV, enteroviruses, rubella, <i>T. cruzi</i>
Pneumonitis	CMV, enteroviruses, HSV, measles, rubella, toxoplasmosis, <i>T. pallidum</i> , VZV
Retinitis	CMV, HSV, lymphocytic choriomeningitis virus, rubella, toxoplasmosis, <i>T. pallidum</i> , West Nile virus
Rhinitis	Enteroviruses, <i>T. pallidum</i>
Skin lesions	Enteroviruses, HSV, measles, rubella, <i>T. pallidum</i> , VZV
Thrombocytopenia	CMV, enteroviruses, HIV, HSV, rubella, toxoplasmosis, <i>T. pallidum</i>
Late sequelae:	
Convulsions	CMV, enteroviruses, rubella, toxoplasmosis
Deafness	CMV, rubella, toxoplasmosis
Dental/skeletal problems	Rubella, <i>T. pallidum</i>
Endocrinopathies	Rubella, toxoplasmosis
Eye pathology	HSV, rubella, toxoplasmosis, <i>T. cruzi</i> , <i>T. pallidum</i> , VZV
Hepatitis	Hepatitis B
Mental retardation	CMV, HIV, HSV, rubella, toxoplasmosis, <i>T. cruzi</i> , VZV
Nephrotic syndrome	Plasmodium, <i>T. pallidum</i>

**Table 109-5** Initial Signs and Symptoms of Infection in Newborn Infants

GENERAL	CARDIOVASCULAR SYSTEM
Fever, temperature instability	Pallor; mottling; cold, clammy skin
"Not doing well"	Tachycardia
Poor feeding	Hypotension
Edema	Bradycardia
GASTROINTESTINAL SYSTEM	CENTRAL NERVOUS SYSTEM
Abdominal distention	Irritability, lethargy
Vomiting	Tremors, seizures
Diarrhea	Hyporeflexia, hypotonia
Hepatomegaly	Abnormal Moro reflex
RESPIRATORY SYSTEM	Irregular respirations
Apnea, dyspnea	Full fontanel
Tachypnea, retractions	High-pitched cry
Flaring, grunting	
Cyanosis	
RENAL SYSTEM	HEMATOLOGIC SYSTEM
Oliguria	Jaundice
	Splenomegaly
	Pallor
	Petechiae, purpura
	Bleeding

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<b>Table 108-6</b> Minor Anomalies and Phenotype Variants*	
<b>CRANIOFACIAL</b>	
Large fontanel	
Flat or low nasal bridge	
Saddle nose, upturned nose	
Mild micrognathia	
Cutis aplasia of scalp	
<b>EYE</b>	
Inner epicanthal folds	
Telecanthus	
Slanting of palpebral fissures	
Hypertelorism	
Brushfield spots	
<b>EAR</b>	
Lack of helical fold	
Posteriorly rotated pinna	
Preauricular with or without auricular skin tags	
Small pinna	
Auricular (preauricular) pit or sinus	
Folding of helix	
Darwinian tubercle	
Crushed (crumpled) ear	
Asymmetric ear sizes	
Low-set ears	
<b>SKIN</b>	
Dimpling over bones	
Capillary hemangioma (face, posterior neck)	
Dermal melanosis (African Americans, Asians)	
Sacral dimple	
Pigmented nevi	
Redundant skin	
Cutis marmorata	
<b>HAND</b>	
Simian creases	
Bridged upper palmar creases	
Clinodactyly of 5th digit	
Hyperextensibility of thumbs	
Single flexion crease of 5th digit (hypoplasia of middle phalanx)	
Partial cutaneous syndactyly	
Polydactyly	
Short, broad thumb	
Narrow, hyperconvex nails	
Hypoplastic nails	
Camptodactyly	
Shortened 4th digit	
<b>FOOT</b>	
Partial syndactyly of 2nd and 3rd toes	
Asymmetric toe length	
Clinodactyly of 2nd toe	
Overlapping toes	
Nail hypoplasia	
Wide gap between hallux and 2nd toe (wide sandal gap)	
Deep plantar crease between hallux and 2nd toe	
<b>OTHERS</b>	
Mild calcaneovalgus	
Hydrocele	
Shawl scrotum	
Hypospadias	
Hypoplasia of labia majora	

\*Approximately 15% of newborns have 1 minor anomaly, 0.8% have 2 minor anomalies, and 0.5% have 3 minor anomalies. If 2 minor anomalies are present, the probability of an underlying syndrome or a major anomaly (congenital heart disease, renal, central nervous system, limbic) is 5-fold that in the general population. If 3 minor anomalies are present, the probability that there is a major anomaly is 20-30%.

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

<b>Table 108-7</b> Clinical Indications for Chromosome Analysis, or Array CGH*	
At least 1 major and 2 minor malformations	
At least 2 major malformations	
Developmental or growth retardation with 2 or more major or minor anomalies	

<b>Table 109-2</b> Etiologic Agents of Neonatal Pneumonia According to Timing of Acquisition	
<b>TRANSPLACENTAL</b>	<b>POSTNATAL</b>
CMV	Adenovirus
HSV	<i>Candida</i> species*
<i>Mycobacterium</i>	Coagulase-negative staphylococci
Tuberculosis	CMV
Rubella virus	Enteric bacteria*
<i>Treponema pallidum</i>	Enteroviruses
VZV	Influenza viruses A, B
<b>PERINATAL</b>	
Anaerobic bacteria	Parainfluenza
Chlamydia	<i>Pseudomonas</i> *
CMV	RSV
Enteric bacteria	<i>Staphylococcus aureus</i>
Group B streptococci	<i>Mycobacterium tuberculosis</i>
<i>Haemophilus influenzae</i>	
HSV	
<i>Listeria monocytogenes</i>	
<i>Mycoplasma</i>	

\*More likely with mechanical ventilation or indwelling catheters, or after abdominal surgery.

<b>Table 109-1</b> Nonbacterial Causes of Systemic Neonatal Infections	
<b>VIRUSES</b>	<b>MYCOPLASMA</b>
Adenovirus	<i>Mycoplasma hominis</i>
CMV	<i>Ureaplasma urealyticum</i>
Enteroviruses	
Parechoviruses	
Hepatitis B virus	
HSV	
HIV	
Parvovirus	
Rubella virus	
VZV	
<b>FUNGI</b>	
<i>Candida</i> species	
<i>Malassezia</i> species	
<b>PROTOZOA</b>	
Plasmodia	
<i>Toxoplasma gondii</i>	
<i>Trypanosoma cruzi</i>	

<b>Table 109-6</b> Clinical Criteria for the Diagnosis of Sepsis in the International Setting	
Integrated Management of Childhood Illness (IMCI) and WHO Criteria for Severe Infections in Children	
NEUROLOGIC:	convulsions, drowsy or unconscious, decreased activity, bulging fontanel
RESPIRATORY:	respiratory rate >60 breaths/min, grunting, severe chest indrawing, central cyanosis
CARDIAC:	poor perfusion, rapid and weak pulse
GASTROINTESTINAL:	jaundice, poor feeding, abdominal distention
DERMATOLOGIC:	skin pustules, perumbilical erythema or purulence
MUSCULOSKELETAL:	edema or erythema overlying bones or joints
OTHER:	Temperature >37.7°C (99.9°F; or feels hot) or <35.5°C (95.9°F; or feels cold)

**Table 108-5** Definitions of Common Clinical Signs of Dysmorphic Syndromes

SIGN	DEFINITION
Brachycephaly	A condition in which head shape is shortened from front to back along the sagittal plane; the back of the skull and face are flatter than normal
Brachydactyly	A condition of having short digits
Brushfield spots	Speckled white rings about $\frac{1}{3}$ of the distance to the periphery of the iris of the eye
Camptodactyly	Permanent flexion of one or more fingers associated with missing inner phalangeal creases indicating lack of finger movement from before 8 wk of gestation
Clinodactyly	A medial or lateral curving of the fingers; usually refers to incurving of the 5th finger
Hypoplastic nail	An unusually small nail on a digit
Low-set ears	This designation is made when the helix meets the cranium at a level below a horizontal plane that is an extension of a line through both inner canthi
Melia	A suffix meaning "limb" (e.g., amelia—missing limb; brachymelia—short limb)
Ocular hypertelorism	Increased distance between the pupils of the 2 eyes, also known as increased interpupillary distance)
Plagiocephaly	A condition in which head shape is asymmetric in the sagittal or coronal plane that can result from asymmetry in suture closure or from asymmetry of brain growth
Posterior parietal hair whorl	A single whorl occurs to the right or left of midline and within 2 cm anterior to the posterior fontanel in 95% of cases. The whorl represents the focal point from which the posterior scalp skin was under growth tension during brain growth between the 10th and 16th wk of fetal development. Aberrant position of the whorl reflects an early defect in brain development
Postaxial polydactyly	Extra finger or toe present on the lateral side of the hand or foot
Preaxial polydactyly	Extra finger or toe present on the medial side of the hand or foot
Prominent lateral palatine ridges	Relative overgrowth of the lateral palatine ridges secondary to a deficit of tongue thrust into the hard palate
Scaphocephaly	A condition in which the head is elongated from front to back in the sagittal plane; most normal skulls are scaphocephalic. Also termed dolichocephaly.
Shawl scrotum	The scrotal skin joins around the superior aspect of the penis and represents a mild deficit in full migration of the labial-scrotal folds
Short palpebral fissures	Decreased horizontal distance of the eyelid folds based on measurement from the inner to the outer canthus
Syndactyly	Incomplete separation of the fingers. It most commonly occurs between the 3rd and 4th fingers and between the 2nd and 3rd toes
Synophrys	Eyebrows that meet in the midline
Telecanthus	Lateral displacement of the inner canthi. The inner canthal distance (ICD) is increased, but the interpupillary distance (IPD) is normal.
Widow's peak	V-shaped midline, downward projection of the scalp hair in the frontal region. It represents an upper forehead intersection of the bilateral fields of periocular hair growth suppression. It usually occurs because the fields are widely spaced, as in ocular hypertelorism

**Table 109-7** Serious Systemic Illness in Newborns:  
Differential Diagnosis of Neonatal Sepsis

**CARDIAC**

Congenital: hypoplastic left heart syndrome, other structural disease, persistent pulmonary hypertension of the newborn (PPHN)  
Acquired: myocarditis, hypovolemic or cardiogenic shock, PPHN

**GASTROINTESTINAL**

Necrotizing enterocolitis  
Spontaneous gastrointestinal perforation  
Structural abnormalities  
Hepatic failure (inborn errors of metabolism, neonatal iron storage disease)

**HEMATOLOGIC**

Neonatal purpura fulminans  
Immune-mediated thrombocytopenia  
Immune-mediated neutropenia  
Severe anemia  
Malignancies (congenital leukemia)  
Langerhans cell histiocytosis  
Hereditary clotting disorders  
Familial hemophagocytosis syndrome

**METABOLIC**

Hypoglycemia  
Adrenal disorders: Adrenal hemorrhage, adrenal insufficiency, congenital adrenal hyperplasia  
Inborn errors of metabolism: Organic acidurias, lactic acidoses, urea cycle disorders, galactosemia

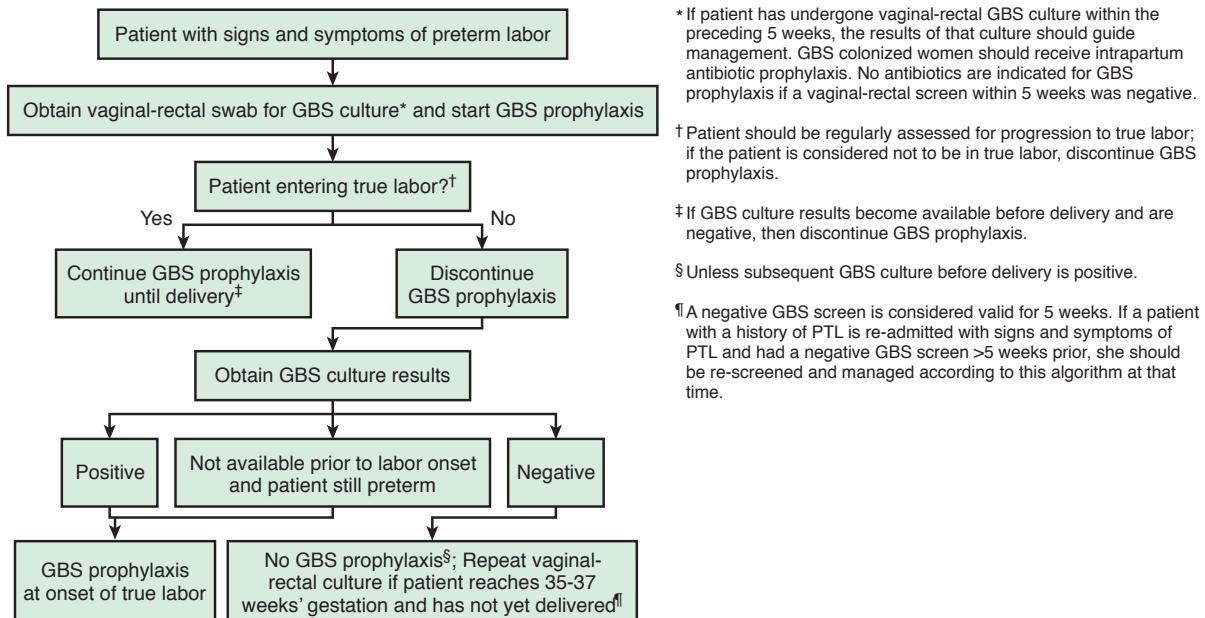
**NEUROLOGIC**

Intracranial hemorrhage: spontaneous, caused by child abuse  
Hypoxic-ischemic encephalopathy  
Neonatal seizures  
Infant botulism

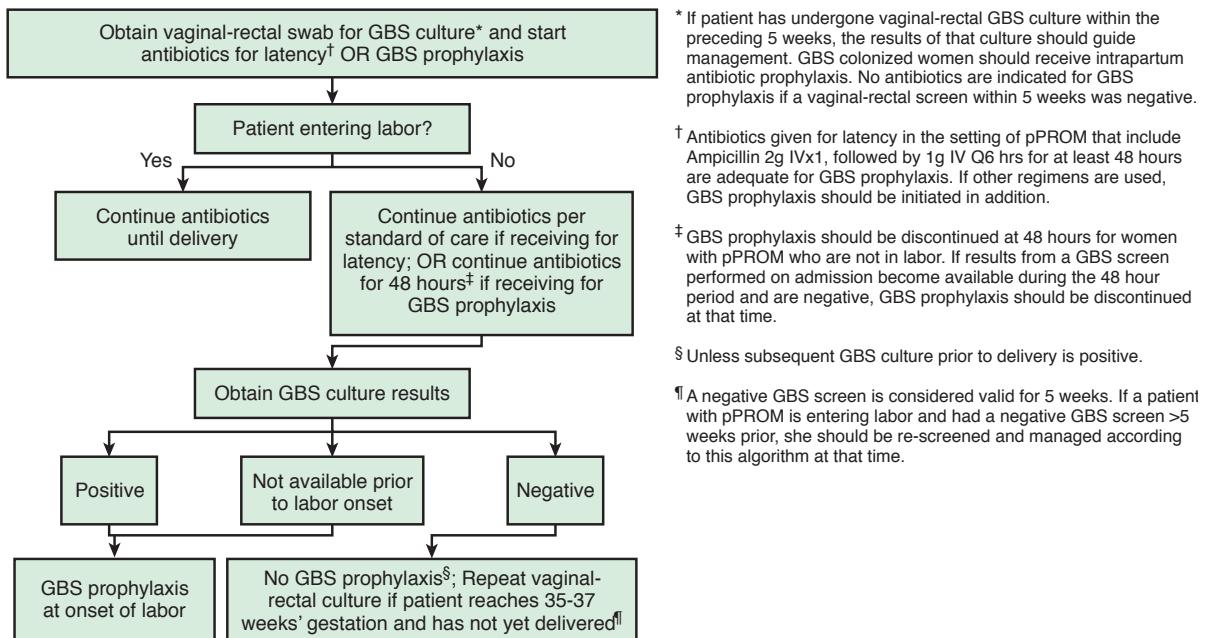
**RESPIRATORY**

Respiratory distress syndrome  
Aspiration pneumonia: amniotic fluid, meconium, or gastric contents  
Lung hypoplasia  
Tracheoesophageal fistula  
Transient tachypnea of the newborn

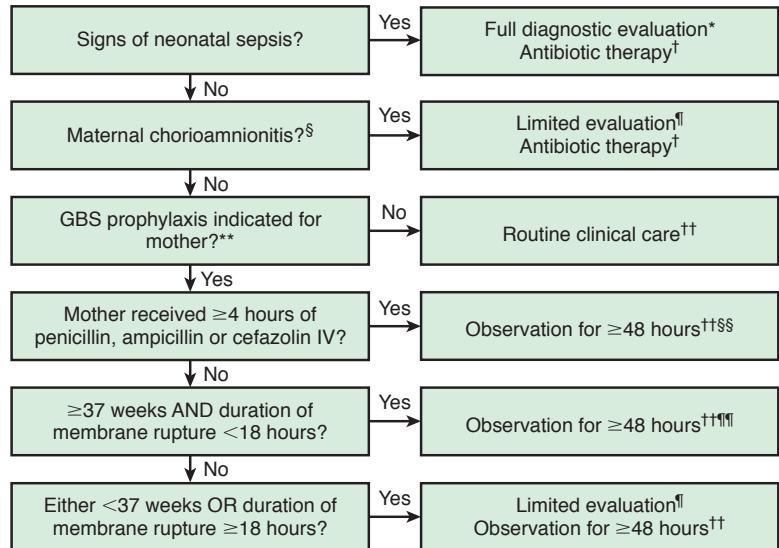
## 918 Part XII ◆ The Fetus and the Neonatal Infant

**Algorithm for GBS intrapartum prophylaxis for women with preterm labor (PTL)**

**Figure 109-6** Algorithm for GBS intrapartum prophylaxis for women with preterm labor. (From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010, MMWR Recomm Rep 59[RR-10]:1–36, 2010.)

**Algorithm for GBS intrapartum prophylaxis for women with preterm premature rupture of membranes (pPROM)**

**Figure 109-7** Algorithm for GBS intrapartum prophylaxis for women with preterm premature rupture of membranes. (From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010, MMWR Recomm Rep 59[RR-10]:1–36, 2010.)

**Algorithm for secondary prevention of early-onset GBS disease among newborns**

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

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

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

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

\*\* GBS prophylaxis indicated in one or more of the following: (1) mother GBS positive within preceding 5 weeks, (2) GBS status unknown with one or more intrapartum risk factors including <37 weeks' gestation, ROM ≥18 hours or T ≥100.4°F (38.0°C), (3) GBS bacteriuria during current pregnancy, (4) history of a previous infant with GBS disease.

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

§§ If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, there is ready access to medical care, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

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

**Figure 109-8** Algorithm for secondary prevention of early-onset GBS disease among newborns. (From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010, MMWR Recomm Rep 59(RR-10):1–36, 2010.)

**Table 109-9** Indications for Intrapartum Antibiotic Prophylaxis to Prevent Early-Onset GBS Disease

INTRAPARTUM GBS PROPHYLAXIS INDICATED	INTRAPARTUM GBS PROPHYLAXIS NOT INDICATED
Previous infant with invasive GBS disease	Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)
GBS bacteriuria during any trimester of the current pregnancy	GBS bacteriuria during previous pregnancy (unless another indication for GBS prophylaxis is present for current pregnancy)
Positive GBS screening culture during current pregnancy (unless a cesarean delivery is performed before onset of labor or amniotic membrane rupture)	Cesarean delivery before onset of labor or amniotic membrane rupture, regardless of GBS colonization status or gestational age
Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following: Delivery at <37 weeks' gestation* Amniotic membrane rupture ≥18 hr Intrapartum temperature ≥38.0°C (100.4°F) Intrapartum NAAT† positive for GBS	Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors

\*Recommendations for the use of intrapartum antibiotics for prevention of early-onset GBS disease in the setting of threatened preterm delivery are presented in Figures 109-7 and 109-8.

†If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

‡If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (delivery at <37 weeks' gestation, amniotic membrane rupture ≥18 hr, or temperature ≥38.0°C [100.4°F]) is present, then intrapartum antibiotic prophylaxis is indicated.

GBS, group B streptococcus; NAAT, nucleic acid amplification test.

From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010, MMWR Recomm Rep 59(RR-10):1–36, 2010.

**Table 109-12** Management and Prevention of Neonatal Sepsis

CONDITION	THERAPY	ADDITIONAL CONSIDERATIONS
Empiric management	Ampicillin + aminoglycoside. 10 days for bacteremia; 14 days for GBS and uncomplicated meningitis; extend to 21-28 days for complicated infections.	Consider a third-generation cephalosporin (cefotaxime preferred) or carbapenem for meningitis. Tailor therapy to pathogen. Consider discontinuation of therapy if pathogen not isolated.
Late-onset sepsis	Vancomycin + aminoglycoside. Duration dependent on pathogen and site.	Alternatives to vancomycin may be considered based on local epidemiology and clinical presentation. Aminoglycoside based regimen preferred to cephalosporin given reduced risk of resistance. Consider cephalosporin if meningitis suspected. Consider a carbapenem if third-generation cephalosporin recently received. Consider amphotericin for fungal etiologies. Tailor therapy to pathogen. Consider discontinuation of therapy if pathogen not isolated.
Nonantimicrobial treatment strategies		
Recombinant G-CSF Recombinant G-MSF	Enhance neutrophil number and function, but no reduction in infection when administered as prophylaxis or improvement in survival when administered as therapy.	Insufficient evidence to support the clinical use of G-CSF or GM-CSF either as treatment or prophylaxis to prevent systemic infections.
IVIG <sup>§</sup>	Augments antibody-dependent cytotoxicity and improves neutrophilic function, but no evidence that IVIG in suspected or proven sepsis reduces death.	Insufficient evidence from 10 RCTs or quasi-RCTs to support use in neonates with confirmed or suspected sepsis.
Prevention strategies		
IAP	Administration of penicillin or ampicillin 4 hr prior to parturition.	Successfully reduces rates of EOS caused by GBS. No effect on LOS GBS.
Fluconazole prophylaxis	Administration of weight-based dosing to neonates weighing less than 1,500 g.	Most beneficial in NICUs with high baseline rates of invasive candidiasis.
BLF supplementation with a probiotic, <i>Lactobacillus rhamnosus</i> (GG)	BLF is a human milk glycoprotein with a role in innate immune response. LGG enhances the activity of lactoferrin.	BLF supplementation with and without LGG reduced the incidence of 1st LOS in 472 VLBW neonates in large randomized, double-blind RCT. Additional confirmatory studies warranted.

BLF, bovine lactoferrin supplementation; EOS, early-onset sepsis; GBS, group B streptococcus; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IAP, intrapartum antimicrobial prophylaxis; IVIG, intravenous immunoglobulin; LGG, *Lactobacillus rhamnosus* GG; LOS, late-onset sepsis; NICUs, neonatal intensive care unit; RCTs, randomized, controlled trials; VLBW, very low birthweight.

Created with data from Carr R, Modi N, Doré C: G-CSF and GM-CSF for treating or preventing neonatal infections. Cochrane Database Syst Rev (3):CD003066, 2003; Brocklehurst P, Farrell B, King A, et al; INIS Collaborative Group: Treatment of neonatal sepsis with intravenous immune globulin. N Engl J Med 365:1201-1211, 2011; Manzoni P, Decembrino L, Stolfi I, et al; Italian Task Force for the Study and Prevention of Neonatal Fungal Infections; Italian Society of Neonatology. Lactoferrin and prevention of late-onset sepsis in the pre-term neonates. Early Hum Dev 86(Suppl 1):59-61, 2010.

Used with permission from Shane AL, Stoll BJ. Recent developments and current issues in the epidemiology, diagnosis, and management of bacterial and fungal neonatal sepsis. Am J Perinatol 30(2):131-141, 2013.

# Adolescent Development

**Table 110-1** Milestones in Early, Middle, and Late Adolescent Development

VARIABLE	EARLY ADOLESCENCE	MIDDLE ADOLESCENCE	LATE ADOLESCENCE
Approximate age range	10-13 yr	14-17 yr	18-21 yr
Sexual maturity rating*	1-2	3-5	5
Physical	<ul style="list-style-type: none"> <li>Females: Secondary sex characteristics (breast, pubic, axillary hair), start of growth spurt</li> <li>Males: testicular enlargement, start of genital growth</li> </ul>	<ul style="list-style-type: none"> <li>Females: peak growth velocity, menarche (if not already attained)</li> <li>Males: growth spurt, secondary sex characteristics, nocturnal emissions, facial and body hair, voice changes</li> <li>Change in body composition</li> <li>Acne</li> </ul>	<ul style="list-style-type: none"> <li>Physical maturation slows</li> <li>Increased lean muscle mass in males</li> </ul>
Cognitive and moral	<ul style="list-style-type: none"> <li>Concrete operations</li> <li>Egocentrism</li> <li>Unable to perceive long-term outcome of current decisions</li> <li>Follow rules to avoid punishment</li> </ul>	<ul style="list-style-type: none"> <li>Emergence of abstract thought (formal operations)</li> <li>May perceive future implications, but may not apply in decision making</li> <li>Strong emotions may drive decision making</li> <li>Sense of invulnerability</li> <li>Growing ability to see others' perspectives</li> </ul>	<ul style="list-style-type: none"> <li>Future-oriented with sense of perspective</li> <li>Idealism</li> <li>Able to think things through independently</li> <li>Improved impulse control</li> <li>Improved assessment of risk vs. reward</li> <li>Able to distinguish law from morality</li> </ul>
Self-concept/identity formation	<ul style="list-style-type: none"> <li>Preoccupied with changing body</li> <li>Self-consciousness about appearance and attractiveness</li> </ul>	<ul style="list-style-type: none"> <li>Concern with attractiveness</li> <li>Increasing introspection</li> </ul>	<ul style="list-style-type: none"> <li>More stable body image</li> <li>Attractiveness may still be of concern</li> <li>Consolidation of identity</li> </ul>
Family	<ul style="list-style-type: none"> <li>Increased need for privacy</li> <li>Exploration of dependence/independence boundaries</li> </ul>	<ul style="list-style-type: none"> <li>Conflicts over control and independence</li> <li>Struggle for greater autonomy</li> <li>Increased separation from the parents</li> </ul>	<ul style="list-style-type: none"> <li>Emotional and physical separation from family</li> <li>Increased autonomy</li> <li>Reestablishment of "adult" relationship with parents</li> </ul>
Peers	<ul style="list-style-type: none"> <li>Same-sex peer affiliations</li> </ul>	<ul style="list-style-type: none"> <li>Intense peer group involvement</li> <li>Preoccupation with peer culture</li> <li>Conformity</li> </ul>	<ul style="list-style-type: none"> <li>Peer group and values recede in importance</li> </ul>
Sexual	<ul style="list-style-type: none"> <li>Increased interest in sexual anatomy</li> <li>Anxieties and questions about pubertal changes</li> <li>Limited capacity for intimacy</li> </ul>	<ul style="list-style-type: none"> <li>Testing ability to attract partner</li> <li>Initiation of relationships and sexual activity</li> <li>Questions of sexual orientation</li> </ul>	<ul style="list-style-type: none"> <li>Consolidation of sexual identity</li> <li>Focus on intimacy and formation of stable relationships</li> <li>Planning for future and commitment</li> </ul>

**Table 110-2** Sexual Maturity Rating Stages in Females

SMR STAGE	PUBIC HAIR	BREASTS
1	Preadolescent	Preadolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast and papilla elevated as small mound; diameter of areola increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant, but less than in adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

SMR, sexual maturity rating.

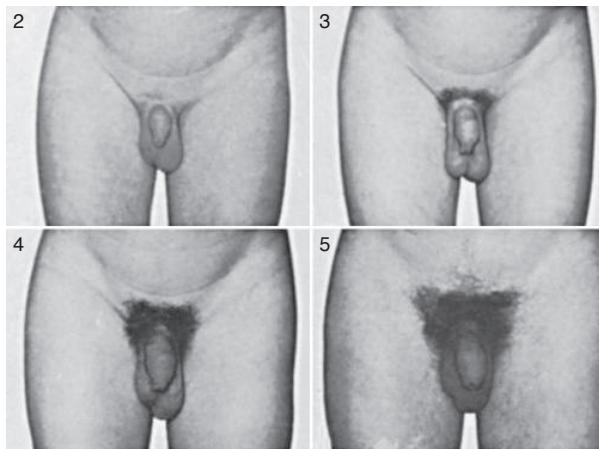
From Tanner JM: Growth at adolescence, ed 2, Oxford, England, 1962, Blackwell Scientific.

**Table 110-3** Sexual Maturity Rating Stages in Males

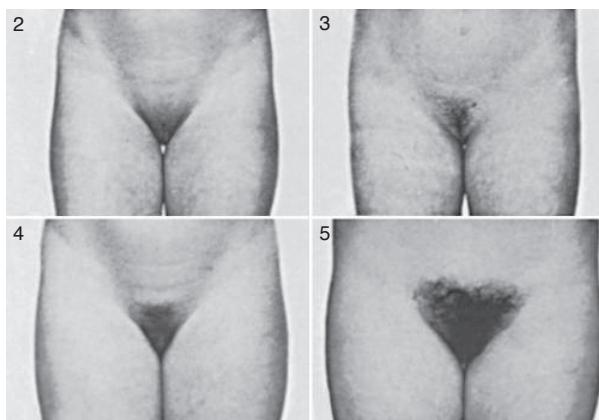
SMR STAGE	PUBIC HAIR	PENIS	TESTES
1	None	Preadolescent	Preadolescent
2	Scanty, long, slightly pigmented	Minimal change/enlargement	Enlarged scrotum, pink, texture altered
3	Darker, starting to curl, small amount	Lengthens	Larger
4	Resembles adult type, but less quantity; coarse, curly	Larger; glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

SMR, sexual maturity rating.

From Tanner JM: Growth at adolescence, ed 2, Oxford, England, 1962, Blackwell Scientific.

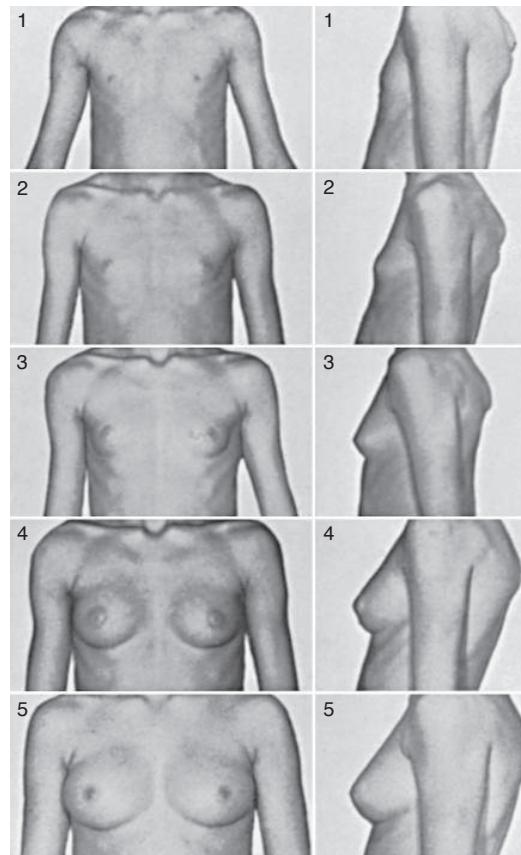


A

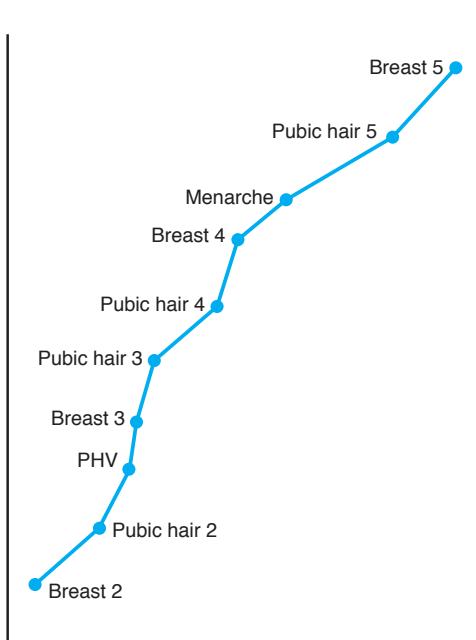


B

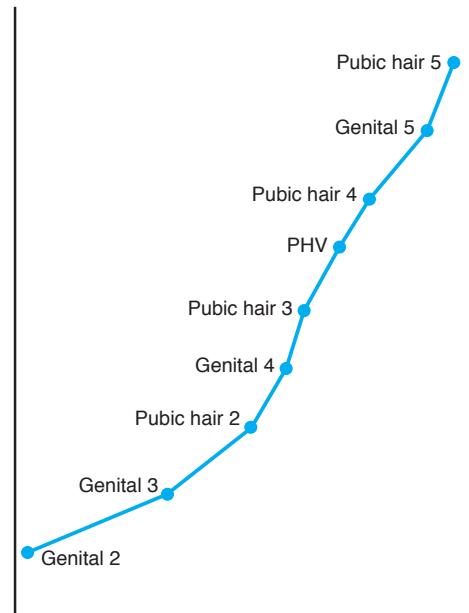
**Figure 110-1** Sexual maturity ratings (2-5) of pubic hair changes in adolescent males (A) and females (B) (see Tables 110-2 and 110-3).



**Figure 110-2** Sexual maturity ratings (1-5) of breast changes in adolescent females. (Courtesy of J.M. Tanner, MD, Institute of Child Health, Department for Growth and Development, University of London, London, England.)



**Figure 110-4** Sequence of pubertal events in females. PHV, peak height velocity.



**Figure 110-3** Sequence of pubertal events in males. PHV, peak height velocity. (From Root AW: Endocrinology of puberty, J Pediatr 83:1, 1973.)

## 934 Part XIII ◆ Adolescent Medicine

**Table 110-4** Summary of DSM 5 Diagnostic Criteria for Gender Dysphoria**GENDER DYSPHORIA IN CHILDREN (302.6) (F64.2)**

- A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 mo duration, as manifested by at least 6 of the following (1 of which must be criterion A1):
1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).
  2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
  3. A strong preferences for cross-gender roles in make-believe play or fantasy play.
  4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.
  5. A strong preference for playmates of the other gender.
  6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.
  7. A strong dislike of one's sexual anatomy.
  8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.
- B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

**SPECIFY IF WITH A DISORDER OF SEX DEVELOPMENT (E.G., CONGENITAL ADRENAL HYPERPLASIA OR ANDROGEN INSENSITIVITY SYNDROME)****GENDER DYSPHORIA IN ADOLESCENTS OR ADULTS**

- A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 mo duration, as manifested by at least 2 of the following:
1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
  2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
  3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
  4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
  5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
  6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).
- B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

**SPECIFY IF WITH A DISORDER OF SEX DEVELOPMENT (E.G., CONGENITAL ADRENAL HYPERPLASIA OR ANDROGEN INSENSITIVITY SYNDROME)**

**SPECIFY IF POSTTRANSITION:** The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen, namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

Adapted from the American Psychiatric Association, Diagnostic and statistical manual of mental disorders, ed 5, Washington, DC, 2013, American Psychiatric Publishing.

**Table 111-2** Leading Causes of Death Among 15-19 Yr Olds by Gender, United States, 2010\*

LEADING CAUSES OF DEATH	MALE	FEMALE
#1	Accidents (unintentional injuries)	Accidents (unintentional injuries)
#2	Assault (homicide)	Intentional self-harm (suicide)
#3	Intentional self-harm (suicide)	Assault (homicide)

\*Based on data from Heron M: Deaths: Leading causes for 2009. National vital statistics reports; vol 62. No. 6. Hyattsville, MD, 2013, National Center for Health Statistics.

**Table 112-3** Adolescent Screening Recommendations

		11-14 YR OLD VISIT	15-17 YR OLD VISIT	18-21 YR OLD VISIT
<b>Universal Screening</b>		Action	Action	Action
<b>Selective Screening</b>		Risk Assessment	Action If RA+	Action If RA+
Vision (once during each of 3 adolescent age groups)	+ on risk screening questions	Snellen test	Snellen test	Snellen test
Dyslipidemia		Lipid screen (once between 9-11 yr)	NA	Lipid screen (once between 18-21 yr)
Vision at other ages	+ on risk screening questions	Snellen test	Snellen test	Snellen test
Hearing	+ on risk screening questions	Audiometry	Audiometry	Audiometry
Anemia	+ on risk screening questions	Hemoglobin or hematocrit	Hemoglobin or hematocrit	Hemoglobin or hematocrit
Tuberculosis	+ on risk screening questions	Tuberculin skin test	Tuberculin skin test	Tuberculin skin test
Dyslipidemia	+ on risk screening questions and not previously screened with normal results	Lipid screen	Lipid screen	Lipid screen
STIs	Sexually active	Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)	Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)	Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)
	Sexually active and + on risk screening questions	Syphilis test	Syphilis test	Syphilis test
HIV	Discuss and offer	HIV test*	HIV test*	HIV test*
Pregnancy	Sexually active, without contraception, late menses or amenorrhea	Urine hCG	Urine hCG	Urine hCG (without late or absent menses or heavy or irregular bleeding)
Cervical dysplasia†	NA	NA	NA	Pap smear at age 21 yr
Alcohol or drug use	+ on risk screening questions	Administer alcohol and drug screening tool	Administer alcohol and drug screening tool	Administer alcohol and drug screening tool

\*CDC recommends universal, voluntary HIV screening of all sexually active people, beginning at age 13 yr. American Academy of Pediatrics recommends routine HIV screening offered to all adolescents at least once by 16-18 yr of age and to those younger if at risk. U.S. Preventive Services Task Force recommends routine HIV screening offered to all adolescents age 15 yr and older at least once and to those younger if at risk. Patients who test positive for HIV should receive prevention counseling and referral to care before leaving the testing site.

†Screening for Cervical Cancer. April 2012. U.S. Preventive Services Task Force. <http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm>.

hCG, human chorionic gonadotropin; NA, not applicable; RA, risk assessment.

Adapted from Hagan JF, Shaw JS, Duncan PM, eds. Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents, 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008; and American Academy of Pediatrics, Committee on Practice and Ambulatory Medicine, Bright Futures Periodicity Schedule Workgroup: 2014 recommendations for pediatric preventive health care, Pediatrics 133(3):568-570, 2014.

**Table 114-6** The Most Common Toxic Syndromes

ANTICHOLINERGIC SYNDROMES	
Common signs	Delirium with mumbling speech, tachycardia, dry, flushed skin, dilated pupils, myoclonus, slightly elevated temperature, urinary retention, and decreased bowel sounds. Seizures and dysrhythmias may occur in severe cases.
Common causes	Antihistamines, antiparkinsonian medication, atropine, scopolamine, amantadine, antipsychotic agents, antidepressant agents, antispasmodic agents, mydriatic agents, skeletal muscle relaxants, and many plants (notably jimson weed and Amanita muscaria).
SYMPATHOMIMETIC SYNDROMES	
Common signs	Delusions, paranoia, tachycardia (or bradycardia if the drug is a pure $\alpha$ -adrenergic agonist), hypertension, hyperpyrexia, diaphoresis, piloerection, mydriasis, and hyperreflexia. Seizures, hypotension, and dysrhythmias may occur in severe cases.
Common causes	Cocaine, amphetamine, methamphetamine (and its derivatives 3,4-methylenedioxymethamphetamine, 3,4-methylenedioxymethamphetamine, 3,4-methylenedioxymethamphetamine, and 2,5-dimethoxy-4-bromoamphetamine), and OTC decongestants (phenylpropanolamine, ephedrine, and pseudoephedrine). In caffeine and theophylline overdoses, similar findings, except for the organic psychiatric signs, result from catecholamine release.
OPIATE, SEDATIVE, OR ETHANOL INTOXICATION	
Common signs	Coma, respiratory depression, miosis, hypotension, bradycardia, hypothermia, pulmonary edema, decreased bowel sounds, hyporeflexia, and needle marks. Seizures may occur after overdoses of some narcotics, notably propoxyphene.
Common causes	Narcotics, barbiturates, benzodiazepines, ethchlorvynol, glutethimide, methyprylon, methaqualone, meprobamate, ethanol, clonidine, and guanabenz.
CHOLINERGIC SYNDROMES	
Common signs	Confusion, central nervous system depression, weakness, salivation, lacrimation, urinary and fecal incontinence, gastrointestinal cramping, emesis, diaphoresis, muscle fasciculations, pulmonary edema, miosis, bradycardia or tachycardia, and seizures.
Common causes	Organophosphate and carbamate insecticides, physostigmine, edrophonium, and some mushrooms.

From Kulig K: Initial management of ingestions of toxic substances, N Engl J Med 326:1678, 1992. ©1992 Massachusetts Medical Society. All rights reserved.

**Table 114-7** CRAFFT Mnemonic Tool

- Have you ever ridden in a Car driven by someone (including yourself) who was high or had been using alcohol or drugs?
- Do you ever use alcohol or drugs to Relax, feel better about yourself or fit in?
- Do you ever use alcohol or drugs while you are by yourself (Alone)?
- Do you ever Forget things you did while using alcohol or drugs?
- Do your Family or Friends ever tell you that you should cut down on your drinking or drug use?
- Have you ever gotten into Trouble while you were using alcohol or drugs?

From the Center for Adolescent Substance Abuse Research (CeASAR). The CRAFFT Screening Interview. © John R. Knight, MD, Boston Children's Hospital, 2015.

**Table 114-8** Urine Screening for Drugs Commonly Abused by Adolescents

DRUG	MAJOR METABOLITE	INITIAL	FIRST CONFIRMATION	SECOND CONFIRMATION	APPROXIMATE RETENTION TIME
Alcohol (blood)	Acetaldehyde	GC	IA		7-10 hr
Alcohol (urine)	Acetaldehyde	GC	IA		10-13 hr
Amphetamines		TLC	IA	GC, GC/MS	48 hr
Barbiturates		IA	TLC	GC, GC/MS	Short-acting (24 hr); long-acting (2-3 wk)
Benzodiazepines		IA	TLC	GC, GC/MS	3 days
Cannabinoids	Carboxy- and hydroxymetabolites	IA	TLC	GC/MS	3-10 days (occasional user); 1-2 mo (chronic user)
Cocaine	Benzoylecgonine	IA	TLC	GC/MS	2-4 days
Methaqualone	Hydroxylated metabolites	TLC	IA	GC/MS	2 wk
Opiates					
Heroin	Morphine Glucuronide	IA	TLC	GC, GC/MS	2 days
Morphine	Morphine Glucuronide	IA	TLC	GC, GC/MS	2 days
Codeine	Morphine Glucuronide	IA	TLC	GC, GC/MS	2 days
Phencyclidine		TLC	IA	GC, GC/MS	8 days

GC, gas chromatography; IA, immunoassay; MS, mass spectrometry; TLC, thin-layer chromatography.

Modified from Drugs of abuse—urine screening [physician information sheet]. Los Angeles, Pacific Toxicology. From MacKenzie RG, Kipke MD: Substance use and abuse. In Friedman SB, Fisher M, Schonberg SK, editors: Comprehensive adolescent health care, St. Louis, 1998, Mosby.

**Table 114-17** Signs and Symptoms of Intoxication and Withdrawal

	OPIATES	AMPHETAMINES/COCAINE	BENZODIAZEPINES
<b>INTOXICATION</b>			
Behavior	Apathy and sedation; disinhibition; psychomotor retardation; impaired attention and judgment	Euphoria and sensation of increased energy; hypervigilance; grandiosity, aggression, argumentative; labile mood; repetitive stereotyped behaviors; hallucinations, usually with intact orientation; paranoid ideation; interference with personal functioning	Euphoria; apathy and sedation; abusiveness or aggression; labile mood; impaired attention; anterograde amnesia; impaired psychomotor performance; interference with personal functioning
Signs	Drowsiness; slurred speech; pupillary constriction (except anoxia from severe overdose—dilation); decreased level of consciousness	Dilated pupils; tachycardia (occasionally bradycardia, cardiac arrhythmias); hypertension; nausea/vomiting; sweating and chills; evidence of weight loss; dilated pupils; chest pain; convulsions	Unsteady gait; difficulty in standing; slurred speech; nystagmus; decreased level consciousness; erythematous skin lesions or blisters
Overdose	Respiratory depression; hypothermia	Sympathomimetic symptoms	Hypotension; hyperthermia; depression of gag reflex; coma
Withdrawal	Craving to use; lacrimation; yawning; rhinorrhea/sneezing; muscle aches or cramps; abdominal cramps; nausea/vomiting/diarrhea; sweating; dilated pupils; anorexia; irritability; tremor; piloerection/chills; restlessness; disturbed sleep	Dysphoric mood (sadness/anhedonia); lethargy and fatigue; psychomotor retardation or agitation; craving; increased appetite; insomnia or hypersomnia; bizarre or unpleasant dreams	Tremor of tongue, eyelids, or outstretched hands; nausea or vomiting; tachycardia; postural hypotension; psychomotor agitation; headache; insomnia; malaise or weakness; transient visual, tactile, or auditory hallucinations or illusions; paranoid ideation; grand mal convulsions

**Table 122-1** Predisposition to Specific Infections in Humans

PATHOGEN	PRESENTATION	AFFECTED GENE/CHROMOSOMAL REGION	FUNCTIONAL DEFECT	NOTES
<b>BACTERIA</b>				
Streptococcus pneumoniae	Invasive disease	IRAK-4, MyD88	Impaired production of inflammatory cytokines following TLR stimulation	Also susceptible to other pyogenic bacteria such as <i>Staphylococcus aureus</i>
Neisseria	Invasive disease	MAC components (C5, C6, C7, C8A, C8B, C8G, C9)	MAC deficiency	
	Invasive disease, poor prognosis	PFC	Properdin deficiency	
Mycobacteria	MSMD	IL12B, IL12RB1, IKBKG IFNGR1, IFNGR2, STAT1	Impaired IFN- $\gamma$ response to IL-12, IL-23 Impaired cellular response to IFN- $\gamma$	Also susceptible to <i>Salmonella typhi</i> infections
<i>Mycobacterium leprae</i>	Leprosy	PARK2 LTA	Unknown Unknown	Possible E3-ubiquitin ligase dysfunction
<b>VIRUSES</b>				
Herpes simplex (type 1)	Herpes simplex encephalitis	UNC93B1, TLR3, STAT1	Impaired production of type 1 IFNs	STAT1 and NEMO deficiency also predispose to HSV infections, amongst other infections
Epstein-Barr virus	XLP	SH2D1A XIAP/BIRC4	SAP deficiency XIAP deficiency	Fulminant infectious mononucleosis, malignant and nonmalignant lymphoproliferative disorders, dysgammaglobulinemia, autoimmunity
Human papillomaviruses	Epidermodysplasia verruciformis WHIM	EVER1/TMC6 EVER2/TMC8 CXCR4	EVER1 deficiency EVER2 deficiency Truncated CXCR4	Altered neutrophil mobilization, T-cell lymphopenia, recurrent bacterial respiratory infections chronic cutaneous/genital papillomavirus disease
<b>PARASITES</b>				
<i>Plasmodium falciparum</i>	Malaria fever episodes Severe malaria	10p15 GNAS	Unknown Unknown	Linkage studies
<i>Schistosoma mansoni</i>	Severe malaria Intensity of infection	IFNR1 5q311-q33	Unknown Unknown	SNP association studies
<i>Leishmania donovani</i>	Hepatic fibrosis Visceral leishmaniasis (kala-azar)	6q22-q23, IFNR1 22q12, 2q35 (NRAMP1)	Unknown Unknown	SNP association studies
<b>YEAST</b>				
<i>Candida</i>	APECED, chronic candidiasis	Aire, STAT1, CARD9	Unknown	APS-1 chronic candidiasis, chronic hyperthyroidism, Addison disease
Deep dermatophytosis	Tissue invasion	CARD9	Unknown	Autosomal recessive

APECED, autoimmune, polyendocrinopathy, candidiasis, ectodermal dystrophy; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; MAC, membrane attack complex; MSMD, mendelian susceptibility to mycobacterial disease; NEMO, nuclear factor kappa B essential modulator; SAP, SLAM-associated protein; SNP, single-nucleotide polymorphism; TLR, Toll-like receptor; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis syndrome; XIAP, X-linked inhibitor of apoptosis; XLP, X-linked lymphoproliferative disease.

Modified from Pessach I, Walter J, Notarangelo LD: Recent advances in primary immunodeficiencies: identification of novel genetic defects and unanticipated phenotypes, Pediatr Res 65:3R-12R, 2009.

# Immunology

**Table 122-2** Characteristic Clinical Patterns in Some Primary Immunodeficiencies

FEATURES	DIAGNOSIS
<b>IN NEWBORNS AND YOUNG INFANTS (0-6 MO)</b>	
Hypocalcemia, unusual facies and ears, heart disease	DiGeorge anomaly
Delayed umbilical cord detachment, leukocytosis, recurrent infections	Leukocyte adhesion defect
Persistent thrush, failure to thrive, pneumonia, diarrhea	Severe combined immunodeficiency
Bloody stools, draining ears, atopic eczema	Wiskott-Aldrich syndrome
<i>Pneumocystis jiroveci</i> pneumonia, neutropenia, recurrent infections	X-linked hyper-IgM syndrome
<b>IN INFANTS AND YOUNG CHILDREN (6 MO-5 YR)</b>	
Severe progressive infectious mononucleosis	X-linked lymphoproliferative syndrome
Recurrent staphylococcal abscesses, staphylococcal pneumonia with pneumatocele formation, coarse facial features, pruritic dermatitis	Hyper-IgE syndrome
Persistent thrush, nail dystrophy, endocrinopathies	Chronic mucocutaneous candidiasis
Short stature, fine hair, severe varicella	Cartilage hair hypoplasia with short-limbed dwarfism
Oculocutaneous albinism, recurrent infection	Chédiak-Higashi syndrome
Abscesses, suppurative lymphadenopathy, antral outlet obstruction, pneumonia, osteomyelitis	Chronic granulomatous disease
<b>IN OLDER CHILDREN (OLDER THAN 5 YR) AND ADULTS</b>	
Progressive dermatomyositis with chronic enterovirus encephalitis	X-linked agammaglobulinemia
Sinopulmonary infections, neurologic deterioration, telangiectasia	Ataxia-telangiectasia
Recurrent neisserial meningitis	C6, C7, or C8 deficiency
Sinopulmonary infections, splenomegaly, autoimmunity, malabsorption	Common variable immunodeficiency

**Table 122-3** Common Clinical Features of Immunodeficiency

Usually present	Recurrent upper respiratory infections Severe bacterial infections Persistent infections with incomplete or no response to therapy Paucity of lymph nodes and tonsils
Often present	Persistent sinusitis or mastoiditis ( <i>Streptococcus pneumoniae</i> , <i>Haemophilus</i> , <i>Pneumocystis jiroveci</i> , <i>Staphylococcus aureus</i> , <i>Pseudomonas</i> spp.) Recurrent bronchitis or pneumonia Failure to thrive or growth retardation for infants or children; weight loss for adults Intermittent fever Infection with unusual organisms Skin lesions: rash, seborrhea, pyoderma, necrotic abscesses, alopecia, eczema, telangiectasia Recalcitrant thrush Diarrhea and malabsorption Hearing loss caused by chronic otitis Chronic conjunctivitis Arthralgia or arthritis Bronchiectasis Evidence of autoimmunity, especially autoimmune thrombocytopenia or hemolytic anemia Hematologic abnormalities: aplastic anemia, hemolytic anemia, neutropenia, thrombocytopenia History of prior surgery, biopsy
Occasionally present	Lymphadenopathy Hepatosplenomegaly Severe viral disease (e.g., EBV, CMV, adenovirus, varicella, herpes simplex) Chronic encephalitis Recurrent meningitis Deep infections: cellulitis, osteomyelitis, organ abscesses Chronic gastrointestinal disease, infections, lymphoid hyperplasia, sprue-like syndrome, atypical inflammatory bowel disease Autoimmune disease such as autoimmune thrombocytopenia, hemolytic anemia, rheumatologic disease, alopecia, thyroiditis, pernicious anemia Pyoderma gangrenosum Adverse reaction to vaccines Delayed umbilical cord detachment Chronic stomatitis or peritonitis

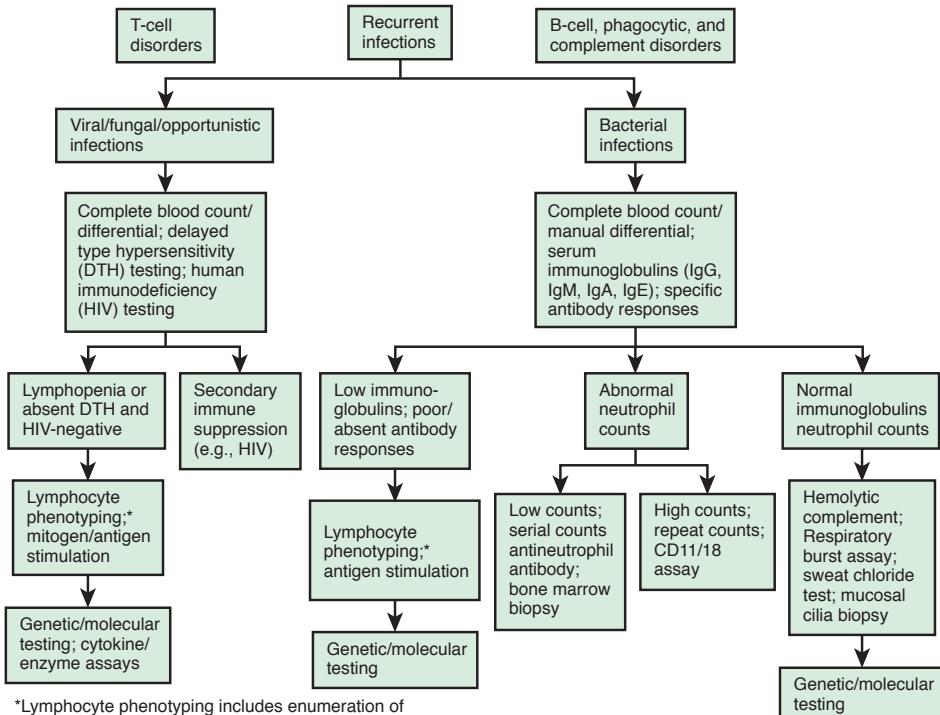
**Table 122-4** Characteristic Features of Primary Immunodeficiency

CHARACTERISTIC	PREDOMINANT T-CELL DEFECT	PREDOMINANT B-CELL DEFECT	GRANULOCYTE DEFECT	COMPLEMENT DEFECT
Age at the onset of infection	Early onset, usually 2-6 mo of age	Onset after maternal antibodies diminish, usually after 5-7 mo of age, later childhood to adulthood	Early onset	Onset at any age
Specific pathogens involved	Bacteria: common Gram-positive and Gram-negative bacteria and mycobacteria  Viruses: CMV, EBV, adenovirus, parainfluenza 3, varicella, enterovirus  Fungi: <i>Candida</i> and <i>Pneumocystis jiroveci</i>	Bacteria: pneumococci, streptococci, staphylococci, <i>Haemophilus</i> , <i>Campylobacter</i> , <i>Mycoplasma</i>  Viruses: enterovirus*	Bacteria: staphylococci, <i>Pseudomonas</i> , <i>Serratia</i> , <i>Klebsiella</i> , <i>Salmonella</i>	Bacteria: pneumococci, <i>Neisseria</i>
Affected organs	Extensive mucocutaneous candidiasis, lungs, failure to thrive, protracted diarrhea	Recurrent sinopulmonary infections, chronic gastrointestinal symptoms, malabsorption, arthritis, enteroviral meningoencephalitis*	Skin: abscesses, impetigo, cellulitis Lymph nodes: suppurative adenitis Oral cavity: gingivitis, mouth ulcers Internal organs: abscesses, osteomyelitis	Infections: meningitis, arthritis, septicemia, recurrent sinopulmonary infections
Special features	Graft-vs-host disease caused by maternal engraftment or nonirradiated blood transfusion  Postvaccination disseminated BCG or varicella  Hypocalcemic tetany in infancy <sup>†</sup>	Autoimmunity Lymphoreticular malignancy: lymphoma, thymoma Postvaccination paralytic polio	Prolonged attachment of umbilical cord, poor wound healing	Autoimmune disorders: SLE, vasculitis, dermatomyositis, scleroderma, glomerulonephritis, angioedema

\*X-linked (Bruton) agammaglobulinemia.

<sup>†</sup>DiGeorge anomaly.

BCG, Bacille Calmette-Guérin; CMV, cytomegalovirus; EBV, Epstein-Barr virus; SLE, systemic lupus erythematosus.

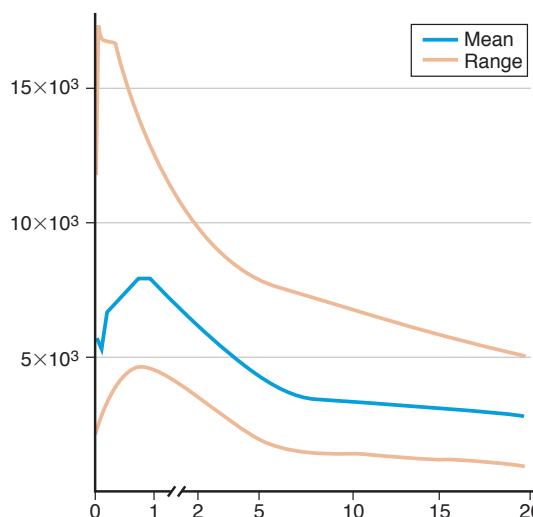
Modified from Woroniecka M, Ballow M: Office evaluation of children with recurrent infection, *Pediatr Clin North Am* 47:1211-1224, 2000.**Figure 122-1** A diagnostic testing algorithm for primary immunodeficiency diseases. DTH, delayed-type hypersensitivity. (From Lindegren ML, Kobrynski L, Rasmussen SA: Applying public health strategies to primary immunodeficiency diseases: a potential approach to genetic disorders, *MMWR Recomm Rep* 53[RR-1]:1-29, 2004.)

<b>Table 122-5</b>   Special Physical Features Associated with Immunodeficiency Disorders	
<b>CLINICAL FEATURES</b>	<b>DISORDERS</b>
<b>DERMATOLOGIC</b>	
Eczema	Wiskott-Aldrich syndrome, IPEX, hyper-IgE syndromes, hypereosinophilia syndromes, IgA deficiency
Sparse and/or hypopigmented hair	Cartilage hair hypoplasia, Chédiak-Higashi syndrome, Griscelli syndrome
Ocular telangiectasia	Ataxia-telangiectasia
Oculocutaneous albinism	Chédiak-Higashi syndrome
Severe dermatitis	Omenn syndrome
Erythroderma	Omenn syndrome, SCID, graft-vs-host disease, Comel-Netherton syndrome
Recurrent abscesses with pulmonary pneumatoceles	Hyper-IgE syndromes
Recurrent organ granulomas or abscesses, lung, liver and rectum especially	Chronic granulomatous disease
Recurrent abscesses or cellulitis	Chronic granulomatous disease, hyper-IgE syndrome, leukocyte adhesion defect
Cutaneous granulomas	Ataxia telangiectasia, SCID, CVID, RAG deficiency
Oral ulcers	Chronic granulomatous disease, severe combined immunodeficiency, congenital neutropenia
Periodontitis, gingivitis, stomatitis	Neutrophil defects
Oral or nail candidiasis	T-cell immune defects, combined defects (SCIDs); mucocutaneous candidiasis; hyper-IgE syndromes; IL-12, -17, -23 deficiencies; CARD9 deficiency; STAT1 deficiency
Vitiligo	B-cell defects, mucocutaneous candidiasis
Alopecia	B-cell defects, mucocutaneous candidiasis
Chronic conjunctivitis	B-cell defects
<b>EXTREMITIES</b>	
Clubbing of the nails	Chronic lung disease due to antibody defects
Arthritis	Antibody defects, Wiskott-Aldrich syndrome, hyper-IgM syndrome
<b>ENDOCRINOLOGIC</b>	
Hypoparathyroidism	DiGeorge syndrome, mucocutaneous candidiasis
Endocrinopathies (autoimmune)	Mucocutaneous candidiasis
Diabetes, hypothyroid	IPEX and IPEX-like syndromes
Growth hormone deficiency	X-linked agammaglobulinemia
Gonadal dysgenesis	Mucocutaneous candidiasis
<b>HEMATOLOGIC</b>	
Hemolytic anemia	B- and T-cell immune defects, ALPS
Thrombocytopenia, small platelets	Wiskott-Aldrich syndrome
Neutropenia	Hyper-IgM syndrome, Wiskott-Aldrich variant, chronic granulomatous disease
Immune thrombocytopenia	B-cell immune defects, ALPS
<b>SKELETAL</b>	
Short-limb dwarfism	Short-limb dwarfism with T- and/or B-cell immune defects
Bony dysplasia	ADA deficiency, cartilage hair hypoplasia

ADA, Adenosine deaminase deficiency; AID, activation-induced cytidine deaminase; ALPS, autoimmune lymphoproliferative syndrome; CVID, common variable immunodeficiency; GVHD, graft-vs-host disease; Ig, immunoglobulin; IPEX, X-linked immune dysfunction enteropathy polyendocrinopathy; SCID, severe combined immunodeficiency.

From Goldman L, Ausiello D: Cecil textbook of medicine, ed 22, Philadelphia, 2004, Saunders, p 1599.

<b>Table 122-6</b>   Initial Screening Immunologic Testing of the Child with Recurrent Infections	
<b>COMPLETE BLOOD COUNT, MANUAL DIFFERENTIAL, AND ERYTHROCYTE SEDIMENTATION RATE</b>	
Absolute lymphocyte count (normal result [Chapter 727] rules against T-cell defect)	
Absolute neutrophil count (normal result [Chapter 727] rules against congenital or acquired neutropenia and [usually] both forms of leukocyte adhesion deficiency, in which elevated counts are present even between infections)	
Platelet count (normal result excludes Wiskott-Aldrich syndrome)	
Howell-Jolly bodies (absence rules against asplenia)	
Erythrocyte sedimentation rate (normal result indicates chronic bacterial or fungal infection unlikely)	
<b>SCREENING TESTS FOR B-CELL DEFECTS</b>	
Immunoglobulin (Ig) A measurement; if abnormal, IgG and IgM measurement	
Isohemagglutinins	
Antibody titers to blood group substances, tetanus, diphtheria, <i>Haemophilus influenzae</i> , and pneumococcus	
<b>SCREENING TESTS FOR T-CELL DEFECTS</b>	
Absolute lymphocyte count (normal result indicates T-cell defect unlikely)	
Flow cytometry to examine for the presence of naïve T cells (CD3+CD45RA+ cells)	
<b>SCREENING TESTS FOR PHAGOCYTIC CELL DEFECTS</b>	
Absolute neutrophil count	
Respiratory burst assay	
<b>SCREENING TEST FOR COMPLEMENT DEFICIENCY</b>	
CH <sub>50</sub>	



**Figure 122-2** Absolute lymphocyte counts in normal individual during maturation. (Data graphed from Altman PL: Blood and other body fluids. Prepared under the auspices of the Committee on Biological Handbooks. Washington, DC, 1961, Federation of American Societies for Experimental Biology.)

**Table 126-5** Diagnostic Criteria for Autoimmune Lymphoproliferative Syndrome

**REQUIRED**

- Chronic nonmalignant lymphoproliferation (>6 mo lymphadenopathy and/or splenomegaly)
- Elevated peripheral blood double-negative T cells

**ACCESSORY**

**Primary**

Defective in vitro Fas-mediated apoptosis (in 2 separate assays)

Somatic or germline mutation in ALPS causative gene (FAS, FASL, CASP10)

**Secondary**

- Elevated biomarkers (Any of following)
  - Plasma soluble FASL >200 pg/mL
  - Plasma IL-10 >20 pg/mL
  - Plasma or serum vitamin B<sub>12</sub> >1500 ng/L
  - Plasma IL-18 >500 pg/mL
- Immunohistochemical findings consistent with ALPS as determined by experienced histopathologist
- Autoimmune cytopenias and polyclonal hypergammaglobulinemia
- Family history of ALPS or nonmalignant lymphoproliferation

**DIAGNOSIS**

Definitive: Required plus 1 primary accessory criterion

Probable: Required plus 1 secondary accessory criterion

Of note, probable and definitive ALPS should be treated the same in the clinic

Modified from Teachey DT: New advances in the diagnosis and treatment of autoimmune lymphoproliferative syndrome. *Curr Opin Pediatr* 24:1–8, 2013, Table 2, p. 4.

**Table 122-7** Laboratory Tests in Immunodeficiency

SCREENING TESTS	ADVANCED TESTS	RESEARCH/SPECIAL TESTS
<b>B-CELL DEFICIENCY</b> IgG, IgM, IgA, and IgE levels Isohemagglutinin titers Ab response to vaccine antigens (e.g., tetanus, diphtheria, pneumococci, <i>Haemophilus influenzae</i> )	B-cell enumeration (CD19 or CD20)  Ab responses to boosters or to new vaccines	Advanced B-cell phenotyping Biopsies (e.g., lymph nodes) Ab responses to special antigens (e.g., bacteriophage φX174), mutation analysis
<b>T-CELL DEFICIENCY</b> Lymphocyte count Chest x-ray examination for thymic size*  Delayed skin tests (e.g., <i>Candida</i> , tetanus toxoid)	T-cell subset enumeration (CD3, CD4, CD8) Proliferative responses to mitogens, antigens, allogeneic cells HLA typing Chromosome analysis	Advanced flow cytometry Enzyme assays (e.g., ADA, PNP) Thymic imaging Mutation analysis T-cell activation studies Apoptosis studies Biopsies
<b>PHAGOCYTIC DEFICIENCY</b> WBC count, morphology  Respiratory burst assay	Adhesion molecule assays (e.g., CD11b/CD18, selectin ligand) Mutation analysis	Mutation analysis  Enzyme assays (e.g., MPO, G6PD, NADPH oxidase)
<b>COMPLEMENT DEFICIENCY</b> CH <sub>50</sub> activity C3 level C4 level	AH50, activity Component assays Activation assays (e.g., C3a, C4a, C4d, C5a)	

\*In infants only.

Ab, antibody; ADA, adenosine deaminase; C, complement; CH, hemolytic complement; G6PD, glucose-6-phosphate dehydrogenase; HLA, human leukocyte antigen; Ig, immunoglobulin; MPO, myeloperoxidase; NADPH, nicotinamide adenine dinucleotide phosphate; PNP, purine nucleoside phosphorylase; WBC, white blood cell; φX, phage antigen.

Modified from Stiehm ER, Ochs HD, Winkelstein JA: Immunologic disorders in infants and children, ed 5, Philadelphia, 2004, Saunders.

**Table 122-8** | 2003 Modified IUIS Classification of Primary and Secondary Immunodeficiencies

GROUPS AND DISEASES	INHERITANCE	GROUPS AND DISEASES	INHERITANCE
<b>A. PREDOMINANTLY ANTIBODY DEFICIENCIES</b>		<b>F. COMPLEMENT DEFICIENCIES</b>	
XL agammaglobulinemia	XL	C1q deficiency	AR
AR agammaglobulinemia	AR	C1r deficiency	AR
Hyper-IgM syndromes	XL and AR	C4 deficiency	AR
a. CD40L defect	XL	C2 deficiency	AR
b. AID defect	AR	C3 deficiency	AR
c. CD40 defect	AR	C5 deficiency	AR
d. UNG defect	AR	C6 deficiency	AR
e. Other hyper-IgM defects	AR	C7 deficiency	AR
Ig heavy-chain gene deletions	AR	C8α deficiency	AR
κ Chain deficiency mutations	AR	C8β deficiency	AR
Selective IgA deficiency	AD	C9 deficiency	AR
Common variable immunodeficiency	AD	C1 inhibitor	AD
<b>B. SEVERE COMBINED IMMUNODEFICIENCIES</b>		<b>G. IMMUNODEFICIENCY ASSOCIATED WITH OR SECONDARY TO OTHER DISEASES</b>	
<i>T<sup>-</sup>B<sup>+</sup>NK<sup>-</sup> SCID</i>		<i>Chromosomal Instability or Defective Repair</i>	
a. X-linked ( $\gamma c$ deficiency)	XL	Bloom syndrome	
b. Autosomal recessive (Jak3 deficiency)	AR	Fanconi anemia	
<i>T<sup>-</sup>B<sup>+</sup>NK<sup>+</sup> SCID</i>		ICF syndrome	
a. IL-7 R $\alpha$ deficiency	AR	Nijmegen breakage syndrome	
b. CD38, CD3ε, or CD3ζ deficiencies	AR	Seckel syndrome	
c. CD45 deficiency	AR	Xeroderma pigmentosum	
<i>Omenn Syndrome</i>		<i>Chromosomal Defects</i>	
a. RAG-1/2 deficiency	AR	Down syndrome	
b. IL-7R $\alpha$ deficiency	AR	Turner syndrome	
c. $\gamma c$ deficiency	XL	Chromosome 18 rings and deletions	
<i>Combined Immunodeficiencies</i>		<i>Skeletal Abnormalities</i>	
a. Purine nucleoside phosphorylase deficiency	AR	Short-limbed skeletal dysplasia	
b CD8 deficiency (ZAP-70 defect)	AR	Cartilage-hair hypoplasia	
c. MHC class II deficiency	AR	<i>Immunodeficiency with Generalized Growth Retardation</i>	
d. MHC class I deficiency caused by TAP-1/2 mutations	AR	Schimke immuno-osseous dysplasia	
Reticular dysgenesis	AR	Immunodeficiency with absent thumbs	
<b>C. OTHER CELLULAR IMMUNODEFICIENCIES</b>		Dubowitz syndrome	
Wiskott-Aldrich syndrome	XL	Growth retardation, facial anomalies, and immunodeficiency	
Ataxia-telangiectasia	AR	Progeria (Hutchinson-Gilford syndrome)	
DiGeorge anomaly	?	<i>Immunodeficiency with Dermatologic Defects</i>	
<b>D. DEFECTS OF PHAGOCYTIC FUNCTION</b>		Partial albinism	
<i>Chronic Granulomatous Disease</i>		Dyskeratosis congenita	
a. XL	XL	Netherton syndrome	
b. AR	AR	Acrodermatitis enteropathica	
1. p22 phox deficiency		Anhidrotic ectodermal dysplasia	
2. p47 phox deficiency		Papillon-Lefèvre syndrome	
3. p67 phox deficiency		<i>Hereditary Metabolic Defects</i>	
Leukocyte adhesion defect 1	AR	Transcobalamin 2 deficiency	
Leukocyte adhesion defect 2	AR	Methylmalonic aciduria	
Neutrophil G6PD deficiency	XL	Type 1 hereditary orotic aciduria	
Myeloperoxidase deficiency	AR	Biotin-dependent carboxylase deficiency	
Secondary granule deficiency	AR	Mannosidosis	
Shwachman syndrome	AR	Glycogen storage disease, type 1b	
Severe congenital neutropenia (Kostmann)	AR	Chédiak-Higashi syndrome	
Cyclic neutropenia (elastase defect)	AR	<i>Hypercatabolism of Immunoglobulin</i>	
Leukocyte mycobacterial defects	AR	Familial hypercatabolism	
IFN-γR1 or R2 deficiency	AR	Intestinal lymphangiectasia	
IFN-γR1 deficiency	AD		
IL-12Rβ1 deficiency	AR	<b>H. OTHER IMMUNODEFICIENCIES</b>	
IL-12p40 deficiency	AR	Hyper-IgE syndromes	AD and AR
STAT1 deficiency	AD	Chronic mucocutaneous candidiasis	
<b>E. IMMUNODEFICIENCIES ASSOCIATED WITH LYMPHOPROLIFERATIVE DISORDERS</b>		Chronic mucocutaneous candidiasis with polyendocrinopathy (APECED)	AR
Fas deficiency	AD	Hereditary or congenital hypoplasia or asplenia	
Fas ligand deficiency		Ivemark syndrome	
FLICE or caspase 8 deficiency		IPEX syndromes	XL
Unknown (caspase 3 deficiency)		Ectodermal dysplasia (NEMO defect)	XL

AD, autosomal dominant; ADA, adenosine deaminase; AID, activation-induced cytidine deaminase; APECED, autoimmune, polyendocrinopathy, candidiasis, ectodermal dystrophy; AR, autosomal recessive; caspase, cysteinyl aspartate specific proteinase; FLICE, Fas-associated protein with death domain-like IL-1-converting enzyme; G6PD, glucose 6-phosphate dehydrogenase; ICF, immunodeficiency, centromeric instability, facial anomalies; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IPEX, immune dysregulation, polyendocrinopathy, enteropathy; IUIS, International Union of Immunological Societies; MHC, major histocompatibility complex; NEMO, nuclear factor B essential modulator; SCID, severe combined immunodeficiency; TAP-2, transporter associated with antigen presentation; UNG, uracil-N-glycosylase; XL, X-linked.

Modified from (no authors listed) Primary immunodeficiency diseases. Report of an International Union of Immunological Studies Scientific Committee, Clin Exp Immunol 118:1–28, 1999; Chapel H, Geha R, Rosen F: IUIS PID (Primary Immunodeficiencies) Classification committee: Primary immunodeficiency diseases: an update, Clin Exp Immunol 132:9–15, 2003; Stiehm ER, Ochs HD, Winkelstein JA: Immunologic disorders in infants and children, ed 5, Philadelphia, 2004, WB Saunders.

**Table 126-3** Hyperimmunoglobulin E Syndromes

		AUTOSOMAL DOMINANT OR SPORADIC (JOB SYNDROME)	AUTOSOMAL RECESSIVE
Gene	STAT3	DOCK8: less often TYK2	
<b>INFECTIONS</b>			
Sinopulmonary			
Recurrent bacterial	<i>S. aureus</i> , pneumococcus, <i>H. influenzae</i>	<i>S. aureus</i> , pneumococcus, <i>H. influenzae</i>	
Pneumatoceles/bronchiectasis	Common	No	
Fungal	Aspergillus species	No	
<b>Cutaneous</b>			
Abscesses	<i>S. aureus</i>	<i>S. aureus</i>	
Viral	No	HPV, HSV, VZV, MCV	
Mucocutaneous candidiasis	Common	Common	
<b>ATOPIC DISORDERS</b>			
Newborn eosinophilic pustules	Common	No	
Eczema	Common	Common	
Asthma	No	Common	
Allergies/Anaphylaxis	No	Common	
<b>MUSCULOSKELETAL</b>			
Osteopenia, pathologic fractures	Common	No	
Scoliosis	Common	No	
Retained primary teeth	Common	No	
Hyperextensible	Common	No	
<b>OTHER FEATURES</b>			
Coarse facies*	Common in adolescent	No	
Coronary artery tortuosity/aneurysm	Common	No	
UBO on brain MRI	Common	No	
Lymphomas	Yes	Higher incidence	
Cutaneous malignancy	No	Yes	
Mortality	Adulthood	Childhood	

\*Coarse facies includes broad nose, prominent forehead and chin, deep set eyes

HPV, human papillomavirus; HSV, herpes simplex virus; MCV, molluscum virus; UBO, unidentified bright objects of cerebral cortex on T<sub>2</sub> MRI; VZV, varicella-zoster virus.

**Table 126-4** Infection in the Host Compromised by B- and T-Cell Immunodeficiency Syndromes

IMMUNODEFICIENCY SYNDROME	OPPORTUNISTIC ORGANISMS ISOLATED MOST FREQUENTLY	APPROACH TO TREATMENT OF INFECTIONS	PREVENTION OF INFECTIONS
B-cell immunodeficiencies	Encapsulated bacteria ( <i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i> , <i>Haemophilus influenzae</i> , and <i>Neisseria meningitidis</i> ), <i>Pseudomonas aeruginosa</i> , <i>Campylobacter</i> sp., enteroviruses, rotaviruses, <i>Giardia lamblia</i> , <i>Cryptosporidium</i> sp., <i>Pneumocystis jiroveci</i> , <i>Ureaplasma urealyticum</i> , and <i>Mycoplasma pneumoniae</i>	1. IVIG 200-800 mg/kg 2. Vigorous attempt to obtain specimens for culture before antimicrobial therapy 3. Incision and drainage if abscess present 4. Antibiotic selection on the basis of sensitivity data	1. Maintenance IVIG for patients with quantitative and qualitative defects in IgG metabolism (400-800 mg/kg q 3-5 wk) 2. In chronic recurrent respiratory disease, vigorous attention to postural drainage 3. In selected cases (recurrent or chronic pulmonary or middle ear), prophylactic administration of ampicillin, penicillin, or trimethoprim-sulfamethoxazole
T-cell immunodeficiencies	Encapsulated bacteria ( <i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>S. aureus</i> ), facultative intracellular bacteria ( <i>Mycobacterium tuberculosis</i> , other <i>Mycobacterium</i> sp., and <i>Listeria monocytogenes</i> ); <i>Escherichia coli</i> ; <i>P. aeruginosa</i> ; <i>Enterobacter</i> sp.; <i>Klebsiella</i> sp.; <i>Serratia marcescens</i> ; <i>Salmonella</i> sp.; <i>Nocardia</i> sp.; viruses (cytomegalovirus, herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, rotaviruses, adenoviruses, enteroviruses, respiratory syncytial virus, measles virus, vaccinia virus, and parainfluenza viruses); protozoa ( <i>Toxoplasma gondii</i> and <i>Cryptosporidium</i> sp.); and fungi ( <i>Candida</i> sp., <i>Cryptococcus neoformans</i> , <i>Histoplasma capsulatum</i> , and <i>P. jiroveci</i> )	1. Vigorous attempt to obtain specimens for culture before antimicrobial therapy 2. Incision and drainage if abscess present 3. Antibiotic selection on the basis of sensitivity data 4. Early antiviral treatment for herpes simplex, cytomegalovirus, and varicella-zoster viral infections 5. Topical and nonadsorbable antimicrobial agents frequently are useful	1. Prophylactic administration of trimethoprim-sulfamethoxazole for prevention of <i>P. jiroveci</i> pneumonia 2. Oral nonadsorbable antimicrobial agents to lower concentration of gut flora 3. No live virus vaccines or bacillus Calmette-Guérin vaccine 4. Careful tuberculosis screening

IVIG, intravenous immunoglobulin.

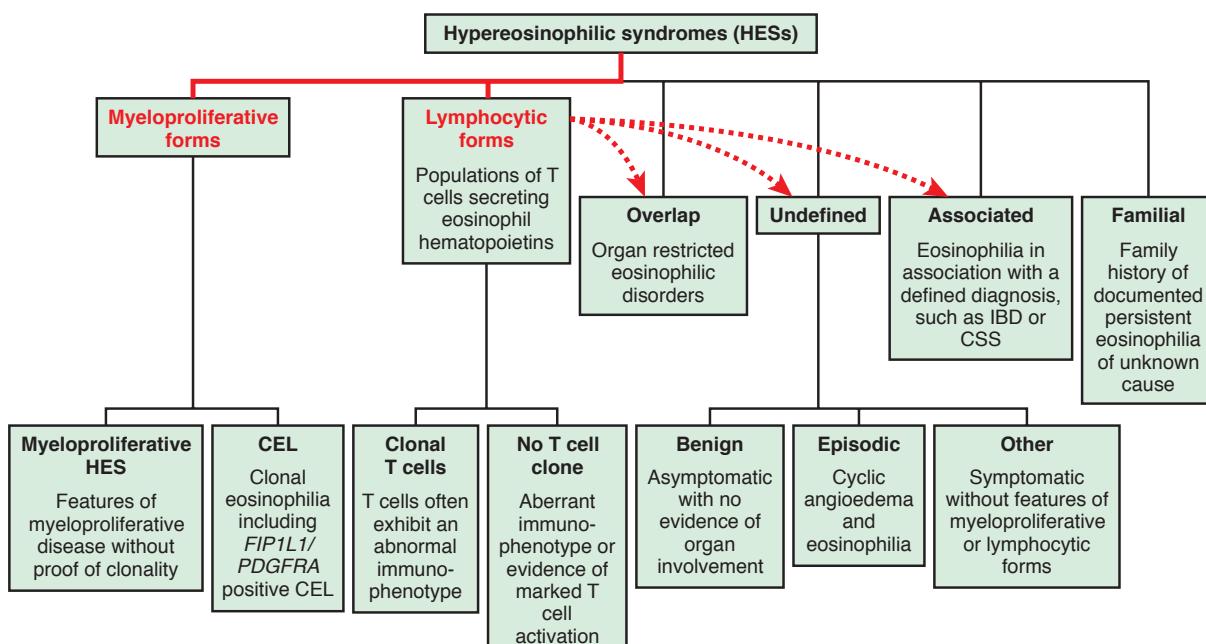
From Stiehm ER, Ochs HD, Winkelstein JA: Immunologic disorders in infants and children, ed 5, Philadelphia, 2004, WB Saunders.

**Table 126-6** Clinical and Laboratory Features of IPEX and IPEX-Like Disorders

	IPEX	CD25	STAT5B	STAT1	ITCH
<b>AUTOIMMUNITY</b>					
Eczema	+++	+++	++	++	++
Enteropathy	+++	+++	++	++	++
Endocrinopathy	+++	++	+	++	++
Allergic disease	+++	+	+	++	++
Cytophenias	++	++	++	-	
Lung disease	+	++	+++	+	+++
<b>INFECTIONS</b>					
Yeast	-	++	-	+++	-
Herpes virus	-	+++ (EBV/CMV)	++ (VZV)	++	-
Bacterial	+/-	++	++	++	+
Associated features	None	None	Growth failure	Vascular anomalies	Dysmorphic growth failure
Serum immunoglobulins	Elevated	Elevated or normal	Elevated or normal	Low, normal, or high	Elevated
Serum IgE	Elevated	Normal or elevated	Normal or elevated	Normal or mildly elevated	Elevated
CD25 expression	Normal	Absent	Normal or low	Normal	Not tested
CD4+CD45RO	Elevated	Elevated	Elevated	Normal or high	Not tested
FOXP3 expression	Absent or normal	Normal or low	Normal or low	Normal	Not tested
IGF-1, IGFBP-3	Normal	Normal	Low	Normal	Not tested
Prolactin	Normal	Normal	Elevated	Normal	Not tested

CMV, cytomegalovirus; EBV, Epstein Barr Virus; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor-binding protein 3; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; VZV, varicella zoster virus; ITCH, ubiquitin ligase deficiency.

From: Verbsky JW, Chatila TA: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) and IPEX-related disorders: an evolving web of heritable autoimmune diseases. *Curr Opin Pediatr* 25:708–715, 2013, Table 1, p. 709.



**Figure 129-1** Revised classification of hypereosinophilic syndromes. Changes from the previous classification are indicated in red. Dashed arrows identify hypereosinophilic syndrome (HES) forms for which at least some patients have T-cell-driven disease. Classification of myeloproliferative forms has been simplified, and patients with HES and eosinophil hematopoietin-producing T cells in the absence of a T-cell clone are included in the lymphocytic forms of HES. IBD, Inflammatory bowel disease. (From Simon HU, Rothenberg ME, Bocher BS, et al: Refining the definition of hypereosinophilic syndrome. *J Allergy Clin Immunol* 126:45–49, 2010, Fig. 1, p. 47.)

**Table 130-3** Leukocyte Adhesion Deficiency Syndromes

LEUKOCYTE ADHESION DEFICIENCY (LAD)	TYPE 1 (LAD1)	TYPE 2 (LAD2 OR CDG-IIC)	TYPE 3 (LAD3)	E-SELECTIN DEFICIENCY	RAC2 DEFICIENCY
OMIM	116920	266265	612840	131210	602049
Inheritance pattern	Autosomal recessive	Autosomal recessive	Autosomal recessive	Unknown	Autosomal dominant
Affected protein(s)	Integrin β <sub>2</sub> common chain (CD18)	Fucosylated proteins (e.g., sialyl-Lewis <sup>x</sup> , CD15s)	Kindlin 3	Endothelial E-selectin expression	Rac2
Neutrophil function affected	Chemotaxis, tight adherence	Rolling, tethering	Chemotaxis, adhesion, superoxide production	Rolling, tethering	Chemotaxis, superoxide production
Delayed umbilical cord separation	Yes (severe phenotype only)	Yes	Yes	Yes	Yes
Leukocytosis/neutrophilia	Yes	Yes	Yes	No (mild neutropenia)	Yes

OMIM, Online Mendelian Inheritance in Man.

From Leung DYM: Pediatric allergy principles and practice, ed 2, Philadelphia, 2010, WB Saunders, Table 12-4, p. 139.

**Table 129-1** Causes of Eosinophilia

ALLERGIC DISORDERS
Allergic rhinitis
Asthma
Acute and chronic urticaria
Pemphigoid
Hypersensitivity drug reactions (drug rash with eosinophilia and systemic symptoms [DRESS])
Eosinophilic gastrointestinal disorders
Interstitial nephritis
INFECTIOUS DISEASES
<i>Tissue-Invasive Helminth Infections</i>
Trichinosis
Toxocariasis
Strongyloidosis
Ascariasis
Filariasis
Schistosomiasis
Echinococcosis
<i>Pneumocystis carinii</i>
Toxoplasmosis
Scarlet fever
Amebiasis
Malaria
Bronchopulmonary aspergillosis
Coccidioidomycosis
Scabies
MALIGNANT DISORDERS
Brain tumors
Hodgkin disease and T-cell lymphoma
Acute myelogenous leukemia
Myeloproliferative disorders
Eosinophilic leukemia
GASTROINTESTINAL DISORDERS
Inflammatory bowel disease
Peritoneal dialysis
Chronic active hepatitis
Eosinophilic gastrointestinal disorders:
• Eosinophilic esophagitis
• Eosinophilic gastroenteritis
• Eosinophilic colitis
RHEUMATOLOGIC DISEASE
Rheumatoid arthritis
Eosinophilic fasciitis
Scleroderma
IMMUNODEFICIENCY DISEASE
Hyperimmunoglobulin E syndromes
Wiskott-Aldrich syndrome
Graft-versus-host disease
Omenn syndrome
Severe congenital neutropenia
Hypersensitivity pneumonia
MISCELLANEOUS
Thrombocytopenia with absent radii
Churg-Strauss syndrome (eosinophilic granulomatosis with vasculitis)
Vasculitis
Adrenal insufficiency
Postirradiation of abdomen
Histiocytosis with cutaneous involvement
Hypereosinophilic syndromes
Autoimmune lymphoproliferative syndromes (ALPS)
Immune dysregulation, polyendocrinopathy, X-linked (IPEX)

**Table 130-1** Infections and WBC Defects: Features That Can Be Seen in Phagocyte Disorders

SEVERE INFECTIONS		RECURRENT INFECTIONS		SPECIFIC INFECTIONS		UNUSUALLY LOCATED INFECTIONS	
TYPE OF INFECTION	DIAGNOSIS TO CONSIDER	SITE OF INFECTION	DIAGNOSIS TO CONSIDER	MICROORGANISM	DIAGNOSIS TO CONSIDER	SITE OF INFECTION	DIAGNOSIS TO CONSIDER
Cellulitis	Neutropenia, LAD CGD, HIES	Cutaneous	Neutropenia, CGD, LAD, HIES	<i>Staphylococcus epidermidis</i>	Neutropenia, LAD	Umbilical cord	LAD
Colitis	Neutropenia, CGD	Gums	LAD, neutrophil motility disorders	<i>Serratia marcescens</i> , <i>Nocardia</i> , <i>Burkholderia cepacia</i>	CGD	Liver abscess	CGD
Osteomyelitis	CGD, MSMD pathway defects	Upper and lower respiratory tract	Neutropenia, HIES, functional neutrophil disorders	<i>Aspergillus</i>	Neutropenia, CGD, HIES	Gums	LAD, neutrophil motility disorders
		Gastrointestinal tract	CGD, MSMD pathway defects (salmonella)	Nontuberculous mycobacteria, BCG	MSMD pathway defects, SCID, CGD		
		Lymph nodes	CGD, MSMD pathway defects (mycobacteria)	<i>Candida</i>	Neutropenia, CGD, MPO		
		Osteomyelitis	CGD, MSMD				

BCG, bacille Calmette-Guérin; CGD, chronic granulomatous disease; HIES, hyperimmunoglobulin E syndrome; LAD, leukocyte adhesion deficiency; MSMD, Mendelian susceptibility to mycobacterial disease; SCID, severe combined immunodeficiency.

From Leung DYM: Pediatric allergy principles and practice, ed 2, Philadelphia, 2010, WB Saunders, Table 12-1, p. 134.

**Table 130-2** Clinical Disorders of Neutrophil Function

DISORDER	ETIOLOGY	IMPAIRED FUNCTION	CLINICAL CONSEQUENCE
<b>DEGRANULATION ABNORMALITIES</b>			
Chédiak-Higashi syndrome	Autosomal recessive; disordered coalescence of lysosomal granules; responsible gene is <i>CHS1/LYST</i> , which encodes a protein hypothesized to regulate granule fusion	Decreased neutrophil chemotaxis, degranulation, and bactericidal activity; platelet storage pool defect; impaired NK function, failure to disperse melanosomes	Neutropenia; recurrent pyogenic infections, propensity to develop marked hepatosplenomegaly as a manifestation of the hemophagocytic syndrome
<b>ADHESION ABNORMALITIES</b>			
Leukocyte adhesion deficiency 1	Autosomal recessive; absence of CD11/CD18 surface adhesive glycoproteins ( $\beta_2$ integrins) on leukocyte membranes most commonly arising from failure to express CD18 messenger RNA	Decreased binding of C3bi to neutrophils and impaired adhesion to ICAM1 and ICAM2	Neutrophilia; recurrent bacterial infection associated with a lack of pus formation
Leukocyte adhesion deficiency 2	Autosomal recessive; loss of fucosylation of ligands for selectins and other glycol-conjugates arising from mutations of the GDP-fucose transporter	Decreased adhesion to activated endothelium expressing ELAM	Neutrophilia; recurrent bacterial infection without pus
Leukocyte adhesion deficiency 3 (LAD-1 variant syndrome)	Autosomal recessive; impaired integrin function arising from mutations of <i>FERMT3</i> which encodes kindlin-3 in hematopoietic cells; kindlin-3 binds to $\beta$ -integrin and thereby transmits integrin activation	Impaired neutrophil adhesion and platelet activation	Neutrophilia; recurrent infections, bleeding tendency

Continued

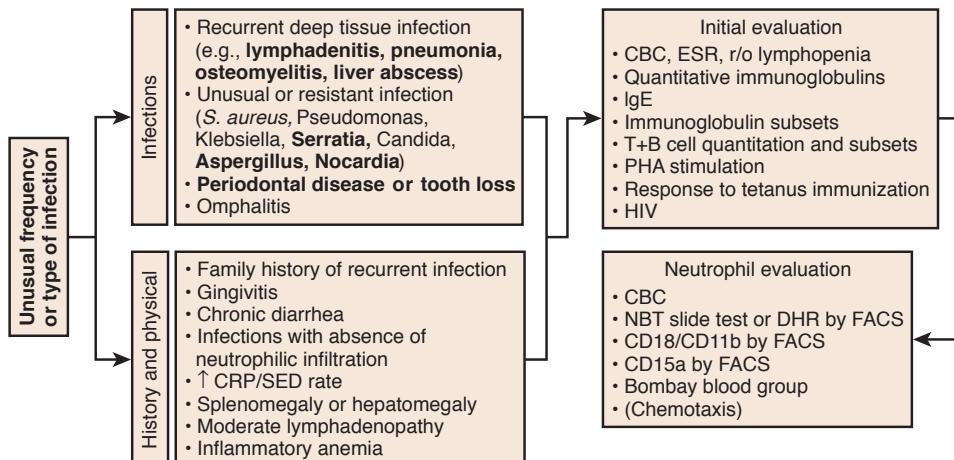
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**Table 130-2** Clinical Disorders of Neutrophil Function—cont'd

DISORDER	ETOLOGY	IMPAIRED FUNCTION	CLINICAL CONSEQUENCE
<b>DISORDERS OF CELL MOTILITY</b>			
Enhanced motile responses; FMF	Autosomal recessive gene responsible for FMF on chromosome 16 which encodes for a protein called pyrin; pyrin regulates caspase-1 and thereby IL-1 $\beta$ secretion; mutated pyrin may lead to heightened sensitivity to endotoxin, excessive IL-1 $\beta$ production, and impaired monocyte apoptosis	Excessive accumulation of neutrophils at inflamed sites, which may be the result of excessive IL-1 $\beta$ production	Recurrent fever, peritonitis, pleuritis, arthritis, and amyloidosis
<b>DEPRESSED MOTILE RESPONSES</b>			
Defects in the generation of chemotactic signals	IgG deficiencies; C3 and properdin deficiency can arise from genetic or acquired abnormalities; mannose-binding protein deficiency predominantly in neonates	Deficiency of serum chemotaxis and opsonic activities	Recurrent pyogenic infections
Intrinsic defects of the neutrophil, e.g., LAD, Chédiak-Higashi syndrome, specific granule deficiency, neutrophil actin dysfunction, neonatal neutrophils	In the neonatal neutrophil there is diminished ability to express $\beta_2$ integrins, and there is a qualitative impairment in $\beta_2$ -integrin function	Diminished chemotaxis	Propensity to develop pyogenic infections
Direct inhibition of neutrophil mobility, e.g., drugs	Ethanol, glucocorticoids, cyclic AMP	Impaired locomotion and ingestion; impaired adherence	Possible cause for frequent infections; neutrophilia seen with epinephrine arises from cyclic AMP release from endothelium
Immune complexes	Bind to Fc receptors on neutrophils in patients with rheumatoid arthritis, systemic lupus erythematosus, and other inflammatory states	Impaired chemotaxis	Recurrent pyogenic infections
Hyper-IgE syndrome	Autosomal dominant; responsible gene is Stat3	Impaired chemotaxis at times; impaired regulation of cytokine production	Recurrent skin and sinopulmonary infections, eczema, mucocutaneous candidiasis, eosinophilia, retained primary teeth, minimal trauma fractures, scoliosis, and characteristic facies
Hyper-IgE syndrome-AR	Autosomal recessive; more than 1 gene likely contributes to its etiology	High IgE levels, impaired lymphocyte activation to staphylococcal antigens	Recurrent pneumonia without pneumatoceles sepsis, enzyme, boils, mucocutaneous candidiasis, neurologic symptoms, eosinophilia
<b>MICROBICIDAL ACTIVITY</b>			
Chronic granulomatous disease	X-linked and autosomal recessive; failure to express functional gp91 $^{\text{phox}}$ in the phagocyte membrane in p22 $^{\text{phox}}$ (AR). Other AR forms of CGD arise from failure to express protein p47 $^{\text{phox}}$ or p67 $^{\text{phox}}$	Failure to activate neutrophil respiratory burst leading to failure to kill catalase-positive microbes	Recurrent pyogenic infections with catalase-positive microorganisms
G6PD deficiency	Less than 5% of normal activity of G6PD	Failure to activate NADPH-dependent oxidase, and hemolytic anemia	Infections with catalase-positive microorganisms
Myeloperoxidase deficiency	Autosomal recessive; failure to process modified precursor protein arising from missense mutation	H <sub>2</sub> O <sub>2</sub> -dependent antimicrobial activity not potentiated by myeloperoxidase	None
Rac2 deficiency	Autosomal dominant; dominant negative inhibition by mutant protein of Rac2-mediated functions	Failure of membrane receptor-mediated O <sub>2</sub> <sup>-</sup> generation and chemotaxis	Neutrophilia, recurrent bacterial infections
Deficiencies of glutathione reductase and glutathione synthetase	AR; failure to detoxify H <sub>2</sub> O <sub>2</sub>	Excessive formation of H <sub>2</sub> O <sub>2</sub>	Minimal problems with recurrent pyogenic infections

AMP, adenosine monophosphate; AR, autosomal recessive; C, complement; CD, cluster of differentiation; CGD, chronic granulomatous disease; ELAM, endothelial-leukocyte adhesion molecule; FMF, familial Mediterranean fever; G6PD, glucose-6-phosphate dehydrogenase; GDP, guanosine diphosphate; ICAM, intracellular adhesion molecule; Ig, immunoglobulin; IL-1, interleukin-1; LAD, leukocyte adhesion deficiency; NADPH, nicotinamide adenine dinucleotide phosphate; NK, natural killer.

Modified from Curnutte JT, Boxer LA: Clinically significant phagocytic cell defects. In Remington JS, Swartz MN, editors: Current clinical topics in infectious disease, ed 6, New York, 1985, McGraw-Hill, p 144.



**Figure 130-1** Algorithm for clinical evaluation of patients with recurrent infections. Shown are the evaluations that can be done in a routine clinical laboratory. The CBC can detect marked leukocytosis in LAD and giant granules of Chédiak-Higashi may be seen on the smear. Chemotaxis and all other neutrophil functions assays require highly specialized research laboratories. CBC, complete blood count; CD, cluster of differentiation; CRP, C-reactive protein; DHR, dihydrorhodamine; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; Ig, immunoglobulin; NBT, nitro blue tetrazolium. (Modified from Dinauer MC, Coates TD, Disorders of neutrophil function. In Hoffman R, Benz EJ, Silberstein LE, Heslop H, Weitz J, Anastasi J, editors: Hematology: basic principles and practice, ed 6, Philadelphia, 2012, WB Saunders, pp. 655-674.)

**Table 131-1** Diagnostic Approach for Patients with Leukopenia

EVALUATION	ASSOCIATED CLINICAL DIAGNOSES
<b>INITIAL EVALUATION</b> <ul style="list-style-type: none"> <li>History of acute or chronic leukopenia</li> <li>General medical history</li> <li>Physical examination: stomatitis, gingivitis, dental defects, congenital anomalies</li> <li>Spleen size</li> <li>History of drug exposure</li> <li>Complete blood count with differential and reticulocyte counts</li> </ul>	Congenital syndromes (Shwachman-Diamond, Wiskott-Aldrich, Fanconi anemia, dyskeratosis congenita, glycogen storage disease type Ib, disorders of vesicular transport) Hypersplenism Drug-associated neutropenia Neutropenia, aplastic anemia, autoimmune cytopenias
<b>IF ANC &lt;1,000/<math>\mu</math>L</b> <b>Evaluation of Acute Onset Neutropenia</b> <ul style="list-style-type: none"> <li>Repeat blood counts in 3-4 weeks</li> <li>Serology and cultures for infectious agents</li> <li>Discontinue drug(s) associated with neutropenia</li> <li>Test for antineutrophil antibodies</li> <li>Measure quantitative immunoglobulins (G, A, and M), lymphocyte subsets</li> </ul>	Transient myelosuppression (e.g., viral) Active or chronic infection with viruses (e.g., EBV, CMV), bacteria, mycobacteria, rickettsia Drug-associated neutropenia Autoimmune neutropenia Neutropenia associated with disorders of immune function
<b>IF ANC &lt;500/<math>\mu</math>L ON 3 SEPARATE TESTS</b> <ul style="list-style-type: none"> <li>Bone marrow aspiration and biopsy, with cytogenetics</li> <li>Glucocorticoid stimulation test</li> <li>Serial CBCs (3/wk for 6 wk)</li> <li>Exocrine pancreatic function</li> <li>Skeletal radiographs</li> </ul>	Severe congenital neutropenia, Shwachman-Diamond syndrome, myelokathexis; chronic benign or idiopathic neutropenia Chronic benign or idiopathic neutropenia, some autoimmune neutropenias Cyclic neutropenia Shwachman-Diamond syndrome Shwachman-Diamond syndrome, cartilage-hair hypoplasia, Fanconi anemia
<b>IF ALC &lt;1000/<math>\mu</math>L</b> <ul style="list-style-type: none"> <li>Repeat blood counts in 3-4 weeks</li> </ul>	Transient leukopenia (e.g., viral)
<b>IF ALC &lt;1000/<math>\mu</math>L ON 3 SEPARATE TESTS</b> <ul style="list-style-type: none"> <li>HIV-1 antibody or RNA test</li> <li>Quantitative immunoglobulins (G, A, and M), lymphocyte subsets</li> </ul>	HIV-1 infection, AIDS Congenital or acquired disorders of immune function
<b>IF THERE IS PANCYTOPENIA</b> <ul style="list-style-type: none"> <li>Bone marrow aspiration and biopsy</li> <li>Bone marrow cytogenetics</li> <li>Vitamin B<sub>12</sub> and folate levels</li> </ul>	Bone marrow replacement by malignancy, fibrosis, granulomata, storage cells; aplastic anemia Myelodysplasia, leukemia Vitamin deficiencies

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CBC, complete blood count; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

**Table 131-2** Causes of Neutropenia Extrinsic to Marrow Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Infection	Viruses, bacteria, protozoa, rickettsia, fungi	Clinical features and laboratory findings of the infectious agent
Drug-induced	Phenothiazines, sulfonamides, anticonvulsants, penicillins, aminopyrine	Usually none; occasional hypersensitivity reaction (fever, lymphadenopathy, rash, hepatitis, nephritis, pneumonitis, aplastic anemia) or antineutrophil antibody
Immune neutropenia	Alloimmune, autoimmune	Myeloid hyperplasia with left shift in bone marrow (may appear to be "arrest" at metamyelocyte or band stage)
Reticuloendothelial sequestration	Hypersplenism	Anemia, thrombocytopenia
Bone marrow replacement	Malignancy (leukemia, lymphoma, metastatic solid tumor, etc.)	Anemia, thrombocytopenia, malignant cells in bone marrow
Cancer chemotherapy or radiation therapy	Suppression of myeloid cell production	Anemia, thrombocytopenia, bone marrow hypoplasia

**Table 131-3** Acquired Disorders of Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Aplastic anemia	Stem cell destruction and depletion	Pancytopenia
Vitamin B <sub>12</sub> or folate deficiency	Malnutrition; congenital deficiency of B <sub>12</sub> absorption, transport, and storage; vitamin avoidance	Megaloblastic anemia, hypersegmented neutrophils
Acute leukemia, chronic myelogenous leukemia	Bone marrow replacement with malignant cells	Pancytopenia, leukocytosis
Myelodysplasia	Dysplastic maturation of stem cells	Bone marrow hypoplasia with megaloblastoid red cell precursors, thrombocytopenia
Prematurity with birth weight <2 kg	Impaired regulation of myeloid proliferation and reduced size of postmitotic pool	Maternal preeclampsia
Chronic idiopathic neutropenia	Impaired myeloid proliferation and/or maturation	None
Paroxysmal nocturnal hemoglobinuria	Acquired stem cell defect secondary to mutation of <i>PIG-A</i> gene	Pancytopenia, thrombosis

**Table 131-4** Infections Associated with Neutropenia

Viral	Cytomegalovirus, dengue, Epstein-Barr virus, hepatitis viruses, HIV, influenza, measles, parvovirus B19, rubella, varicella
Bacterial	<i>Anaplasma</i> (formerly <i>Ehrlichia</i> ) <i>phagocytophilum</i> , brucella, paratyphoid, pertussis, tuberculosis (disseminated), tularemia, typhoid; any form of sepsis
Fungal	Histoplasmosis (disseminated)
Protozoan	Malaria, leishmaniasis (kala-azar)
Rickettsial	Psittacosis, Rocky Mountain spotted fever, typhus, rickettsialpox

**Table 131-5** Forms of Drug-Induced Neutropenia

	IMMUNOLOGIC	TOXIC	HYPERSENSITIVITY
Paradigm drugs	Aminopyrine, propylthiouracil, penicillins	Phenothiazines, clozapine	Phenytoin, phenobarbital
Time to onset	Days to weeks	Weeks to months	Weeks to months
Clinical appearance	Acute, often explosive symptoms	Often asymptomatic or insidious onset	May be associated with fever, rash, nephritis, pneumonitis, or aplastic anemia
Rechallenge	Prompt recurrence with small test dose	Latent period; high doses required	Latent period; high doses required
Laboratory findings	Antineutrophil antibody may be positive; bone marrow myeloid hyperplasia	Bone marrow myeloid hypoplasia	Bone marrow myeloid hypoplasia

**Table 131-6** Intrinsic Disorders of Myeloid Precursor Cells

SYNDROME	INHERITANCE (GENE)	CLINICAL FEATURES (INCLUDING STATIC NEUTROPENIA UNLESS OTHERWISE NOTED)
<b>PRIMARY DISORDERS OF MYELOPOIESIS</b>		
Cyclic neutropenia	AD ( <i>ELANE</i> )	Periodic oscillation (21-day cycles) in ANC
Severe congenital neutropenia	AD (primarily <i>ELANE</i> , also <i>GFI</i> and others) AR ( <i>G6PC3</i> , <i>HAX1</i> ) ( <i>HAX1</i> = Kostmann syndrome) XL ( <i>WAS</i> )	Risk of MDS/AML <i>G6PC3</i> : cardiac and urogenital anomalies, venous angiomas; <i>HAX1</i> : neurologic abnormalities, risk of MDS/AML Neutropenic variant of Wiskott-Aldrich syndrome
<b>DISORDERS OF MOLECULAR PROCESSING</b>		
Shwachman-Diamond syndrome	Ribosomal defect: AR ( <i>SBDS</i> )	Pancreatic insufficiency, metaphysical dysostosis, bone marrow failure, MDS/AML
Dyskeratosis congenita	Telomerase defects: XL ( <i>DKC1</i> ), AD ( <i>TERC</i> ), AR ( <i>TERT</i> )	Nail dystrophy, leukoplakia, abnormal and carious teeth, lacey reticularized hyperpigmentation of the skin, bone marrow failure
<b>DISORDERS OF VESICULAR TRAFFICKING</b>		
Chédiak-Higashi syndrome	AR ( <i>LYST</i> )	Partial albinism, giant granules in myeloid cells, platelet storage pool defect, impaired natural killer cell function, HLH
Griselli syndrome, type II	AR ( <i>RAB27a</i> )	Partial albinism, impaired natural killer cell function, neurological impairment, HLH
Cohen syndrome	AR ( <i>COH1</i> )	Partial albinism, pigmentary retinopathy, developmental delay, facial dysmorphisms
Hermansky-Pudlak syndrome, type II p14 deficiency VPS45 defects	AR ( <i>AP3P1</i> ) Probable AR ( <i>MAPBPIP</i> ) AR ( <i>VPS45</i> )	Cyclic neutropenia, partial albinism, HLH Partial albinism, decreased B and T cells neutrophil dysfunction, bone marrow fibrosis, nephromegaly
<b>DISORDERS OF METABOLISM</b>		
Glycogen storage disease, type 1b	AR ( <i>G6PT1</i> )	Hepatic enlargement, growth retardation, impaired neutrophil motility
Barth syndrome	XL ( <i>TAZ1</i> )	Episodic neutropenia, dilated cardiomyopathy, methylglutaconic aciduria
Pearson syndrome	Mitochondrial (DNA deletions)	Episodic neutropenia, pancytopenia; defects in exocrine pancreas, liver, and kidneys
<b>NEUTROPENIA IN DISORDERS OF IMMUNE FUNCTION</b>		
Common variable immunodeficiency	Familial, sporadic ( <i>TNFRSF13B</i> )	Hypogammaglobulinemia, other immune system defects
IgA deficiency	Unknown (Unknown or <i>TNFRSF13B</i> )	Decreased IgA
Severe combined immunodeficiency	AR, XL (multiple loci)	Absent humoral and cellular immune function
Hyper-IgM syndrome	XL ( <i>HIGM1</i> )	Absent IgG, elevated IgM, autoimmune cytopenias
WHIM syndrome	AD ( <i>CXCR4</i> )	Warts, hypogammaglobulinemia, infections, myelokathexis
Cartilage-hair hypoplasia	AR ( <i>RMKP</i> )	Lymphopenia, short-limbed dwarfism, metaphyseal chondrodysplasia, fine sparse hair
Schimke immunoosseous dysplasia	Probable AR ( <i>SMARCAL1</i> )	Lymphopenia, pancytopenia, spondyloepiphyseal dysplasia, growth retardation, renal failure
X-linked agammaglobulinemia	BTK	Agammaglobulinemia, neutropenia in ~25%

AD, autosomal dominant; AML, acute myelogenous leukemia; ANC, absolute neutrophil count; AR, autosomal recessive; HLH, hemophagocytic lymphohistiocytosis; Ig, immunoglobulin; MDS, myelodysplasia; XL, X-linked; BTK, Bruton tyrosine kinase.

**Table 131-7** Causes of Lymphocytopenia

ACQUIRED	
Infectious diseases	AIDS, hepatitis, influenza, sepsis, tuberculosis, typhoid
Iatrogenic	Corticosteroids, cytotoxic chemotherapy, high-dose PUVA, immunosuppressive therapy, radiation, thoracic duct drainage
Systemic diseases	Hodgkin disease, lupus erythematosus, myasthenia gravis, protein-losing enteropathy, renal failure sarcoidosis
Other	Aplastic anemia, dietary deficiencies, thermal injury
INHERITED	
Aplasia of lymphopoietic stem cells	Cartilage-hair hypoplasia, ataxiatelangiectasia, SCID, thymoma, Wiskott-Aldrich syndrome

PUVA, psoralen and ultraviolet A irradiation; SCID, severe combined immunodeficiency.

**Table 132-1** Causes of Neutrophilia

TYPE	CAUSE	EXAMPLE
Acute acquired	Bacterial infections	
	Surgery	
	Acute stress	Burns, diabetic ketoacidosis, heat stroke, postneutropenia rebound, exercise
	Drugs	Corticosteroids, epinephrine, hematopoietic growth factors, lithium
Chronic acquired	Chronic inflammation	Inflammatory bowel disease, rheumatoid arthritis, vasculitis
	Persistent infection	Tuberculosis
	Persistent stress	Chronic blood loss, hypoxia, sickle cell and other chronic hemolytic anemias
	Drugs	Corticosteroids, lithium; rarely ranitidine, quinidine
Lifelong	Other	Postsplenectomy, tumors, Hodgkin disease
	Congenital asplenia Hereditary disorders	Familial cold urticaria, hereditary neutrophilia, leukocyte adhesion deficiencies, periodic fever syndromes

**Table 132-2** Causes of Monocytosis

CAUSE	EXAMPLE
Infections	
Bacterial infections	Brucellosis, subacute bacterial endocarditis, syphilis, tuberculosis, typhoid
Nonbacterial infections	Fungal infections, kala-azar, malaria, Rocky Mountain spotted fever, typhus
Hematologic disorders	Congenital and acquired neutropenias, hemolytic anemias
Malignant disorders	Acute myelogenous leukemia, chronic myelogenous leukemia, juvenile myelomonocytic leukemia, Hodgkin disease, non-Hodgkin lymphomas, preleukemia
Chronic inflammatory diseases	Inflammatory bowel disease, polyarteritis nodosa, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus
Miscellaneous	Cirrhosis, drug reaction, postsplenectomy, recovery from bone marrow suppression

**Table 132-2** Causes of Monocytosis

CAUSE	EXAMPLE
Infections	
Bacterial infections	Brucellosis, subacute bacterial endocarditis, syphilis, tuberculosis, typhoid
Nonbacterial infections	Fungal infections, kala-azar, malaria, Rocky Mountain spotted fever, typhus
Hematologic disorders	Congenital and acquired neutropenias, hemolytic anemias
Malignant disorders	Acute myelogenous leukemia, chronic myelogenous leukemia, juvenile myelomonocytic leukemia, Hodgkin disease, non-Hodgkin lymphomas, preleukemia
Chronic inflammatory diseases	Inflammatory bowel disease, polyarteritis nodosa, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus
Miscellaneous	Cirrhosis, drug reaction, postsplenectomy, recovery from bone marrow suppression

**Table 136-1** Indications to Autologous Hematopoietic Stem Cell Transplantation for Pediatric Diseases

- Acute lymphoblastic leukemia after an isolated extramedullary relapse
- Relapsed Hodgkin or non-Hodgkin lymphoma
- Stage IV or relapsed neuroblastoma
- High-risk, relapsed, or resistant brain tumors
- Stage IV Ewing sarcoma
- Life-threatening autoimmune diseases resistant to conventional treatments

**Table 132-1** Causes of Neutrophilia

TYPE	CAUSE	EXAMPLE
Acute acquired	Bacterial infections Surgery Acute stress	Burns, diabetic ketoacidosis, heat stroke, postneutropenia rebound, exercise
	Drugs	Corticosteroids, epinephrine, hematopoietic growth factors, lithium
Chronic acquired	Chronic inflammation Persistent infection Persistent stress	Inflammatory bowel disease, rheumatoid arthritis, vasculitis Tuberculosis Chronic blood loss, hypoxia, sickle cell and other chronic hemolytic anemias
	Drugs	Corticosteroids, lithium; rarely ranitidine, quinidine
	Other	Postsplenectomy, tumors, Hodgkin disease
Lifelong	Congenital asplenia Hereditary disorders	Familial cold urticaria, hereditary neutrophilia, leukocyte adhesion deficiencies, periodic fever syndromes

**Table 135-1** Indications for Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric Diseases

- Acute lymphoblastic leukemia
  - First complete remission for patients at very high risk of relapse
  - Translocation t(9;22) or t(4;11)
  - Early thymocyte precursor phenotype
  - Nonresponder after 1 wk of corticosteroid therapy and
    - T-immunophenotype or
    - >100,000 cells/µL at diagnosis
  - Not in remission at the end of the induction phase
  - Marked hypodiploidy (<43 chromosomes)
  - High levels of minimal residual disease at the end of induction therapy
- Second complete remission
  - Third or later complete remission
  - Acute myeloid leukemia in 1st complete remission or in advanced disease phase
  - Philadelphia chromosome-positive chronic myeloid leukemia
  - Myelodysplastic syndromes
  - Hodgkin and non-Hodgkin lymphomas
  - Selected solid tumors
    - Metastatic neuroblastoma
    - Rhabdomyosarcoma refractory to conventional treatment
    - Very-high-risk Ewing sarcoma
  - Severe acquired aplastic anemia
  - Fanconi anemia
  - Congenital dyskeratosis
  - Diamond-Blackfan anemia
  - Thalassemia major
  - Sickle cell disease
  - Variants of severe combined immunodeficiency
  - Hyperimmunoglobulin M syndrome
  - Leukocyte adhesion deficiency
  - Ommen syndrome
  - Wiskott-Aldrich syndrome
  - Chédiak-Higashi syndrome
  - Kostmann syndrome (infantile malignant agranulocytosis), chronic granulomatous disease and other severe neutrophil defects
  - X-linked lymphoproliferative disease (Duncan syndrome)
  - Hemophagocytic lymphohistiocytosis
  - Selected severe variants of platelet function disorders (e.g., Glanzmann thrombasthenia, or congenital amegakaryocytic thrombocytopenia)
  - Selected types of mucopolysaccharidosis (Hurler disease) or other liposomal/peroxisomal disorders (Krabbe disease, adrenoleukodystrophy)
  - Infantile malignant osteopetrosis
  - Life-threatening cytopenia unresponsive to conventional treatments

# Allergic Disorders

<b>Table 141-2</b>	Nonallergic Diseases Associated with Increased Serum IgE Concentrations
<b>PARASITIC INFESTATIONS</b>	
Ascariasis	
Capillariasis	
Echinococcosis	
Fascioliasis	
Filariasis	
Hookworm	
Onchocerciasis	
Malaria	
Paragonimiasis	
Schistosomiasis	
Strongyloidiasis	
Trichinosis	
Visceral larva migrans	
<b>INFECTIONS</b>	
Allergic bronchopulmonary aspergillosis	
Candidiasis, systemic	
Coccidioidomycosis	
Cytomegalovirus mononucleosis	
Human immunodeficiency virus type 1 infections	
Infectious mononucleosis (Epstein-Barr virus)	
Leprosy	
Pertussis	
Viral respiratory infections	
<b>IMMUNODEFICIENCY</b>	
Autosomal dominant hyperimmunoglobulin E syndrome (STAT3 mutations)	
Autosomal recessive hyperimmunoglobulin E syndrome (DOCK8, TYK2 mutations)	
IgA deficiency, selective	
Nezelof syndrome (cellular immunodeficiency with immunoglobulins)	
Thymic hypoplasia (DiGeorge anomaly)	
Wiskott-Aldrich syndrome	
<b>NEOPLASTIC DISEASES</b>	
Hodgkin disease	
IgE myeloma	
Bronchial carcinoma	
<b>OTHER DISEASES AND DISORDERS</b>	
Alopecia areata	
Bone marrow transplantation	
Burns	
Cystic fibrosis	
Dermatitis, chronic acral	
Erythema nodosum, streptococcal infection	
Guillain-Barré syndrome	
Kawasaki disease	
Liver disease	
Medications	
Nephritis, drug-induced interstitial	
Nephrotic syndrome	
Pemphigus, bullous	
Polyarteritis nodosa, infantile	
Primary pulmonary hemosiderosis	
Rheumatoid arthritis	

<b>Table 141-3</b>	Determination of Specific IgE by Skin Testing Versus In Vitro Testing	
VARIABLE	SKIN TEST*	sIgE ASSAY
Risk of allergic reaction	Yes (especially ID)	No
Relative sensitivity	High	High
Affected by antihistamines	Yes	No
Affected by corticosteroids	Usually not	No
Affected by extensive dermatitis or dermatographism	Yes	No
Broad selection of antigens	Fewer	Yes
Immediate results	Yes	No
Expensive	No	Yes
Lability of allergens	Yes	No
Results evident to patient	Yes	No

\*Skin testing may be the prick test or intradermal (ID) injection.

<b>Table 141-1</b>	Differential Diagnosis of Childhood Eosinophilia
<b>PHYSIOLOGIC</b>	
Prematurity	
Infants receiving hyperalimentation	
Hereditary	
<b>INFECTIOUS</b>	
Parasitic (with tissue-invasive helminths, e.g., trichinosis, strongyloidiasis, pneumocystosis, filariasis, cysticercosis, cutaneous and visceral larva migrans, echinococcosis)	
Bacterial (brucellosis, tularemia, cat-scratch disease, <i>Chlamydia</i> )	
Fungal (histoplasmosis, blastomycosis, coccidioidomycosis, allergic bronchopulmonary aspergillosis)	
Mycobacterial (tuberculosis, leprosy)	
Viral (HIV-1, HTLV-1, hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus)	
<b>PULMONARY</b>	
Allergic (rhinitis, asthma)	
Churg-Strauss syndrome	
Loeffler syndrome	
Hypersensitivity pneumonitis	
Eosinophilic pneumonia (chronic, acute)	
Pulmonary interstitial eosinophilia	
<b>DERMATOLOGIC</b>	
Atopic dermatitis	
Pemphigus	
Dermatitis herpetiformis	
Infantile eosinophilic pustular folliculitis	
Eosinophilic fascitis (Schulman syndrome)	
Eosinophilic cellulitis (Wells syndrome)	
Kimura disease (angiolympoid hyperplasia with eosinophilia)	
<b>HEMATOLOGIC/ONCOLOGIC</b>	
Neoplasm (lung, gastrointestinal, uterine)	
Leukemia/lymphoma	
Myelofibrosis	
Myeloproliferative (FIP1L1-PDGFRα-positive) hypereosinophilic syndrome	
Lymphatic hypereosinophilic syndrome	
Systemic mastocytosis	
<b>IMMUNOLOGIC</b>	
T-cell immunodeficiencies	
Hyperimmunoglobulin E (Job) syndrome	
Wiskott-Aldrich syndrome	
Graft-versus-host disease	
Drug hypersensitivity	
Postirradiation	
Postsplenectomy	
<b>ENDOCRINE</b>	
Addison disease	
Hypopituitarism	
<b>CARDIOVASCULAR</b>	
Loeffler disease (fibroplastic endocarditis)	
Congenital heart disease	
Hypersensitivity vasculitis	
Eosinophilic myocarditis	
<b>GASTROINTESTINAL</b>	
Benign proctocolitis	
Inflammatory bowel disease	
Eosinophilic gastrointestinal diseases (EGID)	

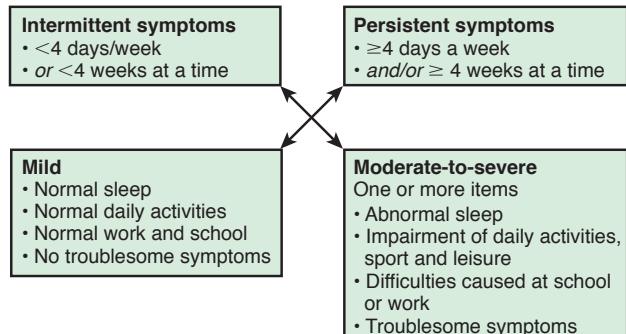
FIP1L1-PDGFRα, FIP1-like 1–platelet-derived growth factor receptorα.

**Table 143-1** Causes of Nonallergic Rhinitis

Structural/mechanical factors:
• Deviated septum/septal wall anomalies
• Hypertrophic turbinates
• Adenoidal hypertrophy
• Foreign bodies
Nasal tumors:
• Benign
• Malignant
• Choanal atresia
Infectious:
• Acute
• Chronic
Inflammatory/immunologic:
• Granulomatosis with polyangiitis
• Sarcoidosis
• Midline granuloma
• Systemic lupus erythematosus
• Sjögren syndrome
• Nasal polypsis
Physiologic:
• Ciliary dyskinesia syndrome
• Atrophic rhinitis
Hormonally induced:
• Hypothyroidism
• Pregnancy
• Oral contraceptives
• Menstrual cycle
• Exercise
• Atrophic
Drug induced:
• Rhinitis medicamentosa
• Oral contraceptives
• Antihypertensive therapy
• Aspirin
• Nonsteroidal antiinflammatory drugs
Reflex induced:
• Gustatory rhinitis
• Chemical or irritant induced
• Posture reflexes
• Nasal cycle
• Environmental factors:
• Odors
• Temperature
• Weather/barometric pressure
• Occupational
• Nonallergic rhinitis with eosinophilia syndrome
• Perennial nonallergic rhinitis (vasomotor rhinitis)
• Emotional factors

**Table 142-2** Classification of Antihistamines (H<sub>1</sub>-Antagonists)

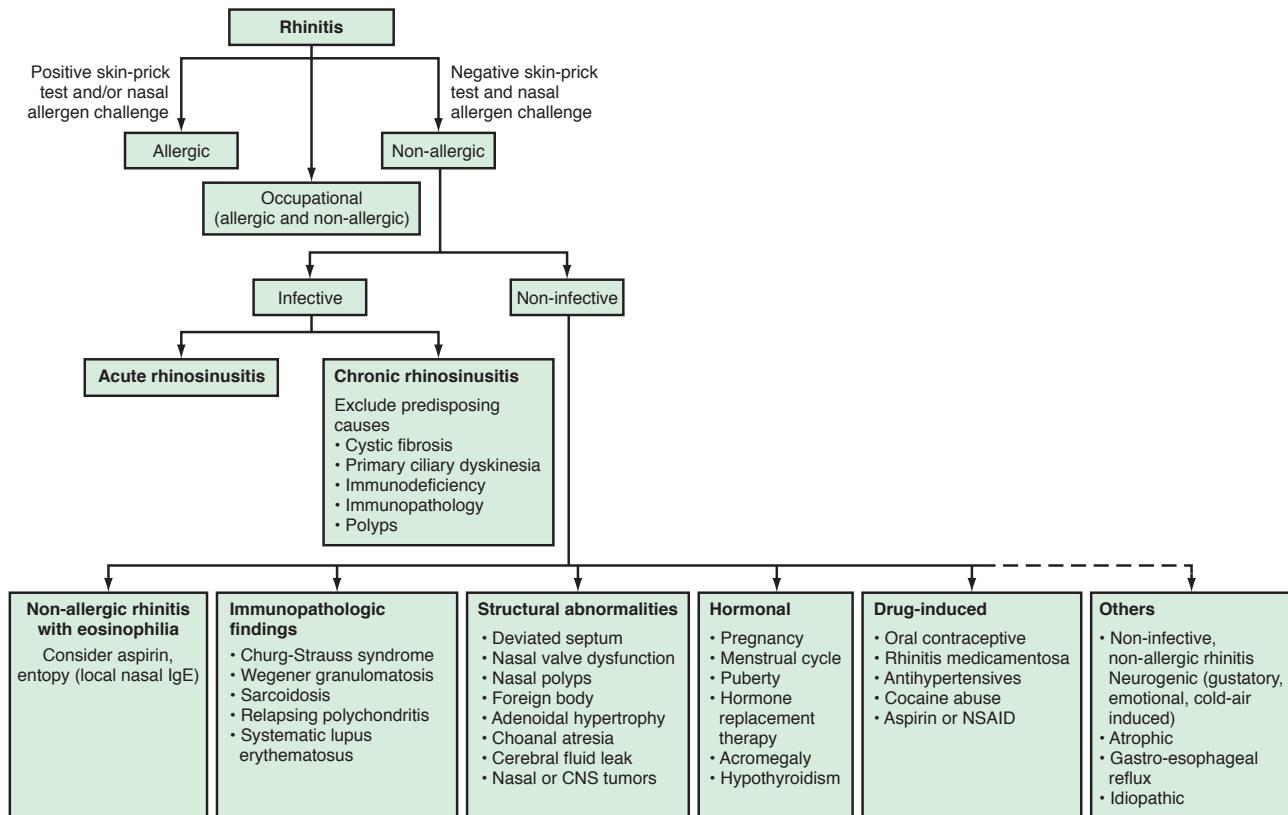
CLASS	EXAMPLES
ETHYLEDIAMINES	
First-generation	Antazoline, pyrilamine, tripelennamine
TYPE II ETHANOLAMINES	
First-generation	Carbinoxamine, clemastine, diphenhydramine
TYPE III ALKYLAMINES	
First-generation	Brompheniramine, chlorpheniramine, triprolidine
Second-generation	Acrivastine
TYPE IV PIPERAZINES	
First-generation	Cyclizine, hydroxyzine, meclizine
Second-generation	Cetirizine, levocetirizine
TYPE V PIPERIDINES	
First-generation	Azatadine, cyproheptadine, ketotifen
Second-generation	Fexofenadine, loratadine, desloratadine
TYPE VI PHENOTHIAZINES	
First-generation	Methdilazine, promethazine



**Figure 143-1** ARIA classification of allergic rhinitis. Every box can be subclassified further into seasonal or perennial on the basis of timing of symptoms or when causative and allergen therapeutic factors are considered. For example, a UK patient with grass pollen allergy might have moderate-to-severe persistent seasonal rhinitis in June and July and be suitable for specific allergen immunotherapy.

**Table 142-1** Environmental Control of Allergen Exposure

ALLERGEN	CONTROL MEASURES
Dust mites	Encase bedding in airtight, allergen-impermeable covers Wash bedding weekly in water at temperatures >54.4°C (130°F) Remove wall-to-wall carpeting Replace curtains with blinds Remove upholstered furniture Reduce indoor humidity Minimize bedroom and living room clutter
Animal dander	Avoid furred pets Keep animals out of patient's bedroom
Cockroaches	Control available food and water sources Keep kitchen/bathroom surfaces dry and free of standing water Seal cracks in walls Use professional extermination services; safe pesticide should be used in baits
Mold	Repair moisture-prone areas Avoid high humidity in patient's bedroom Use high-efficiency particulate air (HEPA) filters in living areas Repair water leaks Replace carpets with hardwood floors Regularly check basements, attics, and crawl spaces for standing water and mold
Pollen	Keep automobile and house windows closed Control timing of outdoor exposure Restrict camping, hiking, and leaf raking Drive in an air-conditioned automobile Air-condition the home Install portable HEPA filters



**Figure 143-2** Diagnostic algorithm for rhinitis. Nasal allergen challenge is a research procedure and is not undertaken routinely. Causes likely to be seen in children are highlighted in italics. NSAID, nonsteroidal antiinflammatory drug. (From Greiner AN, Hellings PW, Rotiroti G, Scadding GK: Allergic rhinitis. Lancet 378:2112-2120, 2011 [Fig. 3, p. 2116].)

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**Table 143-2** Oral Allergic Rhinitis Treatments (Prescription, Examples)

SECOND-GENERATION ANTIHISTAMINES			
GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
Desloratadine			
Claritin Reditabs*	2.5 mg, 5 mg	Orally disintegrating tablet	Children 6-11 mo of age: 1 mg once daily
Claritin Tablets	5 mg	Tabs	Children 12 mo-5 yr of age: 1.25 mg once daily
Claritin Syrup	0.5 mg/mL	Syrup	Children 6-11 yr of age: 2.5 mg once daily
			Adults and adolescents ≥12 yr of age: 5 mg once daily
Levocetirizine dihydrochloride			
Xyzal Oral Solution	0.5 mg/mL	Solution	6 mo-5 yr: max 1.25 mg once daily in the P.M. 6-11 yr: max 2.5 mg once daily in the P.M.
LEUKOTRIENE ANTAGONIST			
Montelukast			
Singulair	10 mg	Tablets	6 mo-5 yr: 4 mg daily
Singulair Chewables*	4 mg, 5 mg	Chewable tablets	6-14 yr: 5 mg daily
Singulair Oral Granules	4 mg/packet	Oral granules	>14 yr: 10 mg daily

\*Contains phenylalanine.

Dosing recommendations taken in part from Arcara K, Tschudy M for the Johns Hopkins Hospital: The Harriet Lane Handbook, ed 19. Philadelphia, 2012 Mosby.

**Table 143-3** Oral Allergic Rhinitis Treatments (Nonprescription, Examples)

FIRST-GENERATION H <sub>1</sub> ANTAGONISTS			
GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
Chlorpheniramine maleate			
Chlor-Trimeton	4 mg	Tablets	2-5 yr: 1 mg every 4-6 hr (maximum 6 mg/day)
Chlor-Trimeton Syrup	2 mg/5 mL	Syrup	6-11 yr: 2 mg every 4-6 hr (maximum 12 mg/day) >12 yr 4 mg every 4-6 hr (maximum 24 mg/day)
SECOND-GENERATION H <sub>1</sub> ANTAGONISTS			
Cetirizine			
Children's Zyrtec Allergy Syrup	1 mg/mL	Syrup	6-12 mo: 2.5 mg once daily
Children's Zyrtec Chewable	5 mg, 10 mg	Chewable tablets	12-23 mo: initial: 2.5 mg once daily; dosage may be increased to 2.5 mg twice daily
Zyrtec tablets	5 mg, 10 mg	Tablets	2-5 yr: 2.5 mg/day; may be increased to a maximum of 5 mg/day given either as a single dose or divided into 2 doses
Zyrtec Liquid Gels	10 mg	Liquid-filled gels	≥6 yr: 5-10 mg/day as a single dose or divided into 2 doses
Fexofenadine HCl			
Children's Allegra	30 mg	Tablet	6 mo-<2 yr: 15 mg (2.5 mL) every 12 hr
Children's Allegra ODT*	30 mg	Orally disintegrating tablets	>2-11 yr: 30 mg every 12 hr
Children's Allegra Oral Suspension	30 mg/5 mL	Suspension	
Allegra	Tabs 30, 60, 180 mg	Tablet	>12 yr-adult: 60 mg every 12 hr; 180 mg once daily
Loratadine			
Alavert ODT*	10 mg 10 mg 10 mg 5 mg 1 mg/mL	Orally disintegrating tablets Tablets Liquid-filled caps Chewable tablets Syrup	2-5 yr: 5 mg once daily. >6 yr: 10 mg once daily or 5 mg twice daily

\*Contains phenylalanine.

Dosing recommendations taken in part from Arcara K, Tschudy M for the Johns Hopkins Hospital: The Harriet Lane Handbook, ed 19, Philadelphia, 2012, Mosby.

**Table 143-4** Combined Antihistamine + Sympathomimetic (Examples)

GENERIC	STRENGTH	FORMULATIONS	DOSING
Chlorpheniramine maleate	4 mg	Tablets	>12 yr: 1 tablet every 4 hr not to exceed 6 tablets per day
Phenylephrine HCl	10 mg		
Sudafed Sinus & Allergy			
Cetirizine + pseudoephedrine	5 mg cetirizine + 120 mg pseudoephedrine	Extended release tablet	>12 yr: 1 tablet every 12 hr
Zyrtec-D 12 hour			

Dosing recommendations taken in part from Arcara K, Tschudy M for the Johns Hopkins Hospital: The Harriet Lane Handbook, ed 19, Philadelphia, 2012, Mosby.

**Table 143-5** | Miscellaneous Intranasal Sprays

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Ipratropium bromide: Atrovent nasal spray (0.06%)	<i>I</i> : Symptomatic relief of rhinorrhea <i>M</i> : Anticholinergic Colds (symptomatic relief of rhinorrhea): 5-12 yr: 2 sprays in each nostril 3 times/day ≥12 yr and adults: 2 sprays in each nostril 3-4 times/day	Atrovent inhalation aerosol is contraindicated in patients with hypersensitivity to soy lecithin Safety and efficacy of use beyond 4 days in patients with the common cold have not been established Adverse effects: Epistaxis, nasal dryness, nausea
Azelastine: Astelin	<i>I</i> : Treatment of rhinorrhea, sneezing, and nasal pruritis <i>M</i> : Antagonism of histamine H <sub>1</sub> -receptor 6-12 yr: 1 spray bid ≥12 yr: 1-2 sprays bid	May cause drowsiness Adverse effects: Headache, somnolence, bitter taste
Cromolyn sodium: NasalCrom	<i>I</i> : AR. <i>M</i> : Inhibition of mast cell degranulation >2 yr: 1 spray tid-qid; max x6 /day	Not effective immediately; requires frequent administration
Oxymetazoline: Afrin, Nostrilla	<i>I</i> : Symptomatic relief of nasal mucosal congestion <i>M</i> : Adrenergic agonist, vasoconstricting agent 0.05% solution: instill 2-3 sprays into each nostril twice daily; therapy should not exceed 3 days	Excessive dosage may cause profound central nervous system (CNS) depression Use in excess of 3 days may result in severe rebound nasal congestion Do not repeat more than once a month Use with caution in patients with hyperthyroidism, heart disease, hypertension, and diabetes Adverse effects: Hypertension, palpitations, reflex bradycardia, nervousness, dizziness, insomnia, headache, CNS depression, convulsions, hallucinations, nausea, vomiting, mydriasis, elevated intraocular pressure, blurred vision
Phenylephrine: Neo-Synephrine	<i>I</i> : Symptomatic relief of nasal mucosal congestion <i>M</i> : Adrenergic, vasoconstricting agent 2-6 yr: 1 drop every 2-4 hr of 0.125% solution as needed. Note: Therapy should not exceed 3 continuous days 6-12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% solution as needed. Note: Therapy should not exceed 3 continuous days >12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% to 0.5% solution as needed; 1% solution may be used in adults with extreme nasal congestion. Note: Therapy should not exceed 3 continuous days	Use in excess of 3 days may result in severe rebound nasal congestion Do not repeat more than once a month 0.16% and 0.125% solutions are not commercially available Adverse effects: Reflex bradycardia, excitability, headache, anxiety, and dizziness

**Table 143-6** | Intranasal Inhaled Corticosteroids

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Betamethasone: Beconase AQ (42 µg/spray) Qnasl (80 µg/spray)	<i>I</i> : AR <i>M</i> : Antiinflammatory, immune modulator 6-12 yr: 1 spray in each nostril bid; may increase if needed to 2 sprays in each nostril bid ≥12 yr: 1 or 2 sprays in each nostril bid	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril Adverse effects: Burning and irritation of nasal mucosa, epistaxis Monitor growth
Flunisolide	6-14 yr: 1 spray each nostril 3 times daily or 2 sprays in each nostril twice daily; not to exceed 4 sprays/day in each nostril ≥15 yr: 2 sprays each nostril twice daily (morning and evening); may increase to 2 sprays 3 times daily; maximum dose: 8 sprays/day in each nostril (400 µg/day)	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril Adverse effects: Burning and irritation of nasal mucosa, epistaxis Monitor growth

Continued

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**Table 143-6** Intranasal Inhaled Corticosteroids—cont'd

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Triamcinolone Nasacort AQ (55 µg/spray)	I: AR M: Antiinflammatory, immune modulator 2-6 yr: 1 spray in each nostril qd 6-12 yr: 1-2 sprays in each nostril qd ≥12 yr: 2 sprays in each nostril qd	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril Adverse effects: Burning and irritation of nasal mucosa, epistaxis Monitor growth
Fluticasone propionate (available as a generic preparation):  Flonase (50 µg/spray)	I: AR M: Antiinflammatory, immune modulator  ≥4 yr: 1-2 sprays in each nostril qd	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril Ritonavir significantly increases fluticasone serum concentrations and may result in systemic corticosteroid effects Use fluticasone with caution in patients receiving ketoconazole or other potent cytochrome P450 3A4 isoenzyme inhibitor Adverse effects: Burning and irritation of nasal mucosa, epistaxis Monitor growth
Fluticasone furoate: Veramyst (27.5 µg/spray)	2-12 yr: Initial dose: 1 spray (27.5 µg/spray) per nostril once daily (55 µg/day) Patients who do not show adequate response may use 2 sprays per nostril once daily (110 µg/day) Once symptoms are controlled, dosage may be reduced to 55 µg once daily Total daily dosage should not exceed 2 sprays in each nostril (110 µg/day) ≥12 yr and adolescents: Initial dose: 2 sprays (27.5 µg/spray) per nostril once daily (110 µg/day) Once symptoms are controlled, dosage may be reduced to 1 spray per nostril once daily (55 µg/day) Total daily dosage should not exceed 2 sprays in each nostril (110 µg/day)	
Mometasone:  Nasonex (50 µg/spray)	I: AR M: Antiinflammatory, immune modulator 2-12 yr: 1 spray in each nostril qd ≥12 yr: 2 sprays in each nostril qd	Mometasone and its major metabolites are undetectable in plasma after nasal administration of recommended doses Preventive treatment of seasonal AR should begin 2-4 wk prior to pollen season Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril Adverse effects: Burning and irritation of nasal mucosa, epistaxis Monitor growth
Budesonide:  Rhinocort Aqua (32 µg/spray)	I: AR M: Antiinflammatory, immune modulator 6-12 yr: 2 sprays in each nostril qd ≥12 yr: up to 4 sprays in each nostril qd (maximum dose)	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril Adverse effects: Burning and irritation of nasal mucosa, epistaxis Monitor growth
Ciclesonide:  Omnaris Zetonna (50 µg/spray)	I: AR M: Antiinflammatory, immune modulator 2-12 yr: 1-2 sprays in each nostril qd ≥12 yr: 2 sprays in each nostril qd	Prior to initial use, gently shake, then prime the pump by actuating 8 times If the product is not used for 4 consecutive days, gently shake and reprime with 1 spray or until a fine mist appears
Azelastine/fluticasone (137 µg azelastine/50 µg fluticasone) Dymista	>12 yr: 1 spray in each nostril bid	Shake bottle gently before using. Blow nose to clear nostrils. Keep head tilted downward when spraying. Insert applicator tip $\frac{1}{4}$ to $\frac{1}{2}$ inch into nostril, keeping bottle upright, and close off the other nostril. Breathe in through nose. While inhaling, press pump to release spray

## 1096 Part XV ◆ Allergic Disorders

**Table 144-2** Asthma Patterns in Childhood, Based on Natural History and Asthma Management**TRANSIENT NONATOPIC WHEEZING**

Common in early preschool years  
Recurrent cough/wheeze, primarily triggered by common respiratory viral infections  
Usually resolves during the preschool and lower school years, without increased risk for asthma in later life  
Reduced airflow at birth, suggestive of relatively narrow airways.  
AHR near birth. Improves by school age

**PERSISTENT ATOPY-ASSOCIATED ASTHMA**

Begins in early preschool years  
Associated with atopy in early preschool years:  

- Clinical (e.g., atopic dermatitis in infancy, allergic rhinitis, food allergy)
- Biologic (e.g., early inhalant allergen sensitization, increased serum immunoglobulin E, increased blood eosinophils)
- Highest risk for persistence into later childhood and adulthood

Lung function abnormalities:  

- Those with onset before 3 yr of age acquire reduced airflow by school age
- Those with later onset of symptoms, or with later onset of allergen sensitization, are less likely to experience airflow limitation in childhood

**ASTHMA WITH DECLINING LUNG FUNCTION**

Children with asthma with progressive increase in airflow limitation  
Associated with hyperinflation in childhood, male gender

**ASTHMA MANAGEMENT TYPES**

(From national and international asthma management guidelines)

**SEVERITY CLASSIFICATION\***

- Intrinsic disease severity while not on asthma medications

**Intermittent****Persistent:**

- Mild
- Moderate
- Severe

**CONTROL CLASSIFICATION\***

- Clinical assessment while asthma being managed and treated

**Well controlled****Not well controlled****Very poorly controlled****MANAGEMENT PATTERNS**

- **Easy-to-treat:** well controlled with low levels of daily controller therapy
- **Difficult-to-treat:** well controlled with multiple and/or high levels of controller therapies
- **Exacerbators:** despite being well controlled, continue to have severe exacerbations
- **Refractory:** continue to have poorly controlled asthma despite multiple and high levels of controller therapies

\*From National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR3): *Guideline for the diagnosis and management of asthma*. NIH Publication No. 07-4051. Bethesda, MD, 2007, U.S. Department of Health and Human Services; National Institutes of Health, National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program. <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>.

AHR, airways hyperresponsiveness.

**Table 144-1** Early Childhood Risk Factors for Persistent Asthma

Parental asthma  
Allergy:  

- Atopic dermatitis (eczema)
- Allergic rhinitis
- Food allergy
- Inhalant allergen sensitization
- Food allergen sensitization

Severe lower respiratory tract infection:  

- Pneumonia
- Bronchiolitis requiring hospitalization

Wheezing apart from colds  
Male gender  
Low birthweight  
Environmental tobacco smoke exposure  
Reduced lung function at birth

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**Table 144-4** Formal Evaluation of Asthma Exacerbation Severity in the Urgent or Emergency Care Setting\*

	MILD	MODERATE	SEVERE	SUBSET: RESPIRATORY ARREST IMMINENT
<b>SYMPTOMS</b>				
Breathlessness	While walking	While at rest (infant—softer, shorter cry, difficulty feeding)	While at rest (infant—stops feeding)	
Talks in Alertness	Can lie down Sentences May be agitated	Prefers sitting Phrases Usually agitated	Sits upright Words Usually agitated	Drowsy or confused
<b>SIGNS</b>				
Respiratory rate <sup>†</sup>	Increased	Increased	Often >30 breaths/min	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate; often only end-expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse rate (beats/min) <sup>‡</sup>	<100	100-120	>120	Bradycardia
Pulsus paradoxus	Absent <10 mm Hg	May be present 10-25 mm Hg	Often present >25 mm Hg (adult) 20-40 mm Hg (child)	Absence suggests respiratory muscle fatigue
<b>FUNCTIONAL ASSESSMENT</b>				
Peak expiratory flow (value predicted or personal best)	≥70%	Approx. 40-69% or response lasts <2 hr	<40%	<25%§
Pao <sub>2</sub> (breathing air) and/or PCO <sub>2</sub>	Normal (test not usually necessary)	≥60 mm Hg (test not usually necessary)	<60 mm Hg; possible cyanosis	
SaO <sub>2</sub> (breathing air) at sea level	<42 mm Hg (test not usually necessary)	<42 mm Hg (test not usually necessary)	≥42 mm Hg; possible respiratory failure	
	>95% (test not usually necessary)	90-95% (test not usually necessary)	<90%	
		Hypercapnia (hypoxilation) develops more readily in young children than in adults and adolescents		

\*Notes:

- The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.
- Many of these parameters have not been systematically studied, especially as they correlate with each other. Thus, they serve only as general guides.
- The emotional impact of asthma symptoms on the patient and family is variable but must be recognized and addressed and can affect approaches to treatment and follow-up.

<sup>†</sup>Normal breathing rates in awake children by age: <2 mo, <60 breaths/min; 2-12 mo, <50 breaths/min; 1-5 yr, <40 breaths/min; 6-8 yr, <30 breaths/min.<sup>‡</sup>Normal pulse rates in children by age: 2-12 mo, <160 beats/min; 1-2 yr, <120 beats/min; 2-8 yr, <110 beats/min.

§Peak expiratory flow testing may not be needed in very severe attacks.

Modified from EPR-3. Expert panel report 3: guidelines for the diagnosis and management of asthma, NIH Publication No. 07-4051, Bethesda, MD, 2007, U.S. Department of Health and Human Services; National Institutes of Health, National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program. <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>.

**Table 144-5** Differential Diagnosis of Childhood Asthma

UPPER RESPIRATORY TRACT CONDITIONS	
Allergic rhinitis*	
Chronic rhinitis*	
Sinusitis*	
Adenoidal or tonsillar hypertrophy	
Nasal foreign body	
MIDDLE RESPIRATORY TRACT CONDITIONS	
Laryngotracheobronchomalacia*	
Laryngotracheobronchitis (e.g., pertussis)*	
Laryngeal web, cyst, or stenosis	
Exercise-induced laryngeal obstruction	
Vocal cord dysfunction*	
Vocal cord paralysis	
Tracheoesophageal fistula	
Vascular ring, sling, or external mass compressing on the airway (e.g., tumor)	
Foreign body aspiration*	
Chronic bronchitis from environmental tobacco smoke exposure*	
Toxic inhalations	
LOWER RESPIRATORY TRACT CONDITIONS	
Bronchopulmonary dysplasia (chronic lung disease of preterm infants)	
Viral bronchiolitis*	
Gastroesophageal reflux*	
Causes of bronchiectasis:	
Cystic fibrosis	
Immune deficiency	
Allergic bronchopulmonary mycoses (e.g., aspergillosis)	
Chronic aspiration	
Immotile cilia syndrome, primary ciliary dyskinesia	
Bronchiolitis obliterans	
Interstitial lung diseases	
Hypersensitivity pneumonitis	
Pulmonary eosinophilia, Churg-Strauss vasculitis	
Pulmonary hemosiderosis	
Tuberculosis	
Pneumonia	
Pulmonary edema (e.g., congestive heart failure)	
Medications associated with chronic cough:	
Acetylcholinesterase inhibitors	
β-Adrenergic antagonists	
Angiotensin-converting enzyme inhibitors	

\*More common asthma masqueraders.

**Table 144-6** Similarities and Differences Between Vocal Cord Dysfunction and Asthma

VOCAL CORD DYSFUNCTION	ASTHMA
Extrathoracic	Intrathoracic
Rare (?never) hypoxemia	+ Hypoxemia
No hypercapnia/acidosis	+ Hypercapnia/acidosis
Normal expiratory spirometry	Reduced expiratory flow
Abnormal inspiratory loop (in some)	Normal inspiratory loop
Start/stop abruptly; few symptoms between episodes	Persistent symptoms
Frequent emergency department/office visits	Frequent emergency department/office visits
Multiple medications	Multiple medications

From Noyes BE, Kemp JS: Vocal cord dysfunction in children. *Paediat Respir Rev* 8:155–163, 2007 (Table 2, p. 159).

**Table 144-7** Lung Function Abnormalities in Asthma

Spirometry (in clinic):
• Airflow limitation:
• Low FEV <sub>1</sub> (relative to percentage of predicted norms)
• FEV <sub>1</sub> /FVC ratio <0.80
Bronchodilator response (to inhaled β-agonist):
• Improvement in FEV <sub>1</sub> ≥12% and ≥200 mL*
Exercise challenge:
• Worsening in FEV <sub>1</sub> ≥15%*
Daily peak flow or FEV <sub>1</sub> monitoring: day to day and/or A.M.-to-P.M. variation ≥20%*

\*Main criteria consistent with asthma.  
FEV<sub>1</sub>, forced expiratory volume in 1 sec; FVC, forced vital capacity.

**Table 144-3** Asthma Triggers

Common viral infections of the respiratory tract  
Aeroallergens in sensitized asthmatic patients

#### INDOOR ALLERGENS

- Animal dander
- Dust mites
- Cockroaches
- Molds

#### SEASONAL AEROALLERGENS

- Pollens (trees, grasses, weeds)
- Seasonal molds

#### AIR POLLUTANTS

- Environmental tobacco smoke
- Ozone
- Nitrogen dioxide
- Sulfur dioxide
- Particulate matter
- Wood- or coal-burning smoke
- Mycotoxins
- Endotoxin
- Dust

#### STRONG OR NOXIOUS ODORS OR FUMES

- Perfumes, hairsprays
- Cleaning agents

#### OCCUPATIONAL EXPOSURES

- Farm and barn exposures
- Formaldehydes, cedar, paint fumes
- Cold dry air
- Exercise
- Crying, laughter, hyperventilation

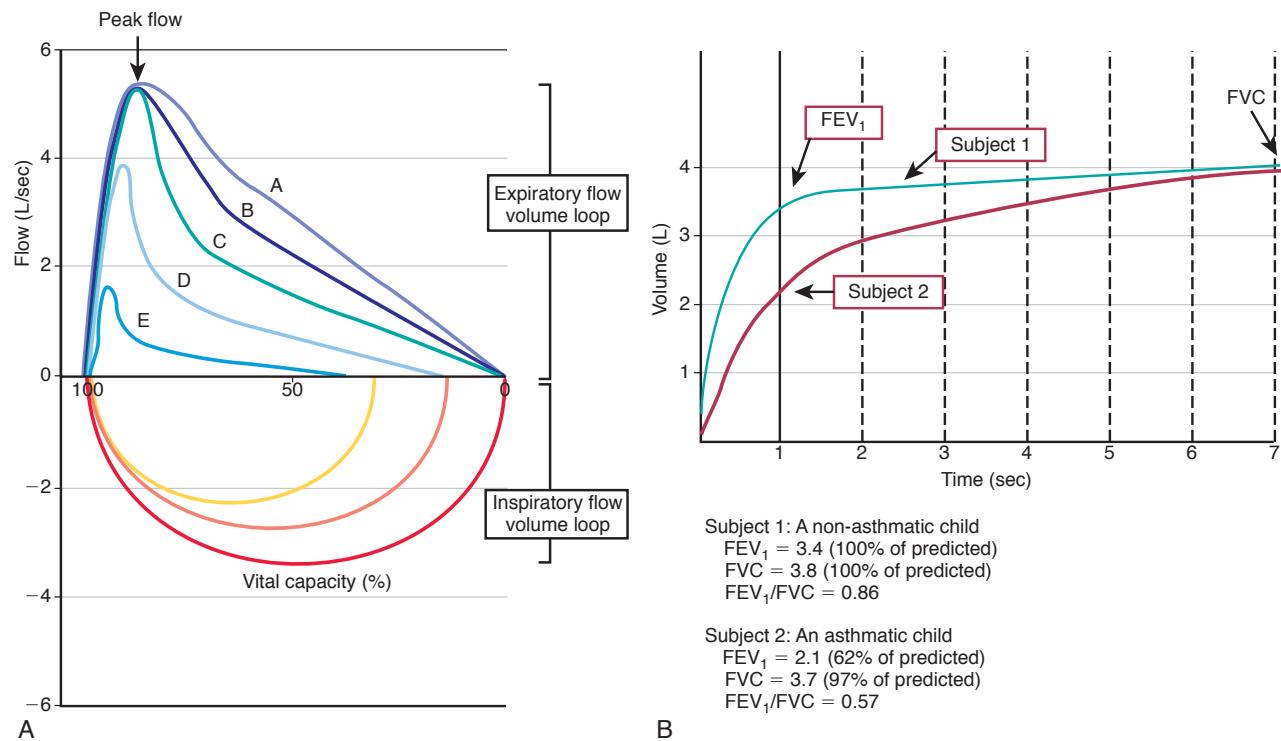
#### COMORBID CONDITIONS

- Rhinitis
- Sinusitis
- Gastroesophageal reflux

#### DRUGS

- Aspirin and other nonsteroidal antiinflammatory drugs
- β-Blocking agents
- Sulfitting agents
- Tartrazine

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**Figure 144-2 Spirometry.** A, Spirometric flow-volume loops. A is an expiratory flow-volume loop of a nonasthmatic person without airflow limitation. B through E are expiratory flow-volume loops in asthmatic patients with increasing degrees of airflow limitation (B is mild; E is severe). Note the "scooped" or concave appearance of the asthmatic expiratory flow-volume loops; with increasing obstruction, there is greater "scooping." B, Spirometric volume-time curves. Subject 1 is a nonasthmatic person; subject 2 is an asthmatic patient. Note how the FEV<sub>1</sub> and FVC lung volumes are obtained. The FEV<sub>1</sub> is the volume of air exhaled in the 1st sec of a forced expiratory effort. The FVC is the total volume of air exhaled during a forced expiratory effort, or forced vital capacity. Note that subject 2's FEV<sub>1</sub> and FEV<sub>1</sub>:FVC ratio are smaller than subject 1's, demonstrating airflow limitation. Also, subject 2's FVC is very close to what is expected.

**Table 144-10** Key Elements of Productive Clinic Visits for Asthma

- Specify goals of asthma management
- Explain basic facts about asthma:

  - Contrast normal vs asthmatic airways
  - Link airways inflammation, "twitchiness," and bronchoconstriction
  - Long-term-control and quick-relief medications
  - Address concerns about potential adverse effects of asthma pharmacotherapy

- Teach, demonstrate, and have patient show proper technique for:

  - Inhaled medication use (spacer use with metered-dose inhaler)
  - Peak flow measures

- Investigate and manage factors that contribute to asthma severity:

  - Environmental exposures
  - Comorbid conditions

- Create written 2-part asthma management plan:

  - Daily management
  - Action plan for asthma exacerbations

- Regular follow-up visits:

  - Twice yearly (more often if asthma not well-controlled)
  - Monitor lung function annually

**Table 144-11** Control of Factors Contributing to Asthma Severity

- ELIMINATE OR REDUCE PROBLEMATIC ENVIRONMENTAL EXPOSURES:**
  - Environmental tobacco smoke elimination or reduction in home and automobiles
  - Allergen exposure elimination or reduction in sensitized asthmatic patients:
    - Animal danders: pets (cats, dogs, rodents, birds)
    - Pests (mice, rats)
    - Dust mites
    - Cockroaches
    - Molds
  - Other airway irritants:
    - Wood- or coal-burning smoke
    - Strong chemical odors and perfumes (e.g., household cleaners)
    - Dusts
- TREAT COMORBID CONDITIONS:**
  - Rhinitis
  - Sinusitis
  - Gastroesophageal reflux

**Table 144-8**

Assessing Asthma Severity and Initiating Treatment for Patients Who Are Not Currently Taking Long-Term Control Medications\*

	CLASSIFICATION OF ASTHMA SEVERITY			
	PERSISTENT			
	Intermittent	Mild	Moderate	Severe
<b>COMPONENTS OF SEVERITY</b>				
<b>Impairment</b>				
Daytime symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
Nighttime awakenings:				
Age 0-4 yr	0	1-2x/mo	3-4x/mo	>1x/wk
Age ≥5 yr	≤2x/mo	3-4x/mo	>1x/wk but not nightly	Often 7x/wk
Short-acting β <sub>2</sub> -agonist use for symptoms (not for prevention of exercise-induced bronchospasm)	≤2 days/wk	>2 days/wk but not daily, and not more than 1x on any day	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extreme limitation
<b>Lung function:</b>				
FEV <sub>1</sub> % predicted, age ≥5 yr	Normal FEV <sub>1</sub> between exacerbations >80% predicted	≥80% predicted	60-80% predicted	<60% predicted
FEV <sub>1</sub> :FVC ratio <sup>t</sup> :				
Age 5-11 yr	>85%	>80%	75-80%	<75%
Age ≥12 yr	Normal	Normal	Reduced 5%	Reduced >5%
<b>Risk</b>				
Exacerbations requiring systemic corticosteroids:				
Age 0-4 yr	0-1/yr (see notes)	≥2 exacerbations in 6 mo requiring systemic corticosteroids or ≥4 wheezing episodes/yr lasting >1 day and risk factors for persistent asthma		
Age ≥5 yr	0-1/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)
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 <sub>1</sub> .				
<b>RECOMMENDED STEP FOR INITIATING THERAPY</b>				
All ages	Step 1	Step 2		
Age 0-4 yr			Step 3	Step 3
Age 5-11 yr			Step 3, medium-dose ICS option	Step 3, medium-dose ICS option or Step 4
Age ≥12 yr			Consider a short course of systemic corticosteroids	Consider a short course of systemic corticosteroids
In 2-6 wk, evaluate level of asthma control that is achieved and adjust therapy accordingly. If no clear benefit is observed within 4-6 wk, consider adjusting therapy or alternative diagnoses.				

\*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 wk. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether a 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 mo, 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.

<sup>t</sup>Normal FEV<sub>1</sub>:FVC: 8-19 yr, 85%; 20-39 yr, 80%.

FEV<sub>1</sub>, forced expiratory volume in 1 sec; FVC, forced vital capacity; ICS, inhaled corticosteroids.

Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—

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**Table 144-9** | Assessing Asthma Control and Adjusting Therapy in Children\*

	CLASSIFICATION OF ASTHMA CONTROL		
	Well-Controlled	Not Well-Controlled	Very Poorly Controlled
<b>COMPONENTS OF CONTROL</b>			
Impairment			
Symptoms	≤2 days/wk but not more than once on each day	>2 days/wk or multiple times on ≤2 days/wk	Throughout the day
Nighttime awakenings:			
Age 0-4 yr	≤1x/mo	>1x/mo	>1x/wk
Age 5-11 yr	≤1x/mo	≥2x/mo	≥2x/wk
Age ≥12 yr	≤2x/mo	1-3x/wk	≥4x/wk
Short-acting β <sub>2</sub> -agonist use for symptoms (not for exercise-induced bronchospasm pretreatment)	≤2 days/wk	>2 days/wk	Several times per day
Interference with normal activity	None	Some limitation	Extremely limited
Lung function:			
Age 5-11 yr:			
FEV <sub>1</sub> (% predicted or peak flow)	>80% predicted or personal best	60-80% predicted or personal best	<60% predicted or personal best
FEV <sub>1</sub> /FVC:	>80%	75-80%	<75%
Age ≥ 12 yr:			
FEV <sub>1</sub> (% predicted or peak flow)	>80% predicted or personal best	60-80% predicted or personal best	<60% predicted or personal best
Validated questionnaires <sup>t</sup> :			
Age ≥ 12 yr:			
ATAQ	0	1-2	3-4
ACQ	≤0.75	≤1.5	N/A
ACT	≥20	16-19	≤15
Risk			
Exacerbations requiring systemic corticosteroids:			
Age 0-4 yr	0-1/yr	2-3/yr	>3/yr
Age ≥5 yr	0-1/yr	≥2/yr (see notes)	
Consider severity and interval since last exacerbation.			
Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Reduction in lung growth or progressive loss of lung function	Evaluation requires long-term follow-up care.		
<b>RECOMMENDED ACTION FOR TREATMENT</b>			
Maintain current step.	Step up <sup>t</sup> (1 step) and reevaluate in 2-6 wk.	Consider short course of oral corticosteroids.	
Regular follow-up every 1-6 mo to maintain control.	If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy.	Step up <sup>s</sup> (1-2 steps) and reevaluate in 2 wk.	
Consider step down if well-controlled for at least 3 mo.	For side effects, consider alternative options.	If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy.	
		For side effects, consider alternative options.	

\*Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2-4 wk. 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.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or intensive care unit admission) indicate poorer disease control. 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 not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

<sup>t</sup>Validated questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain) and definition of minimal important difference (MID) for each:

- ATAQ, Asthma Therapy Assessment Questionnaire; MID = 1.0
- ACQ, Asthma Control Questionnaire; MID = 0.5
- ACT, Asthma Control Test; MID not determined

<sup>s</sup>ACQ values of 0.76-1.40 are indeterminate regarding well-controlled asthma.

<sup>s</sup>Before step-up therapy: (a) review adherence to medications, inhaler technique, and environmental control; (b) if alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

FEV<sub>1</sub>, forced expiratory volume in 1 sec; FVC, forced vital capacity.

Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol 120(Suppl):S94-S138, 2007.

**Table 144-12** Stepwise Approach for Managing Asthma in Children\*

AGE	THERAPY <sup>†</sup>	INTERMITTENT ASTHMA		PERSISTENT ASTHMA: DAILY MEDICATION			
		Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
0-4 yr	Preferred	SABA prn	Low-dose ICS	Medium-dose ICS	Medium-dose ICS + either LABA or LTRA	High-dose ICS + either LABA or LTRA	High-dose ICS + either LABA or LTRA and Oral corticosteroid
	Alternative		Cromolyn or montelukast				
5-11 yr	Preferred	SABA prn	Low-dose ICS	Either low-dose ICS ± LABA, LTRA, or theophylline or Medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA	High-dose ICS + LABA and Oral corticosteroid
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline		Medium-dose ICS + either LTRA or Theophylline	High-dose ICS + either LTRA or Theophylline	High-dose ICS + either LTRA or Theophylline and Oral corticosteroid
≥12 yr	Preferred	SABA prn	Low-dose ICS	Low-dose ICS + LABA or Medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA and Consider omalizumab for patients with allergies	High-dose ICS + LABA + oral corticosteroid and Consider omalizumab for patients with allergies
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline	Low-dose ICS + LTRA, theophylline, or zileuton	Medium-dose ICS + LTRA, theophylline, or zileuton		

Each step: Patient education, environmental control, and management of comorbidities.  
Age ≥5 yr: Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma.  
QUICK-RELIEF MEDICATION FOR ALL PATIENTS  
SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-min intervals as needed. Short course of oral systemic corticosteroids may be needed.  
Caution: Use of SABA >2 days/wk for symptom relief (not prevention of exercise-induced bronchospasm) generally indicates inadequate control and the need to step up treatment.  
For ages 0-4 yr: With viral respiratory infection: SABA q4-6h up to 24 hr (longer with physician consult). Consider short course of systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations.

## \*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 wk and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children age 0-4 yr are limited. The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.
- Theophylline is a less desirable alternative because of the need to monitor serum concentration levels.
- Zileuton is less desirable alternative because of limited studies as adjunctive therapy and the need to monitor liver function.

<sup>†</sup>Alphabetical order is used when more than 1 treatment option is listed within either preferred or alternative therapy.

ICS, inhaled corticosteroid; LABA, inhaled long-acting β<sub>2</sub>-agonist; LTRA, leukotriene receptor antagonist; prn, as needed; SABA, inhaled short-acting β<sub>2</sub>-agonist.

Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol 120(Suppl):S94-S138, 2007.

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**Table 144-13** Usual Dosages for Long-Term Control Medications

Medication	AGE		
	0-4 yr	5-11 yr	≥12 yr
<b>INHALED CORTICOSTEROIDS (see Table 144-13)</b>			
Methylprednisolone: 2, 4, 8, 16, 32 mg tablets	• 0.25-2 mg/kg daily in single dose in A.M. or qod as needed for control	• 0.25-2 mg/kg daily in single dose in A.M. or qod as needed for control	• 7.5-60 mg daily in a single dose in A.M. or qod as needed for control
Prednisolone: 5 mg tablets; 5 mg/5 mL, 15 mg/5 mL	• Short-course "burst": 1-2 mg/kg/day; maximum 30 mg/day for 3-10 days	• Short-course "burst": 1-2 mg/kg/day; maximum 60 mg/day for 3-10 days	• Short-course "burst" to achieve control: 40-60 mg/day as single or 2 divided doses for 3-10 days
Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/mL, 5 mg/5 mL			
Fluticasone/salmeterol: DPI: 100, 250, or 500 mg/50 mg  HFA: 45 µg/21 µg, 115 µg/21 µg, 230 µg/21 µg	NA	1 inhalation bid; dose depends on level of severity or control  2 inhalations bid; dose depends on level of severity or control	1 inhalation bid; dose depends on level of severity or control  2 inhalations bid; dose depends on level of severity or control
Budesonide/formoterol: HFA: 80 µg/4.5 µg, 160 µg/4.5 µg	NA		2 inhalations bid; dose depends on level of severity or control
Mometasone/formoterol HFA: 100 µg/5 µg, 200 µg/5 µg			2 inhalations bid; dose depends on level of severity or control
Cromolyn: Nebulizer 20 mg/ampule	1 ampule qid; NA <2 yr of age	1 ampule qid	1 ampule qid
Leukotriene receptor antagonists:			
Montelukast: 4 or 5 mg chewable tablet 4 mg granule packets 10 mg tablet  Zafirlukast: 10- or 20-mg tablet	4 mg qhs (1-5 yr of age)	5 mg qhs (6-14 yr)	10 mg qhs
NA	10 mg bid (7-11 yr)	40 mg daily (20 mg tablet bid)	
5-Lipoxygenase inhibitor: Zileuton CR: 600-mg tablet	NA	NA	1,200 mg twice daily (give 2 tablets bid)
Theophylline: Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day; usual max: • <1 yr of age: 0.2 (age in wk) + 5 = mg/kg/day • >1 yr of age: 16 mg/kg/day	Starting dose 10 mg/kg/day; usual maximum: 16 mg/kg/day	Starting dose 10 mg/kg/day up to 300 mg maximum; usual maximum 800 mg/day
Immunomodulators: Omalizumab (anti-IgE): Subcutaneous injection, 150 mg/1.2 mL after reconstitution with 1.4 mL sterile water for injection	NA	NA	150-375 mg SC q 2-4 wk, depending on body weight and pretreatment serum IgE level

bid, Twice a day; DPI, dry powder inhaler; HFA, hydrofluoroalkane Ig, immunoglobulin; MDI, metered-dose inhaler; q, every; qhs, every night; qid, 4 times a day; qod, every other day; SC, subcutaneous.

**Table 144-14**

Estimated Comparative Inhaled Corticosteroid Doses

Drug	LOW DAILY DOSE BY AGE			MEDIUM DAILY DOSE BY AGE			HIGH DAILY DOSE BY AGE		
	0-4 yr	5-11 yr	≥12 yr	0-4 yr	5-11 yr	≥12 yr	0-4 yr	5-11 yr	≥12 yr
Bclomethasone HFA, 40 or 80 µg/puff	NA	80-160 µg	80-240 µg	NA	>160-320 µg	>240-480 µg	NA	>320 µg	>480 µg
Budesonide DPI 90, 180, or 200 µg/inhalation	NA	180-400 µg	180-600 µg	NA	>400-800 µg	>600-1200 µg	NA	>800 µg	>1200 µg
Budesonide inhaled suspension for nebulization, 0.25, 0.5, and 1.0 mg dose	0.25-0.5 mg	0.5 mg	NA	>0.5-1.0 mg	1.0 mg	NA	>1.0 mg	2.0 mg	NA
Flunisolide, 250 µg/puff	NA	500-750 µg	500-1000 µg	NA	1000-1250 µg	>1000-2000 µg	NA	>1250 µg	>2000 µg
Flunisolide HFA, 80 µg/puff	NA	160 µg	320 µg	NA	320 µg	>320-640 µg	NA	≥640 µg	>640 µg
Fluticasone HFA/MDI: 44, 110, or 220 µg/puff	176 µg	88-176 µg	88-264 µg	>176-352 µg	>176-352 µg	>264-440 µg	>352 µg	>352 µg	>440 µg
Fluticasone DPI, 50, 100, or 250 µg/inhalation	NA	100-200 µg	100-300 µg	NA	>200-400 µg	>300-500 µg	NA	>400 µg	>500 µg
Mometasone DPI, 110 µg and 220 µg/inhalation	NA	NA	220 µg	NA	NA	440 µg	NA	NA	>440 µg
Triamcinolone acetonide, 75 µg/puff	NA	300-600 µg	300-750 µg	NA	>600-900 µg	>750-1500 µg	NA	>900 µg	>1500 µg

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; NA, not approved and no data available for this age group.

Adapted, from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol 120(Suppl):S94-S138, 2007.

**Table 144-15**

Risk Assessment for Corticosteroid Adverse Effects

	CONDITIONS	RECOMMENDATIONS
Low risk	(≤1 risk factor*) Low- to medium-dose ICS (see Table 144-11)	<ul style="list-style-type: none"> <li>Monitor blood pressure and weight with each physician visit</li> <li>Measure height annually (stadiometry); monitor periodically for declining growth rate and pubertal developmental delay</li> <li>Encourage regular physical exercise</li> <li>Ensure adequate dietary calcium and vitamin D with additional supplements for daily calcium if needed</li> <li>Avoid smoking and alcohol</li> <li>Ensure TSH status if patient has history of thyroid abnormality</li> </ul>
Medium risk	(If >1 risk factor,* consider evaluating as high risk) High-dose ICS (see Table 144-11) At least 4 courses oral corticosteroid/year	<p>As above, plus:</p> <ul style="list-style-type: none"> <li>Yearly ophthalmologic evaluations to monitor for cataracts or glaucoma</li> <li>Baseline bone densitometry (DEXA scan)</li> <li>Consider patient at increased risk for adrenal insufficiency, especially with physiologic stressors (e.g., surgery, accident, significant illness)</li> </ul>
High risk	Chronic systemic corticosteroids (>7.5 mg daily or equivalent for >1 mo) ≥ 7 oral corticosteroid burst treatments/year Very-high-dose ICS (e.g., fluticasone propionate ≥800 µg/day)	<p>As above, plus:</p> <ul style="list-style-type: none"> <li>DEXA scan: if DEXA Z score ≤1.0, recommend close monitoring (every 12 mo)</li> <li>Consider referral to a bone or endocrine specialist</li> <li>Bone age assessment</li> <li>Complete blood count</li> <li>Serum calcium, phosphorus, alkaline phosphatase determinations</li> <li>Urine calcium and creatinine measurements</li> <li>Measurements of testosterone in males, estradiol in amenorrheic premenopausal women, vitamin D (25-OH and 1,25-OH vitamin D), parathyroid hormone, and osteocalcin</li> <li>Urine telopeptides for those receiving long-term systemic or frequent oral corticosteroid treatment</li> <li>Assume adrenal insufficiency for physiologic stressors (e.g., surgery, accident, significant illness)</li> </ul>

\*Risk factors for osteoporosis: Presence of other chronic illness(es), medications (corticosteroids, anticonvulsants, heparin, diuretics), low body weight, family history of osteoporosis, significant fracture history disproportionate to trauma, recurrent falls, impaired vision, low dietary calcium and vitamin D intake, and lifestyle factors (decreased physical activity, smoking, and alcohol intake).

DEXA, dual-energy x-ray absorptiometry; ICS, inhaled corticosteroid; TSH, thyroid-stimulating hormone.

**Table 144-16** Management of Asthma Exacerbation (Status Asthmaticus)**RISK ASSESSMENT ON ADMISSION**

## Focused history

- Onset of current exacerbation
- Frequency and severity of daytime and nighttime symptoms and activity limitation
- Frequency of rescue bronchodilator use
- Current medications and allergies
- Potential triggers
- History of systemic steroid courses, emergency department visits, hospitalization, intubation, or life-threatening episodes
- Physical examination findings: vital signs, breathlessness, air movement, use of accessory muscles, retractions, anxiety level, alteration in mental status
- Pulse oximetry
- Lung function (defer in patients with moderate to severe distress or history of labile disease)

## Clinical assessment

## Risk factors for asthma morbidity and death

See Table 144-17

**TREATMENT**

<b>Drug and Trade Name</b>	<b>Mechanisms of Action and Dosing</b>	<b>Cautions and Adverse Effects</b>
Oxygen (mask or nasal cannula)	Treats hypoxia	<ul style="list-style-type: none"> <li>• Monitor pulse oximetry to maintain O<sub>2</sub> saturation &gt;92%</li> <li>• Cardiorespiratory monitoring</li> <li>• During exacerbations, frequent or continuous doses can cause pulmonary vasodilation, V/Q mismatch, and hypoxemia</li> <li>• Adverse effects: palpitations, tachycardia, arrhythmias, tremor, hypoxemia</li> <li>• Nebulizer: when giving concentrated forms, dilute with saline to 3 mL total nebulized volume</li> </ul>
Inhaled short-acting β-agonists:	Bronchodilator	
Albuterol nebulizer solution (5 mg/mL concentrate; 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)	Nebulizer: 0.15 mg/kg (minimum: 2.5 mg) as often as every 20 min for 3 doses as needed, then 0.15-0.3 mg/kg up to 10 mg every 1-4 hr as needed, or up to 0.5 mg/kg/hr by continuous nebulization	
Albuterol MDI (90 µg/puff)	2-8 puffs up to every 20 min for 3 doses as needed, then every 1-4 hr as needed	<ul style="list-style-type: none"> <li>• For MDI: use spacer/holding chamber</li> </ul>
Levalbuterol (Xopenex) nebulizer solution (1.25 mg/0.5 mL concentrate; 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL)	0.075 mg/kg (minimum: 1.25 mg) every 20 min for 3 doses, then 0.075-0.15 mg/kg up to 5 mg every 1-4 hr as needed, or 0.25 mg/kg/hr by continuous nebulization	<ul style="list-style-type: none"> <li>• Levalbuterol 0.63 mg is equivalent to 1.25 mg of standard albuterol for both efficacy and side effects</li> </ul>
Systemic corticosteroids:	Antiinflammatory	<ul style="list-style-type: none"> <li>• If patient has been exposed to chickenpox or measles, consider passive immunoglobulin prophylaxis; also, risk of complications with herpes simplex and tuberculosis</li> <li>• For daily dosing, 8 A.M. administration minimizes adrenal suppression</li> <li>• Children may benefit from dosage tapering if course exceeds 7 days</li> <li>• Adverse effects monitoring: Frequent therapy bursts risk numerous corticosteroid adverse effects (see Chapter 578); see Table 144-15 for adverse effects screening recommendations</li> </ul>

Continued

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**Table 144-16** Management of Asthma Exacerbation (Status Asthmaticus)—cont'd

Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets Methylprednisolone (Medrol): 2, 4, 8, 16, 24, 32 mg tablets Prednisolone: 5 mg tablets; 5 mg/5 mL and 15 mg/5 mL solution Depo-Medrol (IM); Solu-Medrol (IV)	0.5-1 mg/kg every 6-12 hr for 48 hr, then 1-2 mg/kg/day bid (maximum: 60 mg/day)
Anticholinergics:	Short-course "burst" for exacerbation: 1-2 mg/ kg/day qd or bid for 3-7 days Mucolytic/bronchodilator
Ipratropium: Atrovent (nebulizer solution 0.5 mg/2.5 mL; MDI 18 µg/inhalation) Ipratropium with albuterol: DuoNeb nebulizer solution (0.5 mg ipratropium + 2.5 mg albuterol/3 mL vial)	Nebulizer: 0.5 mg q6-8h (tid-qid) as needed MDI: 2 puffs qid 1 vial by nebulizer qid
Injectable sympathomimetic epinephrine:  Adrenalin 1 mg/mL (1:1000) EpiPen autoinjection device (0.3 mg; EpiPen Jr 0.15 mg)	Bronchodilator  SC or IM: 0.01 mg/kg (max dose 0.5 mg); may repeat after 15-30 min
Terbutaline:  Brethine 1 mg/mL	• Should not be used as first-line therapy; added to β <sub>2</sub> -agonist therapy  • Nebulizer: may mix ipratropium with albuterol  • For extreme circumstances (e.g., impending respiratory failure despite high-dose inhaled SABA, respiratory failure)  • Terbutaline is β-agonist-selective relative to epinephrine • Monitoring with continuous infusion: cardiorespiratory monitor, pulse oximetry, blood pressure, serum potassium • Adverse effects: tremor, tachycardia, palpitations, arrhythmia, hypertension, headaches, nervousness, nausea, vomiting, hypoxemia
<b>RISK ASSESSMENT FOR DISCHARGE</b> Medical stability	Continuous IV infusion (terbutaline only): 2-10 µg/kg loading dose, followed by 0.1-0.4 µg/kg/min Titrate in 0.1-0.2 µg/kg/min increments every 30 min, depending on clinical response
Home supervision	Discharge to home if there has been sustained improvement in symptoms and bronchodilator treatments are at least 3 hr apart, physical findings are normal, PEF >70% of predicted or personal best, and oxygen saturation >92% when breathing room air
Asthma education	Capability to administer intervention and to observe and respond appropriately to clinical deterioration See <a href="#">Table 144-9</a>

IM, intramuscular; MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting β-agonist; SC, subcutaneous; V/Q, ventilation-perfusion.

**Table 148-4** Treatment of Urticaria and Angioedema

CLASS/DRUG	DOSE	FREQUENCY
<b>ANTIHISTAMINES, TYPE H<sub>1</sub> (SECOND GENERATION)</b>		
Fexofenadine	6-11 yr: 30 mg >12 yr: 60 mg	bid
Loratadine	Adult: 180 mg 2-5 yr: 5 mg >6 yr: 10 mg	Once daily Once daily
Desloratadine	6-11 mo: 1 mg 12 mo-5 yr: 1.25 mg 6-11 yr: 2.5 mg >12 yr: 5 mg	Once daily
Cetirizine	6-23 mo: 2.5 mg 2-6 yr: 2.5-5 mg >6 yr: 5-10 mg	Once daily
Levocetirizine	6 mo-5 yr: 1.25 mg 6-11 yr: 2.5 mg >12 yr: 5 mg	Once daily Once daily Once daily
<b>ANTIHISTAMINES, TYPE H<sub>2</sub></b>		
Cimetidine	Infants: 10-20 mg/kg/day Children: 20-40 mg/kg/day	Divided q6-12h
Ranitidine	1 mo-16 yr: 5-10 mg/kg/day	Divided q12h
Famotidine	3-12 mo: 1 mg/kg/day 1-16 yr: 1-2 mg/kg/day	Divided q12h
<b>LEUKOTRIENE PATHWAY MODIFIERS</b>		
Montelukast	12 mo-5 yr: 4 mg 6-14 yr: 5 mg >14 yr: 10 mg	Once daily
Zafirlukast	5-11 yr: 10 mg	bid
<b>IMMUNOMODULATORY DRUGS</b>		
Cyclosporine	4-6 mg/kg/day	Once daily*
Sulfasalazine	>6 yr: 30 mg/kg/day	Divided q6h†
Intravenous immunoglobulin (IVIG)	400 mg/kg/day	5 consecutive days

\*Monitor blood pressure and serum creatinine, potassium, and magnesium levels monthly.

†Monitor complete blood count and liver function tests at baseline, every 2 wk for 3 mo, and then every 1-3 mo.

**Table 144-17** Risk Factors for Asthma Morbidity and Mortality

<b>BIOLOGIC</b>
Previous severe asthma exacerbation (intensive care unit admission, intubation for asthma)
Sudden asphyxia episodes (respiratory failure, arrest)
Two or more hospitalizations for asthma in past year
Three or more emergency department visits for asthma in past year
Increasing and large diurnal variation in peak flows
Use of >2 canisters of short-acting β-agonists per month
Poor response to systemic corticosteroid therapy
Male gender
Low birthweight
Nonwhite (especially black) ethnicity
Sensitivity to <i>Alternaria</i>
<b>ENVIRONMENTAL</b>
Allergen exposure
Environmental tobacco smoke exposure
Air pollution exposure
Urban environment
<b>ECONOMIC AND PSYCHOSOCIAL</b>
Poverty
Crowding
Mother <20 yr old
Mother with less than high school education
Inadequate medical care:
Inaccessible
Unaffordable
No regular medical care (only emergency)
Lack of written asthma action plan
No care sought for chronic asthma symptoms
Delay in care of asthma exacerbations
Inadequate hospital care for asthma exacerbation
Psychopathology in the parent or child
Poor perception of asthma symptoms or severity
Alcohol or substance abuse

**Table 145-1** Clinical Features of Atopic Dermatitis

<b>MAJOR FEATURES</b>
Pruritus
Facial and extensor eczema in infants and children
Flexural eczema in adolescents
Chronic or relapsing dermatitis
Personal or family history of atopic disease
<b>ASSOCIATED FEATURES</b>
Xerosis
Cutaneous infections ( <i>Staphylococcus aureus</i> , group A streptococcus, herpes simplex, coxsackievirus, vaccinia, molluscum, warts)
Nonspecific dermatitis of the hands or feet
Ichthyosis, palmar hyperlinearity, keratosis pilaris
Nipple eczema
White dermatographism and delayed blanch response
Anterior subcapsular cataracts, keratoconus
Elevated serum immunoglobulin E levels
Positive results of immediate-type allergy skin tests
Early age at onset
Dennie lines (Dennie-Morgan infraorbital folds)
Facial erythema or pallor
Course influenced by environmental and/or emotional factors

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<b>Table 145-2</b>	Differential Diagnosis of Atopic Dermatitis
<b>CONGENITAL DISORDERS</b>	
Netherton syndrome	
Familial keratosis pilaris	
<b>CHRONIC DERMATOSES</b>	
Seborrheic dermatitis	
Contact dermatitis (allergic or irritant)	
Nummular eczema	
Psoriasis	
Ichthyoses	
<b>INFECTIONS AND INFESTATIONS</b>	
Scabies	
HIV-associated dermatitis	
Dermatophytosis	
Insect bites	
Onchocerciasis	
<b>MALIGNANCIES</b>	
Cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome)	
Letterer-Siwe disease (Langerhans cell histiocytosis)	
<b>AUTOIMMUNE DISORDERS</b>	
Dermatitis herpetiformis	
Pemphigus foliaceus	
Graft-versus-host disease	
Dermatomyositis	
<b>IMMUNODEFICIENCIES</b>	
Wiskott-Aldrich syndrome	
Severe combined immunodeficiency syndrome	
Hyperimmunoglobulin E syndromes (autosomal dominant and recessive types)	
Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome	
<b>METABOLIC DISORDERS</b>	
Zinc deficiency	
Pyridoxine (vitamin B <sub>6</sub> ) and niacin	
Multiple carboxylase deficiency	
Phenylketonuria	

Modified from Leung DYM, Sampson HA, Geha RS, et al: Pediatric allergy principles and practice, St. Louis, 2003, Mosby, p. 562.

<b>Table 145-5</b>	Selected Topical Corticosteroid Preparations*
<b>GROUP 1</b>	
Clobetasol propionate (Temovate) 0.05% ointment/cream	
Betamethasone dipropionate (Diprolene) 0.05% ointment/lotion/gel	
Fluocinonide (Vanos) 0.1% cream	
<b>GROUP 2</b>	
Mometasone furoate (Elocon) 0.1% ointment	
Halcinonide (Halog) 0.1% cream	
Fluocinolone (Lidex) 0.05% ointment/cream	
Desoximetasone (Topicort) 0.25% ointment/cream	
Betamethasone dipropionate (Diprolene) 0.05% cream	
<b>GROUP 3</b>	
Fluticasone propionate (Cutivate) 0.005% ointment	
Halcinonide (Halog) 0.1% ointment	
Betamethasone valerate (Valisone) 0.1% ointment	
<b>GROUP 4</b>	
Mometasone furoate (Elocon) 0.1% cream	
Triamcinolone acetonide (Kenalog) 0.1% ointment/cream	
Fluocinolone acetonide (Synalar) 0.025% ointment	
<b>GROUP 5</b>	
Fluocinolone acetonide (Synalar) 0.025% cream	
Hydrocortisone valerate (Westcort) 0.2% ointment	
<b>GROUP 6</b>	
Desonide (DesOwen) 0.5% ointment/cream/lotion	
Alclometasone dipropionate (Aclovate) 0.05% ointment/cream	
<b>GROUP 7</b>	
Hydrocortisone (Hytone) 2.5%, 1%, 0.5% ointment/cream/lotion	

\*Representative corticosteroids are listed by group from 1 (superpotent) through 7 (least potent).

**Table 145-3** List of Aggravating Factors and Counselling for AD Patients

Clothing: avoid skin contact with irritating fibers (wool, large-fiber textiles); do not use tight and too warm clothing to avoid excessive sweating. New nonirritating clothing designed for AD children is being evaluated
Tobacco: avoid exposure
Cool temperature in bedroom and avoid too many bed covers
Increase emollient use with cold weather
Avoid exposure to herpes sores; urgent visit if flare of unusual aspect
Vaccines: normal schedule in noninvolved skin, including egg-allergic patients (see text)
Sun exposure: no specific restriction. Usually helpful because of improvement of epidermal barrier. Encourage summer holidays in altitude or at beach resorts
Physical exercise, sports: no restriction. If sweating induces flares of AD, progressive adaptation to exercise. Shower and emollients after swimming pool
Food allergens
Maintain breast feeding until 4 mo if possible
Otherwise normal diet, unless an allergy work-up has proven the need to exclude a specific food
Indoor aeroallergens
House dust mites
Use adequate ventilation of housing; keep the rooms well aerated even in winter
Avoid wall-to-wall carpeting
Remove dust with a wet sponge
Vacuum floors and upholstery with an adequately filtered cleaner once a week
Avoid soft toys in bed (cradle), except washable ones
Wash bed sheets at a temperature higher than 55° every 10 days
Use bed and pillow encasings made of Gore-Tex or similar material
Furred pets: advise to avoid. If allergy is demonstrated, be firm on avoidance measures, such as pet removal
Pollen: close windows during peak pollen season on warm and dry weather and restrict, if possible, stays outdoors. Windows may be open at night and early in the morning or during rainy weather. Avoid exposure to risk situations (lawn mowing). Use pollen filters in car. Clothes and pets can vectorize aeroallergens, including pollen

From Darsow U, Wollenberg A, Simon D, et al: ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol 24:317-328, 2010 (Table 2, p. 321).

**Table 145-4** Categorization of Physical Severity of Atopic Eczema

Clear—Normal skin, with no evidence of atopic eczema  
 Mild—Areas of dry skin, infrequent itching (with or without small areas of redness)  
 Moderate—Areas of dry skin, frequent itching, redness (with or without excoriation and localized skin thickening)  
 Severe—Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation)

From Lewis-Jones S, Muggleson MA; Guideline Development Group: Management of atopic eczema in children aged up to 12 years: summary of NICE guidance, BMJ 335:1263–1264, 2007.

**Table 147-1** Topical Ophthalmic Medications for Allergic Conjunctivitis

DRUG AND TRADE NAMES	MECHANISM OF ACTION AND DOSING	CAUTIONS AND ADVERSE EVENTS
Azelastine hydrochloride 0.05% Optivar	Antihistamine Children ≥3 yr: 1 gtt bid	Not for treatment of contact lens-related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Emedastine difumarate 0.05% Emadine	Antihistamine Children ≥3 yr: 1 gtt qid	Soft contact lenses should not be worn if the eye is red. Wait at least 10 min after administration before inserting soft contact lenses.
Levocabastine hydrochloride 0.05% Livostin	Antihistamine Children ≥12 yr: 1 gtt bid-qid up to 2 wk	Not for use in patients wearing soft contact lenses during treatment.
Pheniramine maleate	Antihistamine/vasoconstrictor	Avoid prolonged use (>3-4 days) to avoid rebound symptoms. Not for use with contact lenses.
0.3%/Naphazoline hydrochloride 0.025% Naphcon-A, Opcon-A	Children >6 yr: 1-2 gtt qid	
Cromolyn sodium 4% Crolom, Opticrom	Mast cell stabilizer Children >4 yr 1-2 gtt q4-6h	Can be used to treat giant papillary conjunctivitis and vernal keratitis. Not for use with contact lenses.
Lodoxamide tromethamine 0.1% Alomide	Mast cell stabilizer Children ≥2 yr: 1-2 gtt qid up to 3 mo	Can be used to treat vernal keratoconjunctivitis. Not for use in patients wearing soft contact lenses during treatment.
Nedocromil sodium 2% Alocrin	Mast cell stabilizer Children ≥3 yr 1-2 gtt bid	Avoid wearing contact lenses while exhibiting the signs and symptoms of allergic conjunctivitis.
Pemirolast potassium 0.1% Alamast	Mast cell stabilizer Children >3 yr: 1-2 gtt qid	Not for treatment of contact lens-related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Epinastine hydrochloride 0.05% Elastat	Antihistamine/mast cell stabilizer Children ≥3 yr 1 gtt bid	Contact lenses should be removed prior to use. Wait at least 15 min after administration before inserting soft contact lenses. Not for the treatment of contact lens irritation.

Continued

**Table 147-1** Topical Ophthalmic Medications for Allergic Conjunctivitis—cont'd

DRUG AND TRADE NAMES	MECHANISM OF ACTION AND DOSING	CAUTIONS AND ADVERSE EVENTS
Ketotifen fumarate 0.025% Zaditor	Antihistamine/mast cell stabilizer Children ≥3 yr 1 gtt bid q8-12h	Not for treatment of contact lens-related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Olopatadine hydrochloride 0.1%, 0.2% Patanol Pataday	Antihistamine/mast cell stabilizer Children ≥3 yr: 1 gtt bid (8 hr apart) 1 gtt q day	Not for treatment of contact lens-related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Alcaftadine, 0.25% Lastacaft	Antihistamine/mast cell stabilizer Children > 2 yr: 1 gtt bid q8-12 hr	Contact lenses should be removed prior to application, may be inserted after 10 minutes. Not for the treatment of contact lens irritation.
Bepotastine besilate 1.5% Bepreve	Antihistamine/mast cell stabilizer Children >2 yr: 1 gtt bid q8-12 hr	Contact lenses should be removed prior to application, may be inserted after 10 minutes. Not for the treatment of contact lens irritation.
Ketorolac tromethamine 0.5% Acular	NSAID Children ≥3 yr: 1 gtt qid	Avoid with aspirin or NSAID sensitivity. Use ocular product with caution in patients with complicated ocular surgeries, corneal denervation or epithelial defects, ocular surface diseases (e.g., dry eye syndrome), repeated ocular surgeries within a short period of time, diabetes mellitus, or rheumatoid arthritis; these patients may be at risk for corneal adverse events that may be sight-threatening. Do not use while wearing contact lenses.
Fluorometholone 0.1%, 0.25% suspension (0.1%, 0.25%) and ointment (0.1%) FML, FML Forte, Flarex	Fluorinated corticosteroid Children ≥2 yr, 1 gtt into conjunctival sac of affected eye(s) bid-qid. During initial 24–48 hr, dosage may be increased to 1 gtt q 4 hr. Ointment (approximately 1.3 cm in length) into the conjunctival sac of affected eye(s) 1–3 times daily. May be applied q 4 hr during initial 24–48 hr of therapy	If improvement does not occur after 2 days, patient should be reevaluated. Patient should remove soft contact lenses prior to administering (contains benzalkonium chloride) and delay reinsertion of lenses for ≥15 minutes after administration. Close monitoring for development of glaucoma and cataracts.

<b>Table 148-3</b> Diagnostic Testing for Urticaria and Angioedema	
DIAGNOSIS	DIAGNOSTIC TESTING
Food and drug reactions	Elimination of offending agent, skin testing, and challenge with suspected foods
Autoimmune urticaria	Autologous serum skin test; antithyroid antibodies; antibodies against the high-affinity IgE receptor
Thyroiditis	Thyroid-stimulating hormone; antithyroid antibodies
Infections	Appropriate cultures or serology
Collagen vascular diseases and cutaneous vasculitis	Skin biopsy, CH <sub>50</sub> , C1q, C4, C3, factor B, immunofluorescence of tissues, antinuclear antibodies, cryoglobulins
Malignancy with angioedema	CH <sub>50</sub> , C1q, C4, C1-INH determinations
Cold urticaria	Ice cube test
Solar urticaria	Exposure to defined wavelengths of light, red blood cell protoporphyrin, fecal protoporphyrin, and coproporphyrin
Dermatographism	Stroking with narrow object (e.g., tongue blade, fingernail)
Pressure urticaria	Application of pressure for defined time and intensity
Vibratory urticaria	Vibration for 4 min
Aquagenic urticaria	Challenge with tap water at various temperatures
Urticaria pigmentosa	Skin biopsy, test for dermatographism
Hereditary angioedema	C4, C2, CH <sub>50</sub> , C1-INH testing by protein and function
Familial cold urticaria	Challenge by cold exposure, measurement of temperature, white blood cell count, erythrocyte sedimentation rate, and skin biopsy
C3b inactivator deficiency	C3, factor B, C3b inactivator determinations
Chronic idiopathic urticaria	Skin biopsy, immunofluorescence (negative result), autologous skin test

<b>Table 148-2</b> Etiology of Chronic Urticaria	
Idiopathic/autoimmune	Approximately 30% of chronic urticaria cases are physical urticaria and 60-70% are idiopathic. Of the idiopathic cases approximately 35-40% have anti-IgE or anti-FcεRI (high-affinity IgE receptor α chain) autoantibodies (autoimmune chronic urticaria)
Physical	Dermatographism Cholinergic urticaria Cold urticaria Delayed pressure urticaria Solar urticaria Vibratory urticaria Aquagenic urticaria
Autoimmune diseases	Systemic lupus erythematosus Juvenile idiopathic arthritis Thyroid (Graves, Hashimoto) Celiac disease Inflammatory bowel disease Leukocytoclastic vasculitis
Autoinflammatory/periodic fever syndromes	NOMID (neonatal onset multisystem inflammatory disease) Muckle-Wells syndrome Familial cold autoinflammatory syndrome Cold urticarial, immunodeficiency, autoimmunity as a result of PLG2 deficiency
Neoplastic	Lymphoma Mastocytosis Leukemia
Angioedema	Hereditary angioedema (autosomal dominant inherited deficiency of C1-esterase inhibitor) Acquired angioedema Angiotensin-converting enzyme inhibitors

<b>Table 148-1</b> Etiology of Acute Urticaria	
Foods	Egg, milk, wheat, peanuts, tree nuts, soy, shellfish, fish, strawberries (direct mast cell degranulation)
Medications	Suspect all medications, even nonprescription or homeopathic
Insect stings	Hymenoptera (honeybee, yellow jacket, hornets, wasp, fire ants), biting insects (papular urticaria)
Infections	Bacterial (streptococcal pharyngitis, <i>Mycoplasma</i> , sinusitis); viral (hepatitis, mononucleosis [Epstein-Barr virus], coxsackieviruses A and B); parasitic ( <i>Ascaris</i> , <i>Ancylostoma</i> , <i>Echinococcus</i> , <i>Fasciola</i> , <i>Filaria</i> , <i>Schistosoma</i> , <i>Strongyloides</i> , <i>Toxocara</i> , <i>Trichinella</i> ); fungal (dermatophytes, <i>Candida</i> )
Contact allergy	Latex, pollen, animal saliva, nettle plants, caterpillars
Transfusion reactions	Blood, blood products, or IV immunoglobulin administration