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

|  |  |
| --- | --- |
| **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 biopterin cofactor biosynthesis Defects of biopterin cofactor regeneration Argininemia  Hypermethioninemia Citrullinemia type II | |
| HEMOGLOBINOPATHICS  Hemoglobin variants (including hemoglobin E) | |
| OTHERS  Galactose epimerase deficiency Galactokinase deficiency | |

\*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](http://genes-r-us/)

.uthscsa.edu/sites/genes-r-us/files/nbsdisorders.pdf.

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

\*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.

|  |  |
| --- | --- |
| **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  β-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-β-thalassemia Hemoglobin SC disease | |
| OTHER DISORDERS  Congenital hypothyroidism Biotinidase deficiency Congenital adrenal hyperplasia Galactosemia  Hearing deficiency Cystic fibrosis | |

Initial findings include

**one or more of the following:**

1. Poor feeding
2. Vomiting (not due to GI anomalies)
3. Lethargy
4. Convulsion
5. Coma

Metabolic disorder

Infection, trauma, CNS anomalies

Obtain plasma ammonia

Not responsive to

intravenous glucose, calcium or vitamin B6

{

High Normal

Obtain

blood pH, CO2, HCO —

3

Obtain

blood pH, CO2, HCO3—

**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.

Normal anion gap

High anion gap

Normal anion gap

Acidosis

Urea cycle defects

Aminoacidopathies

or galactosemia

Organic acidemias

**Chapter 85** ◆ Defects in Metabolism of Amino Acids **637**

Protein synthesis Protein synthesis

PKU

Phenylethylamine

1

CH2 CH  COOH



HO CH2 CH  COOH  Fig. 85-2

Phenylpyruvate

NH2

Phenylalanine

4α-carbinolamine- tetrahydrobiopterin

Tyrosine

NH2

Phenyllactate

4-OH-phenylacetate

Tetrahydrobiopterin (BH4)

**2**



10

Tyrosinemia II

BH4\*

Phenylacetate

Glutamine

**6**

**3**

Dihydrobiopterin quinonoid (BH2)

BH4\*

4-OH-phenylpyruvate

Cysteine

Phenylacetylglutamine

**9 6**

6-Lactoyl tetrahydropterin

**NE**

1'-OH-2'-Oxopropyl tetrahydropterin

7-biopterin (primapterin) (urine)

sin

Dihydrobiopterin

Sepiapterin

**6 7**

6-Pyruvoyl tetrahydropterin

Homogentisic acid



Hawkin

4-OH-cyclo- hexylacetate

Tyrosinemia III

Hawkinsinuria

11



12

BH4\*



**5**

BH4\*

Alkaptonuria

Guanosine triphosphate



**4**

Dihydroneopterin triphosphate

Neopterin (urine)

Succinylacetoacetate

Succinylacetone

Maleylacetoacetate



13

 Fumarylacetoacetate



14 Tyrosinemia I

Fumarate Acetoacetate



CO2 + H2O

**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 BH4 are shown in purple. PKU\* refers to defects of BH4 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

No odor Characteristic odor

1. MSUD\*
2. Isovaleric acidemia\*
3. Methylmalonic acidemia
4. Propionic acidemia
5. Ketothiolase deficiency

**Figure 85-6** Clinical approach to infants with organic acidemia. *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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**Benzoate**

Urine



Gyrate atrophy

Arginino-

succinic acid

Mitochondrial membrane

**Glutamine**

+

**Phenylacetate**

HHH syndrome

**Acetyl CoA**

+

**Glutamic acid**

Citrulline

**Urea**

4

2 **Citrulline**

Argininosuccinic aciduria

**Phenylacetyl**

**glutamine**

NAG

synthetase deficiency

**Carbamyl phosphate**

Putrescine

**Glycine** + **Benzoyl CoA**

Urine

Aspartate

**N-Acetyl-glutamic acid (NAG)**

Ornithine

**Glutamic acid**

γ**-semialdehyde**

Aspartate

**Cytosol**

Fumaric

acid

**Ornithine**

Citrullinemia

Type I

1

Citrullinemia Type II

8

Argininemia

**Glutamate**

+

**Ammonia** + **CO2** + **ATP**

CPS deficiency

CO2

6

5

3

**Hippurate**

7

OTC deficiency

Arginine

Urine

Proline

**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.

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

β-Ketothiolase deficiency Multiple carboxylase deficiencies

Medium-chain fatty acid acyl-coenzyme A dehydrogenase deficiency

Glutaric acidemia type I

3-Hydroxy-3-methylglutaric aciduria Lysinuric protein intolerance

Hyperammonemia-hyperornithinemia-homocitrullinemia syndrome Transient hyperammonemia of the newborn

Congenital hyperinsulinism with hyperammonemia

Inborn Errors of Metabolism Causing Hyperammonemia

**Table 85-3**

|  |  |  |
| --- | --- | --- |
| **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 |
| Hawkinsinuria | | 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 |

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Obtain

blood pH and HCO –

3

Acidosis No acidosis

Obtain

Urine organic acids and

Blood acylcarnitines

Specific amino acid elevation

Obtain

plasma amino acids

No specific amino acid elevation

Normal or

CPS deficiency or NAG synthetase

deficiency

OTC

deficiency

HHH

syndrome

Argininemia

Transient hyperammonemia of the newborn

Argininosuccinic acidemia

Low

Normal or low

Obtain plasma citrulline

High

Obtain

urine orotic acid

Citrullinemia

Organic acidemias

elevated

**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.

1. Provide adequate calories, fluid, and electrolytes intravenously (10% glucose, 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.
2. 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†
  + Sodium phenylacetate 250 mg/kg†
  + Arginine hydrochloride 200-600 mg/kg as a 10% solution

1. Continue infusion of sodium benzoate† (250-500 mg/kg/24 hr), sodium phenylacetate† (250-500 mg/kg/24 hr), and arginine (200-600 mg/kg/24 hr‡) following the above priming doses. These compounds should be added to the daily intravenous fluid.
2. Initiate peritoneal dialysis or hemodialysis if above treatment fails to produce an appreciable decrease in plasma ammonia.

Treatment of Acute Hyperammonemia in an Infant

**Table 85-4**

|  |  |
| --- | --- |
| **Table 86-2** | Classification of Peroxisomal Disorders |
| A: DISORDERS OF PEROXISOME IMPORT  A1: Zellweger syndrome  A2: Neonatal adrenoleukodystrophy A3: Infantile Refsum disease  A4: Rhizomelic chondrodysplasia punctata | |
| B: DEFECTS OF SINGLE PEROXISOMAL ENZYME  B1: X-linked adrenoleukodystrophy B2: Acyl-CoA oxidase deficiency B3: Bifunctional enzyme deficiency B4: Peroxisomal thiolase deficiency B5: Classic Refsum disease  B6: 2-Methylacyl-CoA racemase deficiency B7: DHAP acyltransferase deficiency  B8: Alkyl-DHAP synthase deficiency B9: Mevalonic aciduria  B10: Glutaric aciduria type III B11: Hyperoxaluria type I B12: Acatalasemia | |

CoA, coenzyme A; DHAP, dihydroxyacetone phosphate.

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|  |  |
| --- | --- |
| **Table 86-10** | Major Clinical Characteristics of Smith- Lemli-Opitz Syndrome: Frequent Anomalies (>50% of Patients) |
| CRANIOFACIAL  Microcephaly Blepharoptosis Anteverted nares Retromicrognathia  Low-set, posteriorly rotated ears Midline cleft palate  Broad maxillary alveolar ridges  Cataracts (<50%) | |
| SKELETAL ANOMALIES  Syndactyly of toes II/III Postaxial polydactyly (<50%)  Equinovarus deformity (<50%) | |
| GENITAL ANOMALIES  Hypospadias Cryptorchidism  Sexual ambiguity (<50%) | |
| DEVELOPMENT  Pre- and postnatal growth retardation Feeding problems  Mental retardation Behavioral abnormalities | |

|  |  |
| --- | --- |
| **Table 86-11** | Characteristic Malformations of Internal Organs in Severely Affected Smith-Lemli- Opitz Patients |
| CENTRAL NERVOUS SYSTEM  Frontal lobe hypoplasia Enlarged ventricles Agenesis of corpus callosum Cerebellar hypoplasia Holoprosencephaly | |
| CARDIOVASCULAR  Atrioventricular canal Secundum atrial septal defect Patent ductus arteriosus  Membranous ventricular septal defect | |
| URINARY TRACT  Renal hypoplasia or aplasia Renal cortical cysts Hydronephrosis  Ureteral duplication | |
| GASTROINTESTINAL  Hirschsprung disease Pyloric stenosis Refractory dysmotility  Cholestatic and noncholestatic progressive liver disease | |
| PULMONARY  Pulmonary hypoplasia Abnormal lobation | |
| ENDOCRINE  Adrenal insufficiency | |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 86-13** | Drugs Used for the Treatment of Hyperlipidemia | | | | |
| **DRUG** | |  | **MECHANISM OF ACTION** | **INDICATION** | **STARTING DOSE** |
| 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.

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LDL-C ≥130 to –189 mg/dL Family history (FHx) (–)

Fasting lipid profile (FLP) x 2\*, average

LDL-C <130 mg/dL

 Continue CHILD 2-LDL

 Repeat FLP q. 12 months

TG ≥500 mg/dL,

 Consult lipid specialist

LDL-C ≥250 mg/dL,

 Consult lipid specialist

*Exclude secondary causes. Evaluate for other risk factors (RFs).*

*Start Cardiovascular Health Integrated Lifestyle Diet (CHILD 1)* 

***CHILD 2-LDL*** *+ lifestyle change x 6 months\*\*\**

FLP

LDL-C ≥130, <250 mg/dL\*\*  Target LDL-C TG ≥100, <500 mg/dL, <10 y  Target TG

≥130, <500 mg/dL, 10–19 y

No other RFs

 Continue CHILD 2-LDL, Follow q. 6 mo with FLP, FHx/ RF update

LDL-C ≥190 mg/dL

 Initiate statin therapy

LDL-C ≥160 to –189 mg/dL FHx (+) or

1 high-level RF or

≥2 moderate-level RFs

 Initiate statin therapy

LDL-C ≥130 to –159 mg/dL + 2 high-level RFs or

1 high-level + ≥2 moderate- level RFs OR clinical CVD

 Initiate statin therapy

Follow with FLPs, related chemistries

 LDL-C still ≥130 mg/dL, TG <200 mg/dL, refer to lipid specialist for addition of second lipid-lowering agent; monitor

 In high LDL-C patients, if non-HDL-C ≥145 mg/dL after effective LDL-C treatment,

 Target TG

\* Obtain FLPs at least 2 weeks but no more than 3 months apart.

\*\* Use of drug therapy is limited to children ≥10 y with defined risk profiles.

\*\*\* In a child with LDL-C >190 mg/dL and other RFs, trial of CHILD 2 LDL diet may be abbreviated.

**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** | |
| STATINS |  | |
| 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 >1,000U/L), rhabdomyolysis with | |
|  | renal failure | |
| Immune system | Lupus-like syndrome (lovastatin, simvastatin, or fluvastatin) | |
| Protein binding | Diminished binding of warfarin (lovastatin, simvastatin, fluvastatin) | |
| BILE ACID-BINDING RESINS |  | |
| 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 ≈10% (greater increases in patients with hypertriglyceridemia) | |
| Electrolytes | Hyperchloremic acidosis in children and patients with renal failure (cholestyramine) | |
| Drug interactions | Binding of warfarin, digoxin, thiazide diuretics, thyroxine, statins | |
| NICOTINIC ACID |  | |
| 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: ≈5% higher in patients with diabetes), increase of 10% in serum uric acid | |
| FIBRATES |  | |
| 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 ≈30% | |
| Liver | Increased serum aminotransferases | |

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| --- | --- | --- | --- | --- |
| **Table 86-15** Clinical Findings in | Lysosomal Storage Diseases | | | |
| **NOMENCLATURE** | **ENZYME DEFECT** | **COARSE FACIAL FEATURES**  **HYDROPS DYSOSTOSIS FETALIS MULTIPLEX** | | **HEPATOSPLENOMEGALY** |
| MUCOLIPIDOSES | | | | |
| Mucolipidoses II, I-cell disease | *N*-Acetylglucosaminylphosphotransferase | (+) | ++ | + |
| Mucolipidosis III, Pseudo-Hurler | *N*-Acetylglucosaminylphosphotransferase | – | + | (+) |
| Mucolipidosis IV | Unknown | – | – | + |
| SS | | | | |
| Fabry disease | α-Galactosidase | – | – | – |
| Farber disease | Ceramidase | – | – | (+) |
| Galactosialidosis | β-Galactosidase and sialidase | (+) | ++ | ++ |
| GM1 gangliosidosis | β-Galactosidase | (+) | ++ | + |
| GM2 gangliosidosis (Tay-Sachs disease, Sandhoff disease) | β-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 | β-Galactocerebrosidase | – | – | – |
| LIPID STORAGE DISORDERS | | | | |
| 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 | (+) | – | – |
| OLIGOSACCHARIDOSES | | | | |
| Aspartylglucosaminuria | Aspartylglucosylaminase | – | + | (+) |
| Fucosidosis | α-Fucosidase | – | ++ | (+) |
| α-Mannosidosis | α-Mannosidase | – | ++ | + |
| β-Mannosidosis | β-Mannosidase | – | + | (+) |
| Schindler disease | α-*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.*

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

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

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

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| **Table 87-1** Features of the Disorders of Carbohydrate Metabolism | | |
| **DISORDERS BASIC DEFECTS** | **CLINICAL PRESENTATION** | **COMMENTS** |
| LIVER GLYCOGENOSES  *Type/Common Name*  Ia/Von Gierke Glucose-6-phosphatase  Ib Glucose-6-phosphate  translocase IIIa/Cori or Forbes Liver and muscle  debrancher deficiency (amylo-1,6-glucosidase)  IIIb Liver debrancher deficiency; normal muscle enzyme activity  IV/Andersen Branching enzyme  VI/Hers Liver phosphorylase  Phosphorylase kinase Phosphorylase kinase deficiency  Glycogen synthase Glycogen synthase deficiency  Fanconi-Bickel Glucose transporter 2  syndrome (GLUT-2) | Growth retardation, hepatomegaly, hypoglycemia; elevated blood lactate, cholesterol, triglyceride, and uric acid levels  Same as type Ia, with additional findings of neutropenia and impaired neutrophil function  Childhood: hepatomegaly, growth retardation, muscle weakness, hypoglycemia, hyperlipidemia, elevated transaminase levels; liver symptoms can progress to liver failure later in life  Liver symptoms same as in type IIIa; no muscle symptoms  Failure to thrive, hypotonia, hepatomegaly, splenomegaly, progressive cirrhosis (death usually before 5th yr), elevated transaminase levels  Hepatomegaly, typically mild hypoglycemia, hyperlipidemia, and ketosis  Hepatomegaly, mild hypoglycemia, hyperlipidemia, and ketosis  Early morning drowsiness and fatigue, fasting hypoglycemia, and ketosis, no hepatomegaly  Failure to thrive, rickets, hepatorenomegaly, proximal renal tubular dysfunction, impaired glucose and galactose utilization | Common, severe hypoglycemia  10% of type Ia  Common, intermediate severity of hypoglycemia  15% of type III  Rare neuromuscular variants exist  Rare, typically benign glycogenosis; severe presentation also known  Common, typically a benign glycogenosis, severe progressive forms also present  Decreased liver glycogen store  GLUT-2 expressed in liver, kidney, pancreas, and intestine |
| MUSCLE GLYCOGENOSES  *Type/Common Name*  II/Pompe infantile Acid α-glucosidase (acid  maltase)  II/Late-onset Pompe Acid α-glucosidase (acid (juvenile and adult) maltase)  Danon disease Lysosome-associated membrane protein 2 (LAMP2)  PRKAG2 deficiency Adenosine monophosphate  (AMP)-activated protein kinase γ  V/McArdle Myophosphorylase  VII/Tarui Phosphofructokinase  Phosphoglycerate Phosphoglycerate kinase kinase deficiency  Phosphoglycerate M subunit of  mutase deficiency phosphoglycerate mutase Lactate dehydrogenase M subunit of lactate  deficiency dehydrogenase | Cardiomegaly, hypotonia, hepatomegaly; onset: birth to 6 mo  Myopathy, variable cardiomyopathy, respiratory insufficiency; onset: childhood to adulthood  Hypertrophic cardiomyopathy Hypertrophic cardiomyopathy  Exercise intolerance, muscle cramps, increased fatigability  Exercise intolerance, muscle cramps, hemolytic anemia, myoglobinuria  As with type V As with type V As with type V | Common, cardiorespiratory failure leading to death by age 1-2 yr; minimal to no residual enzyme activity  Residual enzyme activity Rare, X-linked  Autosomal dominant  Common, male predominance  Prevalent in Japanese and Ashkenazi Jews  Rare, X-linked  Rare, majority of patients are African-American  Rare |
| GALACTOSE DISORDERS  Galactosemia with Galactose-1-phosphate transferase deficiency uridyltransferase  Galactokinase Galactokinase deficiency  Generalized uridine Uridine diphosphate diphosphate galactose-4-epimerase galactose-4-  epimerase deficiency | Vomiting, hepatomegaly, cataracts, aminoaciduria, failure to thrive  Cataracts  Similar to transferase deficiency with additional findings of hypotonia and nerve deafness | African-American patients tend to have milder symptoms  Benign  A benign variant also exists |
| FRUCTOSE DISORDERS  Essential fructosuria Fructokinase  Fructose-1-phosphate aldolase  Hereditary fructose intolerance | Urine reducing substance  Acute: vomiting, sweating, lethargy Chronic: failure to thrive, hepatic failure | Benign  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** |
| DISORDERS OF GLUCONEOGENESIS |  |  |
| Fructose-1,6- Fructose-1,6-diphosphatase | Episodic hypoglycemia, apnea, acidosis | Good prognosis, avoid fasting |
| diphosphatase |  |  |
| deficiency |  |  |
| Phosphoenolpyruvate Phosphoenolpyruvate | Hypoglycemia, hepatomegaly, hypotonia, | Rare |
| carboxykinase carboxykinase | failure to thrive |  |
| deficiency |  |  |
| DISORDERS OF PYRUVATE METABOLISM |  |  |
| Pyruvate Pyruvate dehydrogenase | Severe fatal neonatal to mild late onset, lactic | Most commonly caused by E1α |
| dehydrogenase | acidosis, psychomotor retardation, and failure | subunit, defect X-linked |
| complex defect | to thrive |  |
| Pyruvate carboxylase Pyruvate carboxylase | Same as above | Rare, autosomal recessive |
| deficiency |  |  |
| Respiratory chain Complexes I-V, many | Heterogeneous with multisystem involvement | Mitochondrial inheritance |
| defects (oxidative mitochondrial DNA |  |  |
| phosphorylation mutations |  |  |
| disease) |  |  |
| DISORDERS IN PENTOSE METABOLISM |  |  |
| Pentosuria L-Xylulose reductase | Urine-reducing substance | Benign |
| Transaldolase Transaldolase | Liver cirrhosis and failure, cardiomyopathy | Autosomal recessive |
| deficiency |  |  |
| Ribose-5-phosphate Ribose-5-phosphate | Progressive leukoencephalopathy and |  |
| isomerase deficiency isomerase | peripheral neuropathy |  |

Increased 3 Hydroxy butyrate:

Hypoglycemia ± Ketones Normal O2 saturation

Normal to low

3 Hydroxy butyrate: acetoacetate

Abnormal

or diagnostic profile

Increased lactate

Urine organic acids plasma acylcarnitine profile

Hypoglycemia

“Reye-like” syndrome

Metabolic acidosis

Skin rash/alopecia

Biotinidase Holocarboxylase

synthetase deficiency

Propionic acidemia Methylmalonic acidemia Other organic aciduria

Fatty acid oxidation defects

Normal glycemia

No ketosis

Hyperglycemia

Normal

or nonspecific findings

Multisystem involvement “ragged red fiber”

in muscle biopsy

Diabetes mellitus

Pyruvate carboxylase

Pyruvate dehydrogenase complex

Tissue hypoxia

Increased pyruvate Normal lactate/pyruvate ratio

Decreased or normal pyruvate increased lactate/pyruvate ratio

Decreased O2

saturation

Glycogen storage disease type 1 Fructose, 1,6, diphosphatase Phosphoenolypyruvate

carboxykinase

Respiratory chain mitochondrial defects

acetoacetate

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

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| **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**

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| **Table 88-1** | Recognition Pattern of Mucopolysaccharidoses | | | | | | | |
| **Mucopolysaccharidosis Type** | | | | | | | | |
| **MANIFESTATIONS** | | **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 | | + | + | + | + | + | + | + |

|  |
| --- |
| 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 |

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

*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.*

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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 | *IDUA*  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 | *IDUA*  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 | *IDUA*  4p16.4 | Phenotype intermediate between I-H and I-S | α-L-iduronidase | L,F,Ac,Cv | 607015 |
| II | Hunter | XLR | *IDS*  Xq27.3-28 | Severe course similar to I-H but clear corneae. 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 | *SGSH* | Behavioral problems, sleeping disorder, aggression, progressive dementia, mild dysmorphism, coarse hair, clear corneas; survival to adulthood possible | Heparan-S- sulfamidase *N*-Acetyl-α-D-  glucosaminidase  Acetyl-CoA:α- glucosaminide  *N*-acetyltransferase *N*-Acetylglucosamine-  6-sulfatase | L,F,Ac,Cv | 252900 |
|  |  |  | 17q25.3 |  | 605270 |
| II-IB | Sanfilippo B | AR | *NAGLU* | S,F,Ac,Cv | 252920 |
|  |  |  | 17q21 |  |  |
| III-C | Sanfilippo C | AR | *HGSNAT*  8p11.21 | F,Ac | 252930 |
| III-D | Sanfilippo D | AR | *GNS*  12q14 | F,Ac | 252940  607664 |
| IV-A | Morquio A | AR | *GALNS*  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 | *GLB1*  3p21.33 | Same as IV-A, but milder; adult height over 120 cm | β-Galactosidase | L,F,Ac,Cv | 253010  230500 |
| VI | Maroteaux- Lamy | AR | *ARSB*  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 | *GUSB*  7q21.11 | Varying from fetal hydrops to mild dysmorphism; dense inclusions in granulocytes | β-Glucuronidase | S,F,Ac,Cv | 253220 |
| IX | Hyaluronidase deficiency | AR | *HYAL1*  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.

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| **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-sulfate sulfatase.

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| **Table 88-4** | Symptomatic Management of Mucopolysaccharidoses | | |
| **PROBLEM** | | **PREDOMINANTLY IN** | **MANAGEMENT** |
| NEUROLOGIC  Hydrocephalus Chronic headaches Behavioral disturbance  Disturbed sleep/wake circle Seizures  Odontoid hypoplasia Spinal cord compression | | MPS-I, -II, -VI, -VII  All MPS-III  MPS-III  MPS-I, -II, -III MPS-IV  All | Funduscopy, CT scan Ventriculoperitoneal shunting Behavioral medication, sometimes  CT scan, ventriculoperitoneal shunting Melatonin  Electroencephalogram, anticonvulsants Cervical MRI, upper cervical fusion Laminectomy, dural excision |
| OPHTHALMOLOGIC  Corneal opacity Glaucoma  Retinal degeneration | | MPS-I, -VI, -VII  MPS-I, -VI, -VII MPS-I, -II | Corneal transplant Medication, surgery Night light |
| EARS, AIRWAYS  Recurrent otitis media Impaired hearing Obstruction | | MPS-I, -II, -VI, -VII  All except MPS-IV All except MPS-III | Ventilating tubes Audiometry, hearing aids  Adenotomy, tonsillectomy, bronchodilator therapy, continuous positive airway pressure at night, laser excision of tracheal lesions, tracheotomy |
| CARDIAC  Cardiac valve disease Coronary insufficiency Arrhythmias | | MPS-I, -II, -VI, -VII  MPS-I, -II, -VI, -VII  MPS-I, -II, -VI, -VII | Endocarditis prevention, valve replacement Medical therapy  Antiarrhythmic medication, pacemaker |
| ORAL, GASTROINTESTINAL  Hypertrophic gums, poor teeth Chronic diarrhea | | MPS-I, -II, -VI, -VII MPS-II | Dental care  Diet modification, loperamide |
| MUSCULOSKELETAL  Joint stiffness Weakness  Gross long bone malalignment Carpal tunnel syndrome | | All except MPS-IV All  All  MPS-I, -II, -VI, -VII | Physical therapy  Physical therapy, wheelchair Corrective osteotomies  Electromyography, surgical decompression |
| ANESTHESIA | | All except MPS-III | Avoid atlantoaxial dislocation, use angulated video intubation laryngoscope and small endotracheal tubes |

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| **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** | **CUTANEOUS** |
| X-Linked protoporphyria (XLP) | *δ-Aminolevulinate synthase 2 (ALAS2)* | X-linked | Childhood |  | 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 |  |
| Homozygous AIP |  | Homozygous dominant | Childhood | X | X | X |  |
| Congenital erythropoietic porphyria (CEP) | *Uroporphyrinogen III synthase (UROS)* | Autosomal recessive | In utero or infancy |  | X |  | X |
| Porphyria cutanea tarda (PCT) type 1 | *Uroporphyrinogen decarboxylase (UROD)* | Sporadic | Adults | X |  |  | X |
| PCT type 2† |  | Autosomal dominant | Adults | X |  |  | X |
| PCT type 3 |  | Unknown | Adults | 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 | X |
| Variegate porphyria (VP) | *Protoporphyrinogen oxidase (PPOX)* | Autosomal dominant | Post puberty | X |  | X | X |
| Homozygous VP |  | Homozygous dominant | Childhood | X | X | X | X |
| Erythropoietic protoporphyria (EPP) | *Ferrochelatase (FECH)* | Autosomal recessive(most commonly heteroallelic with hypomorphic allele) | Childhood |  | X |  | X |

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

†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.

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| **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 protoporphyria* | | Skin pain and swelling (mostly acute), childhood onset |  | Erythrocyte (or plasma) porphyrins | Beta-carotene |

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| **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

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| **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 |

β-adrenergic blocking agents.

†Common.

‡Most common manifestations in the newborn.

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| **Table 92-2** | Classification of Hypoglycemia in Infants and Children | |
| NEONATAL TRANSITIONAL (ADAPTIVE) HYPOGLYCEMIA  *Associated with Inadequate Substrate or Immature Enzyme Function in Otherwise Normal Neonates*  Prematurity  Small for gestational age Normal newborn  *Transient Neonatal Hyperinsulinism*  Infant of diabetic mother Small for gestational age Discordant twin  Birth asphyxia  Infant of toxemic mother | | *Lipolysis Disorders*  *Fatty Acid Oxidation Disorders*  Carnitine transporter deficiency (primary carnitine deficiency) Carnitine palmitoyltransferase-1 deficiency  Carnitine translocase deficiency  Carnitine palmitoyltransferase-2 deficiency Secondary carnitine deficiencies  Very-long-, long-, medium-, short-chain acyl-CoA dehydrogenase deficiency |
| OTHER ETIOLOGIES  *Substrate-Limited* Ketotic hypoglycemia Poisoning—drugs Salicylates  Alcohol  Oral hypoglycemic agents Insulin  Propranolol Pentamidine Quinine Disopyramide  Ackee fruit (unripe)—hypoglycin Vacor (rat poison)  Trimethoprim-sulfamethoxazole (with renal failure)  *Liver Disease* Reye syndrome Hepatitis Cirrhosis Hepatoma |
| NEONATAL, INFANTILE, OR CHILDHOOD PERSISTENT HYPOGLYCEMIAS  Hyperinsulinism  Recessive KATP channel HI  Recessive HADH (hydroxyl acyl-CoA dehydrogenase) mutation HI  Recessive UCP2 (mitochondrial uncoupling protein 2) mutation HI  Focal KATP channel HI Dominant KATP channel HI  Atypical congenital hyperinsulinemia (no mutations in *ABCC8* or  *KCN11* genes) Dominant glucokinase HI  Dominant glutamate dehydrogenase HI (hyperinsulinism/ hyperammonemia syndrome)  Dominant mutations in HNF-4A and HNF-1A (hepatic nuclear factors 4α and 1α) HI with monogenic diabetes of youth later in life  Dominant mutation in SLC16A1(the pyruvate transporter)— exercise-induced hypoglycemia  Acquired islet adenoma Beckwith-Wiedemann syndrome  Insulin administration (Munchausen syndrome by proxy)  Oral sulfonylurea drugs  Congenital disorders of glycosylation *Counterregulatory Hormone Deficiency* Panhypopituitarism  Isolated growth hormone deficiency Adrenocorticotropic hormone deficiency Addison disease  Epinephrine deficiency  *Glycogenolysis and Gluconeogenesis Disorders*  Glucose-6-phosphatase deficiency (GSD 1a)  Glucose-6-phosphate translocase deficiency (GSD 1b)  Amylo-1,6-glucosidase (debranching enzyme) deficiency (GSD 3)  Liver phosphorylase deficiency (GSD 6) Phosphorylase kinase deficiency (GSD 9) Glycogen synthetase deficiency (GSD 0) Fructose-1,6-diphosphatase deficiency Pyruvate carboxylase deficiency Galactosemia  Hereditary fructose intolerance | |
| AMINO ACID AND ORGANIC ACID DISORDERS  Maple syrup urine disease Propionic acidemia Methylmalonic acidemia Tyrosinosis  Glutaric aciduria  3-Hydroxy-3-methylglutaric aciduria |
| SYSTEMIC DISORDERS  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; KATP, regulated potassium channel.

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| **Table 92-3** | Hypoglycemia in Infants and Children: Clinical and Laboratory Features | | | |
| **GROUP AGE AT DIAGNOSIS (mo)** | | **GLUCOSE\* (mg/dL)** | **INSULIN (µU/mL)** | **FASTING TIME TO HYPOGLYCEMIA (hr)** |
| HYPERINSULINEMIA (*N* **=** 12)  Mean 7.4  SEM 2.0 | | 23.1  2.7 | 22.4  3.2 | 2.1†  0.6 |
| NONHYPERINSULINEMIA (*N* **=** 16)  Mean 41.8  SEM 7.3 | | 36.1  2.4 | 5.8  0.9 | 18.2  2.9 |

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

†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.*

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 92-4** Correlation of Clinical Features with Molecular Defects in Persistent Hyperinsulinemic Hypoglycemia in Infancy | | | | | | | | |
| **TYPE** | **HYPOGLYCEMIA/ FAMILY MACROSOMIA HYPERINSULINEMIA HISTORY** | | | **MOLECULAR DEFECTS** | **ASSOCIATED CLINICAL, BIOCHEMICAL, OR MOLECULAR FEATURES** | **RESPONSE TO MEDICAL MANAGEMENT** | **RECOMMENDED SURGICAL APPROACH** | **PROGNOSIS** |
| Sporadic | Present at birth | Moderate/severe in first days to weeks of life | Negative | ? *SUR1*/KIR 6.2  Mutations not always identified in diffuse hyperplasia | 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 Subtotal >95%  pancreatectomy if  frozen section shows giant nuclei in  β-cells—suggests diffuse hyperplasia | Excellent if focal adenoma is removed, thereby curing hypoglycemia and retaining sufficient pancreas to avoid diabetes  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*/KIR 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 |

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**Chapter 92** ◆ Hypoglycemia **779**

|  |  |
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| **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.

|  |  |
| --- | --- |
| **Table 92-7** | Diagnosis of Acute Hypoglycemia in Infants and Children |
| ACUTE SYMPTOMS PRESENT   1. Obtain blood sample before and 30 min after glucagon administration. 2. 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. 3. Measure glucose in the original blood sample. If hypoglycemia is confirmed, proceed with substrate-hormone measurement as in Table 92-5. 4. If glycemic increment after glucagon exceeds 40 mg/dL above basal, suspect hyperinsulinemia. 5. 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.   1. 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   1. 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. 2. Careful examination for hepatomegaly (glycogen storage disease; defect in gluconeogenesis); pigmentation (adrenal failure); stature and neurologic status (pituitary disease). 3. Admit to hospital for provocative testing:    1. 24 hr fast under careful observation; when symptoms provoked, proceed with steps 1-4 as when acute symptoms present.    2. Pituitary–adrenal function using arginine-insulin stimulation test if indicated. 4. Consider molecular diagnostic test before liver biopsy for histologic and enzyme determinations. 5. Oral glucose tolerance test (1.75 g/kg; max 75 g) if reactive hypoglycemia suspected (dumping syndrome, etc.). | |

†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.

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

Criteria for Diagnosing Hyperinsulinism Based on “Critical” Samples (Drawn at a Time of Fasting Hypoglycemia: Plasma Glucose <50 mg/dL)

**Table 92-6**

\*Depends on sensitivity of insulin assay.

|  |  |  |
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| **Table 93-2** | Levels of In-Hospital Perinatal Care | |
| **MATERNAL** | | **NEONATE** |
| 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 | | Resuscitation Stabilization  Well neonatal care Nursery care Visitation  General pediatrician staff (capable of neonatal resuscitation) |
| 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) | | *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 |
| 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 | | *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.*

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 92-8** Clinical Manifestations and Differential Diagnosis in Childhood Hypoglycemia | | | | | | | | | | | |
| **Condition** | **Hypoglycemia** | **Urinary Ketones or Reducing Sugars** | **Hepatomegaly** | **Serum**  **URIC**  **LIPIDS ACID** | | **GLUCOSE** | **Effect of 24-36 hr Fast on Plasma INSULIN KETONES ALANINE** | **LACTATE** | **Glycemic Response to Glucagon**  **FED FASTED** | **Glycemic Response to Infusion of** | |
| **ALANINE GLYCEROL** | |
| Normal | 0 | 0 | 0 | Normal | Normal | ↓ | ↓ ↑ ↓ | Normal | ↑ ↓ |  | Not  indicated |
| Hyperinsulinemia | Recurrent severe | 0 | 0 | Normal  or ↑ | Normal | ↓↓ | ↑↑ ↓↓ Normal | Normal | ↑ ↑ |  | Not  indicated |
| Ketotic hypoglycemia | Severe with missed meals | Ketonuria  +++ | 0 | 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 | 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 lnfant

**Chapter 93** ◆ Overview of Mortality and Morbidity **793**

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| **Table 93-3** | Morbidities and Sequelae of Perinatal and Neonatal Illness | |
| **MORBIDITIES** | | **EXAMPLES** |
| CENTRAL NERVOUS SYSTEM  Spastic diplegic-quadriplegic cerebral palsy  Choreoathetotic cerebral palsy Microcephaly  Communicating hydrocephalus Seizures  Encephalopathy  Educational failure and/or mental retardation | | Hypoxic–ischemic encephalopathy, periventricular leukomalacia, undetermined antenatal factors  Bilirubin encephalopathy (kernicterus)  Hypoxic-ischemic encephalopathy, intrauterine infection (rubella, CMV) Intraventricular hemorrhage, meningitis  Hypoxic-ischemic encephalopathy, hypoglycemia Congenital infections (rubella, CMV, HIV, toxoplasmosis)  Immaturity, hypoxia, hypoglycemia, cerebral palsy, intraventricular hemorrhage, low socioeconomic status |
| SENSATION—PERIPHERAL NERVES  Reduced visual acuity (blindness) Strabismus  Hearing impairment (deafness)  Poor speech Paralysis–paresis | | Retinopathy of prematurity Undetermined, prematurity  Drug toxicity (furosemide, aminoglycosides), bilirubin encephalopathy, hypoxia ±  hyperventilation  Immaturity, chronic illness, hypoxia, prolonged endotracheal intubation, hearing deficit Birth trauma—brachial plexus, phrenic nerve, spinal cord |
| RESPIRATORY  BPD  Subglottic stenosis  Sudden infant death syndrome  Choanal stenosis, nasal septum destruction | | Oxygen toxicity, barotrauma Endotracheal tube injury  Prematurity, BPD, infant of illicit drug user Nasotracheal intubation  Growth failure |
| CARDIOVASCULAR  Cyanosis Heart failure | | Precorrective palliative care of congenital cyanotic heart disease, cor pulmonale from BPD, reactive airway  Precorrective palliative care of complex congenital heart disease, BPD, ventricular septal defect |
| GASTROINTESTINAL  Short-gut syndrome  Cholestatic liver disease (cirrhosis, hepatic failure) Failure to thrive  Inguinal hernia | | Necrotizing enterocolitis, gastroschisis, malrotation-volvulus, cystic fibrosis, intestinal atresia Hyperalimentation toxicity, sepsis, short-gut syndrome  Short-gut syndrome, cholestasis, BPD, cerebral palsy, severe congenital heart disease Unknown |
| MISCELLANEOUS  Cutaneous scars  Absence of radial artery pulse Hypertension | | Chest tube or intravenous catheter placement, hyperalimentation, subcutaneous infiltration, fetal puncture, intrauterine varicella, cutis aplasia  Frequent arterial puncture  Renal thrombi, repair of coarctation of aorta |

BPD, bronchopulmonary dysplasia; CMV, cytomegalovirus.

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| **Table 93-4** | Incidence of Adverse Outcome According to Completed Week of Gestation at Delivery for Infants Born by Caesarean Section | | | | | | |
|  | | **WK 37** | **WK 38** | **WK 39** | **WK 40** | **WK 41** | **WK 42** |
| **OUTCOME** | | **(N = 934)** | **(N = 3909)** | **(N = 6512)** | **(N = 1385)** | **(N = 1385)** | **(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.*

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| **Table 94-3** | Factors Affecting the Apgar Score\* |
| FALSE-POSITIVE (NO FETAL ACIDOSIS OR HYPOXIA; LOW APGAR SCORE)  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 | |
| FALSE-NEGATIVE (ACIDOSIS; NORMAL APGAR SCORE)  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.

**Table**

**94-1** Disorders Associated with a Large Anterior Fontanel

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

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| **Table 93-2** | Levels of In-Hospital Perinatal Care | |
| **MATERNAL** | | **NEONATE** |
| 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 | | Resuscitation Stabilization  Well neonatal care Nursery care Visitation  General pediatrician staff (capable of neonatal resuscitation) |
| 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) | | *Basic services plus:*  Care of high-risk neonate with short-term problems Stabilization before transfer (<1,500 g, <32 wk, critically ill)  m Accept convalescing back (reverse) transfers |
| 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 | | *Basic plus specialty care plus:*  e Experienced neonatologist (24-hr coverage)  Inborn plus transferred patients  g Evaluation of high-risk therapies  All pediatric medical, radiologic, and surgical subspecialties  d 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.*

Hypop Intraut Kenny Osteo Premat Pykno Russell Trisomi Vitami

Hydrocephaly

Apert s Athyro Cleido Conge Haller

Achondroplasia

hosphatasia

rine growth restriction syndrome

enesis imperfecta urity

ysostosis

-Silver syndrome es 13-, 18-, and 21

n D deficiency rickets

yndrome

tic hypothyroidism cranial dysostosis

nital rubella syndrome ann-Streiff syndrome

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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 × 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

Criteria for Discharge from the Normal Newborn Nursery\*

**Table 94-5**

\*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.*

|  |  |  |
| --- | --- | --- |
| **Table 94-7** | Drugs and Breastfeeding | |
| CONTRAINDICATED  Amphetamines Antineoplastic agents Bromocriptine Chloramphenicol Clozapine  Cocaine Cyclophosphamide Diethylstilbestrol Doxorubicin Ecstasy  Ergots Gold salts Heroin  Immunosuppressants Iodides  Kava Lithium  Methimazole Methamphetamine Phencyclidine (PCP) Radiopharmaceuticals Thiouracil  Yohimbe | | Metoclopramide Metronidazole Meperidine Oxycodone Phenobarbital\* Primidone Psychotropic drugs Reserpine Salicylazosulfapyridine  (sulfasalazine) |
| PROBABLY SAFE  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 |
| AVOID OR GIVE WITH CAUTION  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.

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.

1. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.

Ten Steps to Successful Breastfeeding

**Table 94-6**

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

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| --- | --- | --- | --- | --- |
| **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?** |
| BACTERIA  Mastitis/*Staphylococcus aureus Mycobacterium tuberculosis:*  Active disease  Purified protein derivative skin test result positive, chest radiograph findings negative  *Escherichia coli,* other Gram-negative rods Group B streptococci  *Listeria monocytogenes Coxiella burnetii* Syphilis | | Yes Yes No  Yes, stored Yes  Yes Yes No | No No No  Yes, stored Yes  Yes Yes No | No, unless breast abscess present  Yes, because of aerosol spread, or tuberculosis mastitis  No  —  No\* No\* No\* No† |

###### Continued

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| --- | --- | --- | --- | --- |
| **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?** |
| VIRUSES  HIV  Cytomegalovirus:  Term infant Preterm infant  Hepatitis B virus Hepatitis C virus Hepatitis E virus  Human T-cell leukemia virus (HTLV)-1 HTLV-2  Herpes simplex virus Rubella  Wild type Vaccine  Varicella-zoster virus Epstein-Barr virus  Human herpesvirus (HHV)-6 HHV-7  West Nile virus | | Yes  Yes Yes  Yes, surface antigen Yes  Yes Yes Yes Yes  Yes Yes Yes Yes No Yes  Possible | Yes  Yes Yes No No No Yes  ?  No/?yes  Yes, rare No  No No No No  Possible | Yes, developed countries  No  Evaluate on an individual basis No, developed countries‡  No§ No  Yes, developed countries Yes, developed countries  No, unless breast vesicles present  No No  No, cover active lesions¶ No  No No  Unknown |
| PARASITES  *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 antivaricella 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.*

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| **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.*

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1:5

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| **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 α-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 (*t*oxoplasmosis, *o*ther agents, *r*ubella, *c*ytomegalovirus, *h*erpes simplex) infection | |

1:10

Natural birth prevalence of Down syndrome

1:50

1:100

1:250

1:500

1:1,000

1:2,000

15 20 25 30 35 40 45 50

Maternal age at expected date of delivery

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

|  |  |
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| **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 | |

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| **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  Severe | Large for gestational age, hypoglycemia Growth restriction | Fetal hyperglycemia—produces hyperinsulinemia; insulin promotes growth  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 |

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| **Table 95-3** | Maternal Infections Affecting the Fetus or Newborn | | |
| **INFECTION** | | **MODE(S) OF TRANSMISSION** | **OUTCOME** |
| BACTERIA  Group B streptococcus  *Escherichia coli*  *Listeria monocytogenes Ureaplasma urealyticum Mycoplasma hominis Chlamydia trachomatis* Syphilis  *Borrelia burgdorferi Neisseria gonorrhoeae Mycobacterium tuberculosis* Granulocytic ehrlichiosis | | Ascending cervical Ascending cervical Transplacental Ascending cervical Ascending cervical Vaginal passage  Transplacental, vaginal passage Transplacental  Vaginal passage Transplacental Transplacental | Sepsis, pneumonia Sepsis, pneumonia Sepsis, pneumonia Pneumonia, meningitis Pneumonia  Conjunctivitis, pneumonia Congenital syphilis Prematurity, fetal demise  Ophthalmia (conjunctivitis), sepsis, meningitis Prematurity, fetal demise, congenital tuberculosis Sepsis |
| VIRUS  Rubella Cytomegalovirus HIV  Hepatitis B  Hepatitis C  Lymphocytic choriomeningitis Herpes simplex type 2 or 1  Varicella-zoster  Parvovirus Coxsackie B Poliomyelitis Epstein-Barr Rubeola West Nile Dengue virus | | Transplacental  Transplacental, breast milk (rare) Transplacental, vaginal passage, breast milk Vaginal passage, transplacental, breast milk  Transplacental Transplacental Transplacental  Vaginal passage, ascending Transplacental:  Early Late  Transplacental Fecal-oral Transplacental Transplacental Transplacental Transplacental Transplacental | Congenital rubella  Congenital cytomegalovirus or asymptomatic Congenital acquired immunodeficiency syndrome  Neonatal hepatitis, chronic hepatitis B surface antigen carrier state  Uncommon, but neonatal hepatitis, chronic carrier state possible Fetal, neonatal death; hydrocephalus, chorioretinitis  Congenital herpes simplex virus  Neonatal encephalitis, disseminated viremia  Congenital anomalies Neonatal varicella Fetal anemia, hydrops  Myocarditis, meningitis, hepatitis Congenital poliomyelitis Anomalies(?)  Abortion, fetal measles Chorioretinitis, focal cerebral necrosis Thrombocytopenia, lymphocytosis |
| PARASITES  Toxoplasmosis Malaria Trypanosomiasis Hookworm | | Transplacental Transplacental Transplacental None | Congenital toxoplasmosis or asymptomatic Abortion, prematurity, intrauterine growth restriction Congenital Chagas disease  Maternal anemia, low birthweight |
| FUNGI  *Candida* | | Ascending, cervical | Sepsis, pneumonia, rash |
| PRION  Creutzfeldt-Jakob disease | | Transplacental, colostrum | Hypothetical route, no long-term data |

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| **Table 97-1** | Factors That Define an Infant as Being High Risk | |
| DEMOGRAPHIC SOCIAL FACTORS  Maternal age <16 or >40 yr  Illicit drug, alcohol, cigarette use  Poverty Unmarried  Emotional or physical stress | | 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 |
| PAST MEDICAL HISTORY  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) | |
| LABOR AND DELIVERY  Premature labor (<37 wk) Postdates pregnancy (≥42 wk) Fetal distress  Immature lethicin : sphingomyelin ratio; absence of phosphatidylglycerol  Breech presentation Meconium-stained fluid Nuchal cord  Cesarean section Forceps delivery  Apgar score <4 at 1 min |
| PREVIOUS PREGNANCY  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 | |
| NEONATE  Birthweight <2,500 or >4,000 g Birth <37 or ≥42 wk of gestation Small or large for gestational age  Respiratory distress, cyanosis Congenital malformation Pallor, plethora, petechiae |
| PRESENT PREGNANCY  Vaginal bleeding (abruptio placentae, placenta previa)  Sexually transmitted infections (colonization: herpes simplex, group B streptococcus, chlamydia, syphilis, hepatitis B, HIV) | |

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| **Table 96-1** | Fetal Diagnosis and Assessment |
| **METHOD COMMENT(S) AND INDICATION(S)** | |
| IMAGING  Ultrasound (real-time) Biometry (growth), anomaly (morphology) detection Biophysical profile  Amniotic fluid volume, hydrops  Ultrasound (Doppler) Velocimetry (blood flow velocity)  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 | |
| FLUID ANALYSIS  Amniocentesis Fetal maturity (L : S ratio), karyotype (cytogenetics), biochemical enzyme analysis, molecular genetic DNA diagnosis, bilirubin, or α-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) | |
| FETAL TISSUE ANALYSIS  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 Molecular DNA genetic analysis including microarray analysis, chromosome plasma number, specific gene testing, or genetic sequencing | |
| MATERNAL SERUM α-FETOPROTEIN CONCENTRATION  Elevated Twins, neural tube defects (anencephaly, spina bifida), intestinal atresia, hepatitis,  nephrosis, fetal demise, incorrect gestational age  Reduced Trisomies, aneuploidy | |
| MATERNAL CERVIX  Fetal fibronectin Indicates risk of preterm birth  Bacterial culture Identifies risk of fetal infection (group B streptococcus, *Neisseria gonorrhoeae*)  Fluid Determination of premature rupture of membranes | |
| ANTEPARTUM BIOPHYSICAL MONITORING  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.

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| **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 ≥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 ≥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.*

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| **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 ≥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 ≥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 ≥15 beats/min, lasting ≥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.*

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| **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, ≥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 | |

1,500

Females (*n* = 1,327)

1,500

Males (*n* = 1,453)

1,400



0.1

0.2

0.3

0.4

0.5

0.6

0.7

0.8

1,300

1,200

1,100

Birthweight (g)

1,000

900

800

700

600

500

22 23

24 25 26

27 28 29 30

1,400

1,300

0.1

0.2

0.3

0.4

0.5

0.6

0.7

0.8

1,200

1,100

Birthweight (g)

1,000

900

800

700

600

500

22 23

24 25 26

27 28 29 30

Gestational age (wk) Gestational age (wk)

**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/el*.)*](http://www.pediatrics.org.cgi/content/full/107/1/el.))

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| **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 |
| 17α-Ethinyl testosterone (Progestoral) | | 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 |

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| **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, VACTERAL |
| 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 |

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#### **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

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

Agents Acting on Pregnant Women That May Adversely Affect the Newborn Infant—cont’d

**Table 96-6**

\*See also Table 96-5.

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

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| **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 |

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| **Table 96-7** | Significance of Fetal Ultrasonographic Anatomic Findings | | | | |
| **PRENATAL OBSERVATION** | | **DEFINITION** | **DIFFERENTIAL DIAGNOSIS** | **SIGNIFICANCE** | **POSTNATAL EVALUATION** |
| Dilated cerebral ventricles | | Ventriculomegaly  ≥10 mm | Hydrocephalus Hydranencephalous 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 megacystics- 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 |

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| **Table 99-2** | Multiorgan Systemic Effects of Asphyxia | |
| **SYSTEM** | | **EFFECT(S)** |
| CNS | | HIE, infarction, intracranial hemorrhage, seizures, cerebral edema, hypotonia, hypertonia |
| 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 |

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| **Table 96-8** | Fetal Therapy | |
| **DISORDER** | | **POSSIBLE TREATMENT** |
| HEMATOLOGIC  Anemia with hydrops (erythroblastosis fetalis) Thalassemia  Isoimmune thrombocytopenia Autoimmune thrombocytopenia (ITP) Chronic granulomatous disease | | Umbilical vein packed red blood cell transfusion Fetal stem cell transplantation  Umbilical vein platelet transfusion, maternal IVIG Maternal steroids and IVIG  Fetal stem cell transplantation |
| METABOLIC-ENDOCRINE  Maternal phenylketonuria (PKU) Fetal galactosemia  Multiple carboxylase deficiency Methylmalonic acidemia  21-Hydroxylase deficiency Maternal diabetes mellitus Fetal goiter  Bartter syndrome  Neonatal iron storage disease (alloimmune) | | Phenylalanine restriction Galactose-free diet (?) Biotin if responsive Vitamin B12 if responsive Dexamethasone  Tight insulin control during pregnancy, labor, and delivery Maternal hyperthyroidism—maternal propylthiouracil Fetal hypothyroidism—intra-amniotic thyroxine  Maternal indomethacin may prevent nephrocalcinosis and postnatal sodium losses Maternal IVIG |
| FETAL DISTRESS  Hypoxia  Intrauterine growth restriction  Oligohydramnios, premature rupture of membranes with variable deceleration  Polyhydramnios Supraventricular tachycardia Lupus anticoagulant Meconium-stained fluid Congenital heart block Premature labor | | Maternal oxygen, position  Maternal oxygen, position, improve macronutrients and micronutrients if deficient Amnioinfusion (antepartum and intrapartum)  Amnioreduction (serial), indomethacin (if from increased urine output) if indicated Maternal digoxin,\* flecainide, procainamide, amiodarone, quinidine  Maternal aspirin, prednisone Amnioinfusion  Dexamethasone, pacemaker (with hydrops)  Magnesium sulfate, antibiotics sympathomimetics, indomethacin |
| RESPIRATORY  Pulmonary immaturity  Bilateral chylothorax—pleural effusions | | Betamethasone  Thoracentesis, pleuroamniotic shunt |
| CONGENITAL ABNORMALITIES†  Neural tube defects  Posterior urethral valves, urethral atresia (lower urinary tract obstruction)  Cystic adenomatoid malformation (with hydrops) Fetal neck masses | | Folate, vitamins (prevention); fetal surgery‡ Percutaneous vesicoamniotic shunt  Pleuroamniotic shunt or resection‡ Secure an airway with EXIT procedure‡ |
| INFECTIOUS DISEASE  Group B streptococcus colonization Chorioamnionitis  Toxoplasmosis Syphilis Tuberculosis Lyme disease Parvovirus  Chlamydia trachomatis HIV-AIDS  Cytomegalovirus | | Ampicillin, penicillin Antibiotics  Spiramycin, pyrimethamine, sulfadiazine, and folic acid Penicillin  Antituberculosis drugs Penicillin, ceftriaxone  Intrauterine red blood cell transfusion for hydrops, severe anemia Erythromycin  Maternal and neonatal antiretroviral therapy (see Chapter 276) Ganciclovir by umbilical vein |

###### Continued

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| **Table 96-8** | Fetal Therapy |
| **DISORDER POSSIBLE TREATMENT** | |
| OTHER  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.

†Detailed fetal ultrasonography is needed to detect other anomalies; karyotype is also indicated.

‡EXIT permits surgery and other procedures.

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

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| **Table 97-3** | Identifiable Causes of Preterm Birth |
| FETAL  Fetal distress Multiple gestation Erythroblastosis Nonimmune hydrops | |
| PLACENTAL  Placental dysfunction Placenta previa Abruptio placentae | |
| UTERINE  Bicornuate uterus  Incompetent cervix (premature dilation) | |
| MATERNAL  Preeclampsia  Chronic medical illness (cyanotic heart disease, renal disease)  Infection (*Listeria monocytogenes,* group B streptococcus, urinary tract infection, bacterial vaginosis, chorioamnionitis)  Drug abuse (cocaine) | |
| OTHER  Premature rupture of membranes Polyhydramnios  Iatrogenic Trauma | |

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| **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) | |

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| **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 Micrognathia, cleft palate, airway obstruction Stickler syndrome | |
| 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, Polyhydramnios, bile-stained emesis, abdominal distention ileal atresia Suspect trisomy 21, cystic fibrosis, cocaine | |
| Gastroschisis, omphalocele Polyhydramnios, intestinal obstruction | |
| Renal agenesis, Potter syndrome Oligohydramnios, anuria, pulmonary hypoplasia, pneumothorax | |
| Neural tube defects: anencephalus, Polyhydramnios, elevated α-fetoprotein, decreased fetal activity meningomyelocele | |
| Ductus-dependent congenital heart disease Cyanosis, hypotension, murmur | |

* 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.

Pain in the Neonate: General Considerations

**Table 98-2**

*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.*

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| **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 anomalads, chromosomal- genetic disorders, oligohydramnios- induced deformation, TORCH (*t*oxoplasmosis, *o*ther agents, *r*ubella, *c*ytomegalovirus, *h*erpes 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.

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| **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 | 42 | 53 |  |  |
| Posture |  |  |  |  |  |  |  |
| Square window (wrist) | >90° | 90° | 60° | 45° | 30° | 0° |
| Arm recoil |  | 180° | 140-180° | 110-140° | 90-110° | <90° |
| Popliteal angle | 180° | 160° | 140° | 120° | 100° | 90° | <90° |
| Scarf sign |  |  |  |  |  |  |  |
| Heel to ear |  |  |  |  |  |  |

**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 | Impercep- tible | 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 |

**Figure 97-5** Physical criteria for maturity. The expanded New Ballard score includes extremely premature infants and has

|  |  |
| --- | --- |
| 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 |

been refined to improve accuracy in more mature infants.

Maturity Rating

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

|  |  |  |
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| **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 |
| NaHCO3 | | 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 |
| Furosemide | | Deafness, hyponatremia, hypokalemia, hypochloremia, nephrocalcinosis, biliary stones |
| Heparin (not low-dose prophylactic use) | | Bleeding, intraventricular hemorrhage, thrombocytopenia |
| Erythromycin | | Pyloric stenosis |

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| **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 |

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| **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 |

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| **Table 98-1** | Differential Diagnosis of Cyanosis in the Newborn |
| CENTRAL OR PERIPHERAL NERVOUS SYSTEM HYPOVENTILATION  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 O2 or less O2 delivered than expected (rare) Disconnection of O2 supply to nasal cannula, head hood Connection of air, rather than O2, 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 | |

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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)

Readiness for Discharge of High-Risk Infants Criteria

**Table 97-9**

*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.*

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

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**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 (bilitranslocase) 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



Circulating unconjugated bilirubin

Intestinal lumen

Unconjugated bilirubin

Meconium Bilirubin MG Bilirubin DG

BMG BDG

Unconjugated

bilirubin

Recirculated

unconjugated bilirubin

β-glucuronidases to facilitate placental transfer of lipid-soluble uncon- jugated bilirubin across the placental lipid membranes. After birth, intestinal or milk-containing glucuronidases contribute to the entero-

hepatic recirculation of bilirubin and possibly to the development of hyperbilirubinemia.

\*Race as defined by mother’s description.

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| **Table 102-2** | Risk Factors for Development of Severe Hyperbilirubinemia in Infants ≥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-title 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 ≥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 ≥41 wk  Exclusive bottle-feeding  Black race  Discharge from hospital after 72 hr | |

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 ≥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 ETCOc, 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 |

ETCOc, 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.*

Increased direct bilirubin

Sepsis

Intrauterine infection Toxoplasmosis Cytomegalovirus Rubella

Herpes Syphilis

Paucity of bile ducts

Disorders of bile acid metabolism Severe hemolytic disease

Biliary atresia Giant cell hepatitis Choledochal cyst Cystic fibrosis Galactosemia

Alpha1-antitrypsin deficiency Tyrosinemia Hyperalimentation cholestasis

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Isoimmunization Rh

ABO

Other blood group

Positive Coombs test

Increased indirect bilirubin

Normal or low

Increased

Reticulocyte count

Prolonged hyperbilirubinemia

**Normal**

Enclosed hemorrhage

Increased enterohepatic circulation, delayed or infrequent stooling, bowel obstruction

Inadequate caloric intake Neonatal asphyxia

Red cell morphology

**Nonspecific**

G6PD deficiency PK deficiency Other enzyme

deficiency Disseminated

intravascular coagulation

**Characteristic**

Spherocytosis Elliptocytosis Stomatocytosis Pyknocytosis Fragmented cells

Hemoglobin

High (polycythemia)

Twin transfusion Maternal–fetal

transfusion Delayed cord

clamping

Small for gestational age infant

Negative Coombs test

Gilbert syndrome Down syndrome Hypothyroidism Breast-feeding

Crigler-Najjar syndrome

**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† for <30% oxygen at 36 wk postmenstrual age or discharge home, whichever comes first | Need† for <30% oxygen at 56 days postnatal age or discharge home, whichever comes first |
| Severe BPD |  | Need† for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 36 wk postmenstrual age or discharge home, whichever comes first | Need† 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.

†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.*

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 102-4** | Diagnostic Features of the Various Types of Neonatal Jaundice | | | | | | | |
| **DIAGNOSIS** | | **NATURE OF VAN DEN BERGH REACTION** | **JAUNDICE**    **Appears Disappears** | | **PEAK BILIRUBIN CONCENTRATION**  **Age in**  **mg/dL Days** | | **BILIRUBIN RATE OF**  **ACCUMULATION**  **(mg/dL/day)** | **REMARKS** |
| “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  <5 | Usually relates to degree of maturity |
| Hyperbilirubinemia caused by metabolic factors:  Full-term Premature | | Indirect Indirect | 2-3 days  3-4 days | Variable Variable | >12  >15 | 1st wk 1st wk | <5  <5 | Metabolic factors: hypoxia, respiratory distress, lack of carbohydrate  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 |

|  |  |  |  |
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| **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 H2O and FIO2 >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 H2O and FIO2 ≤0.4) | 15 mL/kg PRBCs over 2-4 hr |
| ≤25 | ≤8 | Infants not requiring mechanical ventilation but who are receiving supplemental O2 or CPAP with an FIO2 ≤0.4 and in whom 1 or more of the following is present:   * ≤24 hr of tachycardia (heart rate >180 beats/min) or tachypnea (respiratory rate >80 breaths/min) * 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 H2O)   * Weight gain <10 g/kg/day over the previous 4 days while infant is receiving ≥100 kcal/kg/day * An increase in episodes of apnea and bradycardia (>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 * Undergoing surgery | 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; FIO2, 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.*

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A

Low

Low-intermediate

Assign bilirubin risk zone

If discharging <72 h, follow-up within 2 d

If discharging <72 h, follow-up within 2 d Consider TSB/TcB at follow-up

Predischarge TcB/TSB

Gestational age

35-376/7 wk + other hyperbilirubinemia risk factors

High

Evaluate for phototherapy TSB in 4-8 h

High-intermediate

Evaluate for phototherapy TSB/TcB in 4-24 h

Low

Low-intermediate

Assign bilirubin risk zone

Predischarge TcB/TSB

If discharging <72 h, follow-up within 2-3 d

If discharging <72 h, follow-up within 2 d

High

Evaluate for phototherapy TSB in 4-24 h

High-intermediate

Evaluate for phototherapy TSB/TcB within 24 h

|  |
| --- |
| **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 |

Gestation 35-376/7 wk, no hyperbilirubinemia risk factors or

Gestation ≥38 wk + other hyperbilirubinemia risk factors

B

C

Low

Low-intermediate

Assign bilirubin risk zone

If discharging <72 h, time follow-up according to age at discharge or concerns other than jaundice (e.g., breastfeeding)

If discharging <72 h, follow-up within 2-3 d

Predischarge TcB/TSB

Gestation ≥38 wk, no hyperbilirubinemia risk factor

High

Evaluate for phototherapy TSB in 4-24 h

High-intermediate

Follow-up within 2 d Consider TcB/TSB at follow-up

**Figure 102-10** Algorithm providing recommendations for management and follow-up according to predischarge bili- rubin measurements, gestation, and risk factors for subse- quent 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.)

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| **Table 103-1** Normal | Red Blood Cell | Values | from | 18 Wk of Gestation | to | 14 | Wk | of Life | |
| **AGE** | **HEMOGLOBIN**  **(g/dL)** | **HEMATOCRIT (%)** | | | **MCV (µ3)** | | | | **RETICULOCYTES (%)** |
| GESTATIONAL (WK) |  |  | | |  | | | |  |
| 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 |
| POSTNATAL (DAYS) |  |  | | |  | | | |  |
| 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 |
| POSTNATAL (WK) |  |  | | |  | | | |  |
| 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.*

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| **Table 103-3** | 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 |
| Tumors and Neuroblastoma storage diseases Hepatoblastoma  Gaucher disease Niemann-Pick disease Mucolipidosis  GM1 gangliosidosis Mucopolysaccharidosis | |
| Cardiac dysrhythmias | Supraventricular tachycardia Atrial flutter  Congenital heart block |
| 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 |
| 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 |
| Bone diseases | Osteogenesis imperfecta Asphyxiating thoracic dystrophy Skeletal dysplasias |
| 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 |
| Congenital infections | Cytomegalovirus Parvovirus Rubella Toxoplasmosis Syphilis Leptospirosis Chagas disease |
| 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 |
| Lymphatic | Lymphangiectasia Cystic hygroma  Chylothorax, chylous ascites Noonan syndrome  Multiple pterygium syndrome |
| Central nervous system | Absent corpus callosum Encephalocele Intracranial hemorrhage Holoprosencephaly |
| Idiopathic | Multiple congenital anomaly syndromes |
| Thoracic lesions | Cystic adenomatoid malformation of lung Mediastinal teratoma  Diaphragmatic hernia Sequestered lung |

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

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

**Chapter 106** ◆ Metabolic Disturbances **893**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Positive | |  |
|  | |  | |
| Immune hemolytic anemia   * ABO * Rh * Minor blood group (e.g., Kell) | | | |

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

Hemoglobin concentration

Normal

Rare misc. causes (e.g., hexokinase deficiency)

Infection

Blood loss

1. Latrogenic (sampling)
2. Fetomaternal/fetoplacental Twin to twin

Internal hemorrhage

1. Placental hemorrhage
2. Umbilical cord hemorrhage

Peripheral blood smear

Normal or high

Negative

MCV

Coombs test

* Chronic intrauterine blood loss
* α-Thalassemia syndromes

Low

Reticulocyte count

Abnormal

Hereditary spherocytosis Hereditary elliptocytosis Stomatocytosis Pyropoikilocytosis Pyruvate kinase deficiency G6PD deficiency

DIC

Normal or high

Low

Congenital hypoplastic anemias

Congenital infections Congenital leukemia

|  |  |
| --- | --- |
| **Table 106-1** | 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−1 dose−1 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−1 dose−1, add phenobarbital or clonidine | Decrease by 10% every 24 hr, while scores <8. Discontinue when 0.15 kg−1 dose−1 |
| Methadone | 0.1 mg kg−1 dose−1 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−1 dose−1 every 4 hr while scoring >8. Max dose  0.5 mg kg−1 dose−1 | When max dosing has been reached | Decrease by 10% every  1-2 wk. Discontinue when  0.05 mg kg−1 dose−1 |
| Buprenorphine | 15.9 μg kg−1 dose−1 divided in 3 doses,  orally | Increase by 25% | Max dose 60 μg kg−1 dose−1 |  | 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−1 day−1,  divided every 4−6 hr |  | Adjuvant | No taper required |

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

[(LPT) Infants 34–366/7 weeks and SGA (screen 0–24 hrs); IDM and LGA ≥34 weeks (screen 0–12 hrs)]

##### Birth to 4 hours of age

Refeed/IV glucose\* as needed

IV glucose\*

Screen <35 mg/dL

Refeed/IV glucose\* as needed

IV glucose\*

IV glucose

Asymptomatic

Initial screen <25 mg/dL

Feed and check in 1 hour

Feed and check in 1 hour

Symptomatic and <40 mg/dL

INITIAL FEED WITHIN 1 hour

Screen glucose 30 minutes after 1st feed

##### Birth to 4 hours of age

Continue feeds q 2–3 hours Screen glucose prior to each feed

<25 mg/dL

25–40 mg/dL

<35 mg/dL

35–45 mg/dL

Target glucose screen ≥45 mg/dL prior to feeds

\*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 | Amnionic 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 |

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 (PaO2 <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

Definitions of Systemic Inflammatory Respiratory Response Syndrome and Sepsis in Pediatric Patients

**Table 109-8**

**Chapter 108** ◆ Dysmorphology **901**

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| **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 *DLL3* mutations; mutations can also be present in Neural tube defects other genes | |
| Rubinstein-Taybi syndrome | | Mendelian autosomal recessive | Mental retardation Broad thumbs, toes Hypoplastic maxillae Prominent nose Congenital heart disease | *CBP* mutations or haploinsufficiency |
| X-linked lissencephaly | | Mendelian X-linked | Male:  Severe mental retardation Seizures  Female: Variable | *DCX* mutation |
| Aniridia | | Autosomal semidominant | Reduced or absent iris | *PAX6* mutations |
| Waardenburg syndrome | | Autosomal semidominant | Deafness White forelock  Wide-spaced eyes Pale eye pigment | *PAX3* mutations  *MITF* mutations |
| Holoprosencephaly | | Loss of function or heterozygosity | Microcephaly Cyclopia  Single central incisor | *SHH* mutations |
| Velocardiofacial syndrome | | Microdeletion 22q11.2 | Conotruncal congenital heart disease  Cleft palate T-cell defects  Facial anomalies | *TBX1* haploinsufficiency/mutations; haploinsufficiency for other genes in the deleted interval |
| Down syndrome | | Chromosomal | Mental retardation 50% increase of estimated 250 genes on chromosome 21  Characteristic dysmorphic features Trisomy 21 Congenital heart disease  Increased risk of leukemia Alzheimer disease | |
| 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 |

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| **Table 108-4** | Childhood Diseases and Syndromes Associated with Motile and Sensory Ciliopathies | | |
| **PEDIATRIC CILIOPATHY** | | **CLINICAL MANIFESTATIONS** | **GENE(S)** |
| MOTOR  Primary ciliary dyskinesia | | Chronic bronchitis, rhinosinusitis, otitis media, laterality defects, infertility, CHD | *DNAI1, DNAH5, DNAH11, DNAI2, KTU, TXNDC3, LRRC50, RSPH9, RSPH4A, CCDC40, CCDC39* |
| SENSORY | |  |  |
| Autosomal recessive | | RFD, CHF | *PKHD1* |
| polycystic kidney disease | |  |  |
| Nephronophthisis | | RFD, interstitial nephritis, CHF, RP | *NPHP1-8, ALMS1, CEP290* |
| Bardet-Biedl syndrome | | Obesity, polydactyly, ID, RP, renal anomalies, anosmia, CHD | *BBS1-12, MKS1, MKS3, CEP290* |
| Meckel-Gruber syndrome | | RFD, polydactyly, ID, CNS anomalies, CHD, cleft lip, cleft | *MKS1-6, CC2D2A, CEP290, TMEM216* |
|  | | palate |  |
| Joubert syndrome | | CNS anomalies, ID, ataxia, RP, polydactyly, cleft lip, cleft | *NPHP1, JBTS1, JBTS3, JBTS4, CORS2, AHI1,* |
|  | | palate | *CEP290, TMEM216* |
| Alstrom syndrome | | Obesity, RP, DM, hypothyroidism, hypogonadism, skeletal | *ALMS1* |
|  | | dysplasia, cardiomyopathy, pulmonary fibrosis |  |
| Orofaciodigital syndrome | | Polydactyly, syndactyly, cleft lip, cleft palate, CNS anomalies, | *OFD1* |
| type 1 | | ID, RFD |  |
| Ellis van Creveld syndrome | | Chondrodystrophy, polydactyly, ectodermal dysplasia, CHD | *EVC, EVC2* |
| Jeune asphyxiating thoracic | | Narrow thorax, RFD, RP, dwarfism, polydactyly | *IFT80* |
| dystrophy | |  |  |
| Sensenbrenner syndrome | | Dolichocephaly, ectodermal dysplasia, dental dysplasia, | *IFT122, IFT43, WDR35* |
|  | | narrow thorax, RFD, CHD |  |
| Short rib-polydactyly syndromes | | Narrow thorax, short limb dwarfism, polydactyly, renal dysplasia | *WDR35, DYNC2H1, NEK1* |

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.*

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| **Table 109-4** | Clinical Manifestations of Transplacental Infections | |
| **MANIFESTATION** | | **PATHOGEN** |
| Intrauterine growth restriction | | CMV, *Plasmodium*, rubella, toxoplasmosis, *Treponema pallidum, Trypanosoma cruzi,* VZV |
| Congenital anatomic defects: Cataracts  Cardiac defects Hydrocephalus | | Rubella Rubella  HSV, lymphocytic choriomeningitis virus, rubella, toxoplasmosis  CMV, HIV, toxoplasmosis, *T. cruzi*  VZV  CMV, HSV, rubella, toxoplasmosis CMV, rubella, toxoplasmosis |
| Intracranial calcification Limb hypoplasia Microcephaly Microphthalmos | |
| Neonatal organ involvement: Anemia | | CMV, parvovirus, *Plasmodium,*  rubella, toxoplasmosis, *T. cruzi,*  *T. pallidum*  Coxsackieviruses, rubella, *T. cruzi*  CMV, enteroviruses, HSV, rubella, toxoplasmosis, *T. cruzi, T. pallidum*  CMV, enteroviruses, HSV CMV, enteroviruses, HIV, HSV,  *Plasmodium,* rubella, *T. cruzi,*  *T. pallidum*  Parvovirus, *T. pallidum,*  toxoplasmosis  CMV, HIV, rubella, toxoplasmosis,  *T. pallidum*  Rubella, *T. pallidum*  CMV, enteroviruses, rubella, *T. cruzi*  CMV, enteroviruses, HSV, measles, rubella, toxoplasmosis, *T. pallidum,* VZV  CMV, HSV, lymphocytic choriomeningitis virus, rubella, toxoplasmosis, *T. pallidum,* West Nile virus  Enteroviruses, *T. pallidum*  Enteroviruses, HSV, measles, rubella,  *T. pallidum,* VZV  CMV, enteroviruses, HIV, HSV, rubella, toxoplasmosis, *T. pallidum* |
| Carditis Encephalitis | |
| Hepatitis Hepatosplenomegaly | |
| Hydrops | |
| Lymphadenopathy | |
| Osteitis  Petechiae, purpura Pneumonitis | |
| Retinitis | |
| Rhinitis Skin lesions | |
| Thrombocytopenia | |
| Late sequelae: Convulsions | | CMV, enteroviruses, rubella, toxoplasmosis  CMV, rubella, toxoplasmosis Rubella, *T. pallidum* Rubella, toxoplasmosis  HSV, rubella, toxoplasmosis, *T. cruzi,*  *T. pallidum,* VZV Hepatitis B  CMV, HIV, HSV, rubella, toxoplasmosis, *T. cruzi,* VZV  *Plasmodium, T. pallidum* |
| Deafness  Dental/skeletal problems Endocrinopathies  Eye pathology | |
| Hepatitis  Mental retardation | |
| Nephrotic syndrome | |

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| **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, XXY  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 Isotretinoin (vitamin A)  D-Penicillamine Valproic acid | |
| UNKNOWN ETIOLOGIES  Polygenetic  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 | |

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| **Table 109-5** | Initial Signs and Symptoms of Infection in Newborn Infants | |
| GENERAL  Fever, temperature instability “Not doing well”  Poor feeding Edema | | CARDIOVASCULAR SYSTEM  Pallor; mottling; cold, clammy skin  Tachycardia Hypotension Bradycardia |
| GASTROINTESTINAL SYSTEM  Abdominal distention Vomiting  Diarrhea Hepatomegaly | |
| CENTRAL NERVOUS SYSTEM  Irritability, lethargy Tremors, seizures Hyporeflexia, hypotonia Abnormal Moro reflex Irregular respirations Full fontanel  High-pitched cry |
| RESPIRATORY SYSTEM  Apnea, dyspnea Tachypnea, retractions Flaring, grunting Cyanosis | |
| HEMATOLOGIC SYSTEM  Jaundice Splenomegaly Pallor  Petechiae, purpura Bleeding |
| RENAL SYSTEM  Oliguria | |

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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

Clinical Indications for Chromosome Analysis, or Array CGH\*

**Table 108-7**

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

\*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%.

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| **Table 108-6** | Minor Anomalies and Phenotype Variants\* |
| CRANIOFACIAL  Large fontanel  Flat or low nasal bridge Saddle nose, upturned nose Mild micrognathia  Cutis aplasia of scalp | |
| EYE  Inner epicanthal folds Telecanthus  Slanting of palpebral fissures Hypertelorism  Brushfield spots | |
| EAR  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 | |
| SKIN  Dimpling over bones  Capillary hemangioma (face, posterior neck) Dermal melanosis (African Americans, Asians) Sacral dimple  Pigmented nevi Redundant skin Cutis marmorata | |
| HAND  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 | |
| FOOT  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 | |
| OTHERS  Mild calcaneovalgus Hydrocele  Shawl scrotum Hypospadias  Hypoplasia of labia majora | |

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| **Table 109-6** | 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, periumbilical 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) | |

*From Kliegman RM, Greenbaum LA, Lye PS:* Practical strategies in pediatric

diagnosis and therapy, *ed 2, Philadelphia, Elsevier Saunders, 2004.*

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

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

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| **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 23 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 |

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| **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 |

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

\* If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative.

Obtain vaginal-rectal swab for GBS culture\* and start GBS prophylaxis

Patient entering true labor?†

Yes No

Discontinue GBS prophylaxis

Obtain GBS culture results

Positive

Not available prior to labor onset

and patient still preterm

Negative

GBS prophylaxis

at onset of true labor

No GBS prophylaxis§; Repeat vaginal-

weeks’ gestation and has not yet delivered

rectal culture if patient reaches 35-37

¶

Patient with signs and symptoms of preterm labor

Continue GBS prophylaxis until delivery‡

† Patient should be regularly assessed for progression to true labor; if the patient is considered not to be in true labor, discontinue GBS prophylaxis.

‡ If GBS culture results become available before delivery and are negative, then discontinue GBS prophylaxis.

§ Unless subsequent GBS culture before delivery is positive.

¶ A negative GBS screen is considered valid for 5 weeks. If a patient with a history of PTL is re-admitted with signs and symptoms of PTL and had a negative GBS screen >5 weeks prior, she should be re-screened and managed according to this algorithm at that time.

**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)

\* If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative.

Patient entering labor?

Yes No

Continue antibiotics per standard of care if receiving for latency; OR continue antibiotics for 48 hours‡ if receiving for GBS prophylaxis

Obtain GBS culture results

Positive

Not available prior

to labor onset

Negative

GBS prophylaxis

at onset of labor

No GBS prophylaxis§; Repeat vaginal-

weeks’ gestation and has not yet delivered

rectal culture if patient reaches 35-37

¶

Obtain vaginal-rectal swab for GBS culture\* and start antibiotics for latency† OR GBS prophylaxis

Continue antibiotics until delivery

† Antibiotics given for latency in the setting of pPROM that include Ampicillin 2g IVx1, followed by 1g IV Q6 hrs for at least 48 hours are adequate for GBS prophylaxis. If other regimens are used, GBS prophylaxis should be initiated in addition.

‡ GBS prophylaxis should be discontinued at 48 hours for women with pPROM who are not in labor. If results from a GBS screen performed on admission become available during the 48 hour period and are negative, GBS prophylaxis should be discontinued at that time.

§ Unless subsequent GBS culture prior to delivery is positive.

¶ A negative GBS screen is considered valid for 5 weeks. If a patient with pPROM is entering labor and had a negative GBS screen >5 weeks prior, she should be re-screened and managed according to this algorithm at that time.

**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.)*

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

Yes

Full diagnostic evaluation\* Antibiotic therapy†

Signs of neonatal sepsis?

Limited evaluation¶ Antibiotic therapy†

Routine clinical care††

Observation for ≥48 hours††§§

Observation for ≥48 hours††¶¶

Limited evaluation¶ Observation for ≥48 hours††

Yes

Yes

Yes

Yes

Mother received ≥4 hours of penicillin, ampicillin or cefazolin IV?

No

≥37 weeks AND duration of membrane rupture <18 hours?

No

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

No

No

GBS prophylaxis indicated for mother?\*\*

Yes

No

Maternal chorioamnionitis?§

\* 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 anough 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).

**Figure 109-8** Algorithm for secondary preven- tion of early-onset GBS disease among new- borns. *(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.)*

\*\* 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.

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| **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.*

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| **Table 109-12** Management and | Prevention of Neonatal Sepsis | |
| **CONDITION** | **THERAPY** | **ADDITIONAL CONSIDERATIONS** |
| Empiric management Early-onset sepsis  Late-onset sepsis | Ampicillin + aminoglycoside.  10 days for bacteremia; 14 days for GBS  and uncomplicated meningitis; extend to 21-28 days for complicated infections.  Vancomycin + aminoglycoside. Duration dependent on pathogen and site. | Consider a third-generation cephalosporin (cefotaxime preferred) or carbapenem for meningitis.  Tailor therapy to pathogen.  Consider discontinuation of therapy if pathogen not isolated.  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  IVIG§ | Enhance neutrophil number and function, but no reduction in infection when administered as prophylaxis or improvement in survival when administered as therapy.  Augments antibody-dependent cytotoxicity and improves neutrophilic function, *but* no evidence that IVIG in suspected or proven sepsis reduces death. | Insufficient evidence to support the clinical use of G-CSF or GM-CSF either as treatment or prophylaxis to prevent systemic infections.  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.  Fluconazole prophylaxis Administration of weight-based dosing to neonates weighing less than 1,500 g.  BLF supplementation with a probiotic, BLF is a human milk glycoprotein with a  *Lactobacillus rhamnosus* (GG) role in innate immune response. LGG  enhances the activity of lactoferrin. | | Successfully reduces rates of EOS caused by GBS. No effect on LOS GBS.  Most beneficial in NICUs with high baseline rates of invasive candidiasis.  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

**Chapter 110** ◆ Adolescent Development **927**

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| **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 | | * Females: Secondary sex characteristics (breast, pubic, axillary hair), start of growth spurt * Males: testicular enlargement, start of genital growth | * Females: peak growth velocity, menarche (if not already attained) * Males: growth spurt, secondary sex characteristics, nocturnal emissions, facial and body hair, voice changes * Change in body composition * Acne | * Physical maturation slows * Increased lean muscle mass in males |
| Cognitive and moral | | * Concrete operations * Egocentricity * Unable to perceive long-term outcome of current decisions * Follow rules to avoid punishment | * Emergence of abstract thought (formal operations) * May perceive future implications, but may not apply in decision making * Strong emotions may drive decision making * Sense of invulnerability * Growing ability to see others’ perspectives | * Future-oriented with sense of perspective * Idealism * Able to think things through independently * Improved impulse control * Improved assessment of risk vs. reward * Able to distinguish law from morality |
| Self-concept/identity formation | | * Preoccupied with changing body * Self-consciousness about appearance and attractiveness | * Concern with attractiveness * Increasing introspection | * More stable body image * Attractiveness may still be of concern * Consolidation of identity |
| Family | | * Increased need for privacy * Exploration of dependence/ independence boundaries | * Conflicts over control and independence * Struggle for greater autonomy * Increased separation from the parents | * Emotional and physical separation from family * Increased autonomy * Reestablishment of “adult” relationship with parents |
| Peers | | * Same-sex peer affiliations | * Intense peer group involvement * Preoccupation with peer culture * Conformity | * Peer group and values recede in importance |
| Sexual | | * Increased interest in sexual anatomy * Anxieties and questions about pubertal changes * Limited capacity for intimacy | * Testing ability to attract partner * Initiation of relationships and sexual activity * Questions of sexual orientation | * Consolidation of sexual identity * Focus on intimacy and formation of stable relationships * Planning for future and commitment |

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| **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.

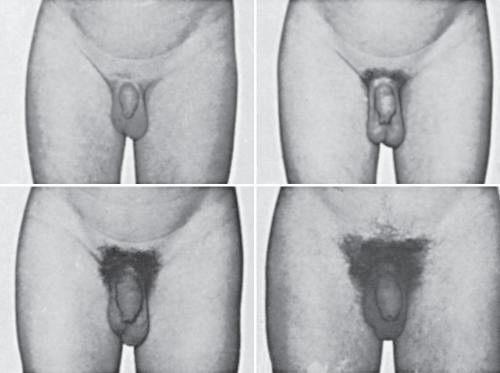
*From Tanner JM:* Growth at adolescence, *ed 2, Oxford, England, 1962, Blackwell Scientific.*

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| **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.*

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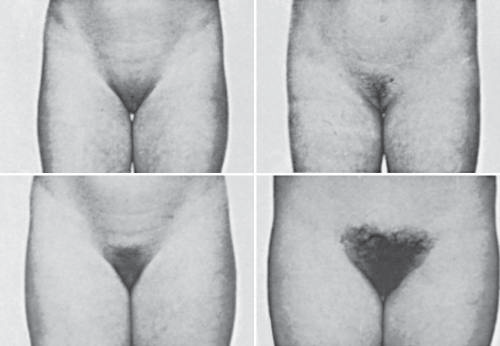
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A

B

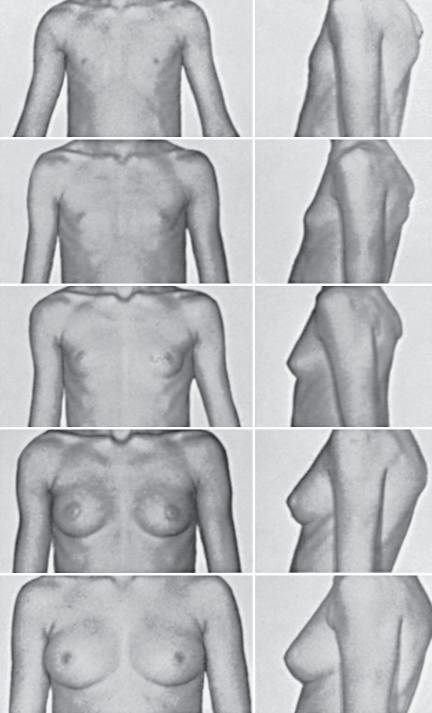


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**Figure 110-1** Sexual maturity ratings (2-5) of pubic hair changes in adolescent males *(A)* and females *(B)* (see Tables 110-2 and 110-3).

**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.)*

Pubic hair 5

Genital 5

Pubic hair 4 PHV

Pubic hair 3

Genital 4

Pubic hair 2

Genital 3

Genital 2

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

Breast 5

Pubic hair 5

Menarche

Breast 4

Pubic hair 4

Pubic hair 3

Breast 3 PHV

Pubic hair 2

Breast 2

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

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| **Table 110-4** | Summary of DSM 5 Diagnostic Criteria for Gender Dysphoria |
| GENDER DYSPHORIA IN CHILDREN (302.6) (F64.2)   1. 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. 2. 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   1. 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). 2. 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.*

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| **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.

**Chapter 112** ◆ Delivery of Healthcare to Adolescents **941**

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| **Table 112-3** Adolescent Screening Recommendations | | | | |
|  | | **11-14 YR OLD VISIT** | **15-17 YR OLD VISIT** | **18-21 YR OLD VISIT** |
| **Universal Screening** | | **Action** | **Action** | **Action** |
| Vision (once during each of 3 adolescent age groups) | | Snellen test | Snellen test | Snellen test |
| Dyslipidemia | | Lipid screen (once between 9-11 yr) | NA | Lipid screen (once between 18-21 yr) |
| **Selective Screening** | **Risk Assessment** | **Action If RA+** | **Action If RA+** | **Action If RA+** |
| 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  Sexually active and + on risk screening questions | Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)  Syphilis test | Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)  Syphilis test | Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)  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.](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.*

**Chapter 114** ◆ Substance Abuse **953**

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| **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 α-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-methylenedioxyamphetamine, 3,4-met hylenedioxymethamphetamine, 3,4-methylenedioxyethamphetamine, 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.*

* 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?

CRAFFT Mnemonic Tool

**Table 114-7**

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

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| **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.*

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* Substance Abuse **961**

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| **Table 114-17** | Signs and Symptoms of Intoxication and Withdrawal | | |
| **OPIATES** | | **AMPHETAMINES/COCAINE** | **BENZODIAZEPINES** |
| INTOXICATION  Behavior Apathy and sedation; disinhibition;  psychomotor retardation; impaired attention and judgment  Signs Drowsiness; slurred speech; pupillary  constriction (except anoxia from severe overdose—dilation); decreased level of consciousness  Overdose Respiratory depression; hypothermia  Withdrawal Craving to use; lacrimation; yawning;  rhinorrhea/sneezing; muscle aches or cramps; abdominal cramps; nausea/ vomiting/diarrhoea; sweating; dilated pupils; anorexia; irritability; tremor; piloerection/chills; restlessness; disturbed sleep | | 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  Dilated pupils; tachycardia (occasionally bradycardia, cardiac arrhythmias); hypertension; nausea/vomiting; sweating and chills; evidence of weight loss; dilated pupils; chest pain; convulsions  Sympathomimetic symptoms  Dysphoric mood (sadness/anhedonia); lethargy and fatigue; psychomotor retardation or agitation; craving; increased appetite; insomnia or hypersomnia; bizarre or unpleasant dreams | Euphoria; apathy and sedation; abusiveness or aggression; labile mood; impaired attention; anterograde amnesia; impaired psychomotor performance; interference with personal functioning  Unsteady gait; difficulty in standing; slurred speech; nystagmus; decreased level consciousness; erythematous skin lesions or blisters  Hypotension; hyperthermia; depression of gag reflex; coma  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 |

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| **Table 122-1** | Predisposition to Specific Infections in Humans | | | | |
| **PATHOGEN** | | **PRESENTATION** | **AFFECTED GENE/ CHROMOSOMAL REGION** | **FUNCTIONAL DEFECT** | **NOTES** |
| BACTERIA  *Streptococcus pneumoniae* | | Invasive disease  Invasive disease  Invasive disease, poor prognosis  MSMD  Leprosy | *IRAK-4, MyD88* | Impaired production of inflammatory cytokines following TLR stimulation  MAC deficiency Properdin deficiency  Impaired IFN-γ response to IL-12, IL-23  Impaired cellular response to IFN-γ  Unknown  Unknown | Also susceptible to other pyogenic bacteria such as *Staphylococcus aureus*  Also susceptible to *Salmonella typhi* infections  Possible E3-ubiquitin ligase dysfunction |
| *Neisseria* | | MAC components (C5, C6, C7, C8A, C8B, C8G, C9)  *PFC* |
| Mycobacteria | | *IL12B, IL12RB1, IKBKG* |
|  | | *IFNGR1, IFNGR2, STAT1* |
| *Mycobacterium leprae* | | *PARK2 LTA* |
| VIRUSES  Herpes simplex (type 1) | | Herpes simplex encephalitis  XLP  Epidermodysplasia verruciformis  WHIM | *UNC93B1, TLR3, STAT1* | Impaired production of type 1 IFNs | STAT1 and NEMO deficiency also predispose to HSV infections, amongst other infections  Fulminant infectious mononucleosis, malignant and nonmalignant lymphoproliferative disorders, dysgammaglobulinemia, autoimmunity  Altered neutrophil mobilization, T-cell lymphopenia, recurrent bacterial respiratory infections chronic cutaneous/genital papillomavirus disease |
| Epstein-Barr virus | | *SH2DIA XIAP/BIRC4* | SAP deficiency XIAP deficiency |
| Human papillomaviruses | | *EVER1/TMC6 EVER2/TMC8 CXCR4* | EVER1 deficiency EVER2 deficiency Truncated CXCR4 |
| PARASITES  *Plasmodium falciparum*  *Schistosoma mansoni Leishmania donovani* | | Malaria fever episodes Severe malaria  Severe malaria Intensity of infection Hepatic fibrosis Visceral leishmaniasis  (kala-azar) | 10p15 *GNAS IFNR1* 5q311-q33  6q22-q23, *IFNR1*  22q12, 2q35 *(NRAMP1)* | Unknown Unknown Unknown Unknown Unknown Unknown | Linkage studies  SNP association studies SNP association studies |
| YEAST  *Candida*  Deep dermatophytosis | | APECED, chronic candidiasis  Tissue invasion | *Aire, STAT1, CARD9*  *CARD9* | Unknown  Unknown | APS-1 chronic candidiasis, chronic hyperthyroidism, Addison disease  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.*

## lmmunology

**Chapter 122** ◆ Evaluation of Suspected Immunodeficiency **1001**

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| **Table 122-2** | Characteristic Clinical Patterns in Some Primary Immunodeficiencies |
| **FEATURES DIAGNOSIS** | |
| IN NEWBORNS AND YOUNG INFANTS (0-6 MO)  Hypocalcemia, unusual facies DiGeorge anomaly and ears, heart disease  Delayed umbilical cord Leukocyte adhesion defect detachment, leukocytosis,  recurrent infections  Persistent thrush, failure to Severe combined thrive, pneumonia, diarrhea immunodeficiency  Bloody stools, draining ears, Wiskott-Aldrich syndrome atopic eczema  *Pneumocystis jiroveci* X-linked hyper-IgM syndrome pneumonia, neutropenia,  recurrent infections | |
| IN INFANTS AND YOUNG CHILDREN (6 MO-5 YR)  Severe progressive infectious X-linked lymphoproliferative mononucleosis syndrome  Recurrent staphylococcal Hyper-IgE syndrome abscesses, staphylococcal  pneumonia with pneumatocele formation, coarse facial features, pruritic dermatitis  Persistent thrush, nail dystrophy, Chronic mucocutaneous endocrinopathies candidiasis  Short stature, fine hair, severe Cartilage hair hypoplasia with varicella short-limbed dwarfism  Oculocutaneous albinism, Chédiak-Higashi syndrome recurrent infection  Abscesses, suppurative Chronic granulomatous  lymphadenopathy, antral disease outlet obstruction, pneumonia,  osteomyelitis | |
| IN OLDER CHILDREN (OLDER THAN 5 YR) AND ADULTS  Progressive dermatomyositis X-linked agammaglobulinemia with chronic enterovirus  encephalitis  Sinopulmonary infections, Ataxia-telangiectasia neurologic deterioration,  telangiectasia  Recurrent neisserial meningitis C6, C7, or C8 deficiency Sinopulmonary infections, Common variable  splenomegaly, autoimmunity, immunodeficiency malabsorption | |

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| **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 (*Streptococcus pneumoniae, Haemophilus, Pneumocystis jiroveci, Staphylococcus aureus, Pseudomonas* 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 |

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| **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: *Candida* and  *Pneumocystis jiroveci* | Bacteria: pneumococci, streptococci, staphylococci, *Haemophilus, Campylobacter, Mycoplasma*  Viruses: enterovirus\*  Fungi and parasites: giardia, cryptosporidia | Bacteria: staphylococci, *Pseudomonas, Serratia, Klebsiella, Salmonella* | Bacteria: pneumococci,  *Neisseria* |
|  | Fungi and parasites: *Candida, Nocardia, Aspergillus* |
| 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 Autoimmunity  by maternal engraftment or Lymphoreticular malignancy: nonirradiated blood lymphoma, thymoma  transfusion Postvaccination paralytic Postvaccination disseminated polio  BCG or varicella Hypocalcemic tetany in  infancy† | | Prolonged attachment of umbilical cord, poor wound healing | Autoimmune disorders: SLE, vasculitis, dermatomyositis, scleroderma, glomerulonephritis, angioedema |

\*X-linked (Bruton) agammaglobulinemia.

†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.*

\*Lymphocyte phenotyping includes enumeration of B, T, and NK cells.



Hemolytic complement; Respiratory burst assay; sweat chloride test; mucosal cilia biopsy

Genetic/molecular testing

T-cell disorders

B-cell, phagocytic, and complement disorders

Recurrent infections

Viral/fungal/opportunistic infections

Complete blood count/

differential; delayed type hypersensitivity (DTH) testing; human immunodeficiency (HIV) testing

Lymphopenia or Secondary

absent DTH and immune HIV-negative suppression

(e.g., HIV)

Lymphocyte phenotyping;\* mitogen/antigen stimulation

Genetic/molecular testing; cytokine/ enzyme assays

Bacterial infections

Complete blood count/ manual differential; serum immunoglobulins (IgG, IgM, IgA, IgE); specific antibody responses

Genetic/molecular testing

Abnormal neutrophil counts

High counts;

repeat counts; CD11/18

assay

Low counts;

serial counts antineutrophil antibody; bone marrow biopsy

Lymphocyte

phenotyping;\* antigen stimulation

Normal

immunoglobulins neutrophil counts

Low immuno-

globulins; poor/ absent antibody responses

**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.)*

**Chapter 122** ◆ Evaluation of Suspected Immunodeficiency **1003**

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

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| **Table 122-6** | Initial Screening Immunologic Testing of the Child with Recurrent Infections |
| COMPLETE BLOOD COUNT, MANUAL DIFFERENTIAL, AND ERYTHROCYTE SEDIMENTATION RATE  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) | |
| SCREENING TESTS FOR B-CELL DEFECTS  Immunoglobulin (Ig) A measurement; if abnormal, IgG and IgM measurement Isohemagglutinins  Antibody titers to blood group substances, tetanus, diphtheria, *Haemophilus influenzae*, and pneumococcus | |
| SCREENING TESTS FOR T-CELL DEFECTS  Absolute lymphocyte count (normal result indicates T-cell defect unlikely)  Flow cytometry to examine for the presence of naïve T cells (CD3+CD45RA+ cells) | |
| SCREENING TESTS FOR PHAGOCYTIC CELL DEFECTS  Absolute neutrophil count Respiratory burst assay | |
| SCREENING TEST FOR COMPLEMENT DEFICIENCY  CH50 | |

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15×103

Mean Range

|  |  |
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| **Table 126-5** | Diagnostic Criteria for Autoimmune Lymphoproliferative Syndrome |
| REQUIRED   1. Chronic nonmalignant lymphoproliferation (>6 mo lymphadenopathy and/or splenomegaly) 2. 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*   1. Elevated biomarkers (Any of following)    1. Plasma soluble FASL >200 pg/mL    2. Plasma IL-10 >20 pg/mL    3. Plasma or serum vitamin B12 >1500 ng/L    4. Plasma IL-18 >500 pg/mL 2. Immunohistochemical findings consistent with ALPS as   determined by experienced histopathologist   1. Autoimmune cytopenias and polyclonal hypergammaglobulinemia 2. 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 | |

10×103

5×103

0 1 2 5 10 15 20

**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 Biologi- cal Handbooks. Washington, DC, 1961, Federation of American Societ- ies for Experimental Biology.)*

*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.*

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| **Table 122-7** | Laboratory Tests in Immunodeficiency |
| **SCREENING TESTS ADVANCED TESTS RESEARCH/SPECIAL TESTS** | |
| B-CELL DEFICIENCY  IgG, IgM, IgA, and IgE levels B-cell enumeration (CD19 or CD20) Advanced B-cell phenotyping Isohemagglutinin titers Biopsies (e.g., lymph nodes)  Ab response to vaccine antigens (e.g., Ab responses to boosters or to new vaccines Ab responses to special antigens (e.g., tetanus, diphtheria, pneumococci, bacteriophage φX174), mutation analysis *Haemophilus influenzae*) | |
| T-CELL DEFICIENCY  Lymphocyte count T-cell subset enumeration (CD3, CD4, CD8) Advanced flow cytometry  Chest x-ray examination for thymic size\* Proliferative responses to mitogens, antigens, Enzyme assays (e.g., ADA, PNP)  allogeneic cells Thymic imaging  Delayed skin tests (e.g., *Candida*, tetanus HLA typing Mutation analysis  toxoid) Chromosome analysis T-cell activation studies Apoptosis studies Biopsies | |
| PHAGOCYTIC DEFICIENCY  WBC count, morphology Adhesion molecule assays (e.g., CD11b/CD18, Mutation analysis  selectin ligand)  Respiratory burst assay Mutation analysis Enzyme assays (e.g., MPO, G6PD, NADPH oxidase) | |
| COMPLEMENT DEFICIENCY  CH50 activity AH50, activity  C3 level Component assays  C4 level 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.*

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| **Table 122-8** 2003 Modified IUIS Classification | of Primary and | | Secondary Immunodeficiencies | |
| **GROUPS AND DISEASES** | **INHERITANCE** | **GROUPS AND DISEASES** | | **INHERITANCE** |
| A. PREDOMINANTLY ANTIBODY DEFICIENCIES  XL agammaglobulinemia AR agammaglobulinemia Hyper-IgM syndromes   1. CD40L defect 2. AID defect 3. CD40 defect 4. UNG defect 5. Other hyper-IgM defects Ig heavy-chain gene deletions κ Chain deficiency mutations Selective IgA deficiency   Common variable immunodeficiency | XL AR  XL and AR XL  AR AR AR AR AR AR AD AD | F. COMPLEMENT DEFICIENCIES  C1q deficiency C1r deficiency C4 deficiency C2 deficiency C3 deficiency C5 deficiency C6 deficiency C7 deficiency C8α deficiency  C8β deficiency  C9 deficiency  C1 inhibitor Factor I deficiency  Factor H deficiency Factor D deficiency Properdin deficiency | | AR AR AR AR AR AR AR AR AR AR AR AD AR AR AR XL |
| B. SEVERE COMBINED IMMUNODEFICIENCIES  *T* **−***B* **+***NK***−** *SCID*   1. X-linked (γc deficiency) 2. Autosomal recessive (Jak3 deficiency)   *T* **−***B* **+***NK* **+** *SCID*   1. IL-7 Rα deficiency 2. CD3δ, CD3ε, or CD3ζ deficiencies 3. CD45 deficiency   *T* **−***B***−***NK***+** *SCID*   1. RAG-1/2 deficiency 2. Artemis defect   *Omenn Syndrome*   1. RAG-1/2 deficiency 2. IL-7Rα deficiency 3. γc deficiency   *Combined Immunodeficiencies*   1. Purine nucleoside phosphorylase deficiency b CD8 deficiency (ZAP-70 defect)   c. MHC class II deficiency  d. MHC class I deficiency caused by TAP-1/2 mutations  Reticular dysgenesis | XL AR  AR AR AR  AR AR  AR AR XL  AR AR AR AR  AR |
| G. IMMUNODEFICIENCY ASSOCIATED WITH OR SECONDARY TO OTHER DISEASES  *Chromosomal Instability or Defective Repair*  Bloom syndrome Fanconi anemia ICF syndrome  Nijmegen breakage syndrome Seckel syndrome  Xeroderma pigmentosum *Chromosomal Defects* Down syndrome  Turner syndrome  Chromosome 18 rings and deletions  *Skeletal Abnormalities*  Short-limbed skeletal dysplasia Cartilage-hair hypoplasia  *Immunodeficiency with Generalized Growth Retardation*  Schimke immuno-osseous dysplasia Immunodeficiency with absent thumbs Dubowitz syndrome  Growth retardation, facial anomalies, and immunodeficiency  Progeria (Hutchinson-Gilford syndrome) *Immunodeficiency with Dermatologic Defects* Partial albinism  Dyskeratosis congenita Netherton syndrome Acrodermatitis enteropathica Anhidrotic ectodermal dysplasia Papillon-Lefèvre syndrome *Hereditary Metabolic Defects* Transcobalamin 2 deficiency Methylmalonic acidemia  Type 1 hereditary orotic aciduria  Biotin-dependent carboxylase deficiency Mannosidosis  Glycogen storage disease, type 1b Chédiak-Higashi syndrome *Hypercatabolism of Immunoglobulin* Familial hypercatabolism  Intestinal lymphangiectasia | | |
| C. OTHER CELLULAR IMMUNODEFICIENCIES  Wiskott-Aldrich syndrome Ataxia-telangiectasia DiGeorge anomaly | XL AR  ? |
| D. DEFECTS OF PHAGOCYTIC FUNCTION  *Chronic Granulomatous Disease*   1. XL 2. AR    1. p22 phox deficiency    2. p47 phox deficiency    3. p67 phox deficiency Leukocyte adhesion defect 1 Leukocyte adhesion defect 2 Neutrophil G6PD deficiency Myeloperoxidase deficiency Secondary granule deficiency Shwachman syndrome   Severe congenital neutropenia (Kostmann) Cyclic neutropenia (elastase defect) Leukocyte mycobacterial defects  IFN-γR1 or R2 deficiency IFN-γR1 deficiency  IL-12Rβ1 deficiency  IL-12p40 deficiency  STAT1 deficiency | XL AR  AR AR XL AR AR AR AR AR AR AR AD AR AR AD |
| H. OTHER IMMUNODEFICIENCIES  Hyper-IgE syndromes  Chronic mucocutaneous candidiasis Chronic mucocutaneous candidiasis with  polyendocrinopathy (APECED)  Hereditary or congenital hyposplenia or asplenia Ivemark syndrome  IPEX syndromes  Ectodermal dysplasia (NEMO defect) | | AD and AR AR  XL XL |
| E. IMMUNODEFICIENCIES ASSOCIATED WITH LYMPHOPROLIFERATIVE DISORDERS  Fas deficiency  Fas ligand deficiency  FLICE or caspase 8 deficiency Unknown (caspase 3 deficiency) | AD |

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-associating 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.*

**Chapter 126** ◆ Primary Combined Antibody and Cellular Immunodeficiencies **1029**

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| **Table 126-3** | Hyperimmunoglobulin | E | Syndromes | |
|  | | **AUTOSOMAL DOMINANT OR SPORADIC (JOB SYNDROME)** | | **AUTOSOMAL RECESSIVE** |
| Gene | | *STAT3* | | *DOCK8:* less often *TYK2* |
| INFECTIONS  Sinopulmonary Recurrent bacterial  Pneumatoceles/bronchiectasis Fungal  *Cutaneous* Abscesses Viral  Mucocutaneous candidiasis | | *S. aureus*, pneumococcus, *H. influenzae*  Common Aspergillus species  *S. aureus* No Common | | *S. aureus*, pneumococcus, *H. influenzae*  No No  *S. aureus*  HPV, HSV, VZV, MCV  Common |
| ATOPIC DISORDERS  Newborn eosinophilic pustules Eczema  Asthma Allergies/Anaphylaxis | | Common Common No  No | | No Common Common Common |
| MUSCULOSKELETAL  Osteopenia, pathologic fractures Scoliosis  Retained primary teeth Hyperextensible | | Common Common Common Common | | No No No No |
| OTHER FEATURES  Coarse facies\*  Coronary artery tortuosity/aneurysm UBO on brain MRI  Lymphomas Cutaneous malignancy Mortality | | Common in adolescent Common  Common Yes  No Adulthood | | No No No  Higher incidence Yes  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 T2 MRI; VZV, varicella-zoster virus.

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| **Table 126-4** | Infection in the Host Compromised by B- and T-Cell Immunodeficiency Syndromes |
| **IMMUNODEFICIENCY OPPORTUNISTIC ORGANISMS ISOLATED APPROACH TO TREATMENT**  **SYNDROME MOST FREQUENTLY OF INFECTIONS PREVENTION OF INFECTIONS** | |
| B-cell immunodeficiencies Encapsulated bacteria (*Streptococcus* 1. IVIG 200-800 mg/kg 1. Maintenance IVIG for patients *pneumoniae, Staphylococcus aureus,* 2. Vigorous attempt to obtain with quantitative and qualitative *Haemophilus influenzae*, and *Neisseria* specimens for culture defects in IgG metabolism *meningitidis*), *Pseudomonas aeruginosa,* before antimicrobial (400-800 mg/kg q 3-5 wk) *Campylobacter* sp., enteroviruses, therapy 2. In chronic recurrent respiratory rotaviruses, *Giardia lamblia,* 3. Incision and drainage if disease, vigorous attention to *Cryptosporidium* sp., *Pneumocystis* abscess present postural drainage  *jiroveci, Ureaplasma urealyticum*, and 4. Antibiotic selection on the 3. In selected cases (recurrent or  *Mycoplasma pneumoniae* basis of sensitivity data chronic pulmonary or middle ear), prophylactic administration of ampicillin, penicillin, or trimethoprim-sulfamethoxazole | |
| T-cell immunodeficiencies Encapsulated bacteria (*S. pneumoniae,* 1. Vigorous attempt to obtain 1. Prophylactic administration of *H. influenzae, S. aureus*), facultative specimens for culture trimethoprim-sulfamethoxazole intracellular bacteria (*Mycobacterium* before antimicrobial for prevention of *P. jiroveci tuberculosis*, other *Mycobacterium* sp., and therapy pneumonia  *Listeria monocytogenes*); *Escherichia coli;* 2. Incision and drainage if 2. Oral nonadsorbable  *P. aeruginosa; Enterobacter* sp.; *Klebsiella* abscess present antimicrobial agents to lower sp.; *Serratia marcescens; Salmonella* sp.; 3. Antibiotic selection on the concentration of gut flora *Nocardia* sp.; viruses (cytomegalovirus, basis of sensitivity data 3. No live virus vaccines or herpes simplex virus, varicella-zoster 4. Early antiviral treatment for bacillus Calmette-Guérin virus, Epstein-Barr virus, rotaviruses, herpes simplex, vaccine  adenoviruses, enteroviruses, respiratory cytomegalovirus, and 4. Careful tuberculosis screening syncytial virus, measles virus, vaccinia varicella-zoster viral  virus, and parainfluenza viruses); protozoa infections  (*Toxoplasma gondii* and *Cryptosporidium* 5. Topical and nonadsorbable sp.); and fungi (*Candida* sp., *Cryptococcus* antimicrobial agents *neoformans, Histoplasma capsulatum*, and frequently are useful  *P. jiroveci*) | |

IVIG, intravenous immunoglobulin.

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

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| **Table 126-6** | Clinical and Laboratory Features of IPEX and IPEX-Like Disorders | | | | | |
|  | | **IPEX** | **CD25** | **STAT5B** | **STAT1** | **ITCH** |
| AUTOIMMUNITY  Eczema Enteropathy Endocrinopathy Allergic disease Cytopenias Lung disease | | +++  +++  +++  +++  ++  + | +++  +++  ++  +  ++  ++ | ++  ++  +  +  ++  +++ | ++  ++  ++  ++  –  + | ++  ++  ++  ++  +++ |
| INFECTIONS  Yeast Herpes virus Bacterial  Associated features Serum  immunoglobulins Serum IgE  CD25 expression CD4+CD45RO  FOXP3 expression  IGF-1, IGFBP-3  Prolactin | | –  –  +/– None Elevated  Elevated Normal Elevated  Absent or normal Normal  Normal | ++  +++ (EBV/CMV)  ++  None  Elevated or normal  Normal or elevated Absent  Elevated Normal or low Normal Normal | –  ++ (VZV)  ++  Growth failure  Elevated or normal  Normal or elevated Normal or low Elevated  Normal or low Low  Elevated | +++  ++  ++  Vascular anomalies  Low, normal, or high  Normal or mildly elevated Normal  Normal or high Normal Normal Normal | –  –  +  Dysmorphic growth failure  Elevated  Elevated Not tested Not tested Not tested Not tested 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.*

**Benign**

Asymptomatic with no evidence of organ involvement

**Other**

Symptomatic without features of myeloproliferative or lymphocytic forms

**Episodic**

Cyclic angioedema and eosinophilia

**No T cell clone**

Aberrant immuno- phenotype or evidence of marked T cell activation

**Clonal T cells**

T cells often exhibit an abnormal immuno- phenotype

**CEL**

Clonal eosinophilia including *FIP1L1/ PDGFRA*

positive CEL

**Myeloproliferative HES**

Features of myeloproliferative disease without proof of clonality

**Familial**

Family history of documented persistent eosinophilia of unknown cause

**Associated**

Eosinophilia in association with a defined diagnosis, such as IBD or CSS

**Undefined**

**Overlap**

Organ restricted eosinophilic disorders

**Lymphocytic forms**

Populations of T cells secreting eosinophil hematopoietins

**Myeloproliferative forms**

**Hypereosinophilic syndromes (HESs)**

**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.)*

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| **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 β2 common chain (CD18) | Fucosylated proteins (e.g., sialyl-Lewisx, 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.*

**Chapter 129** ◆ Eosinophils **1039**

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| **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  *Tissue-Invasive Helminth Infections*  Trichinosis Toxocariasis Strongyloidosis Ascariasis Filariasis Schistosomiasis Echinococcosis  *Pneumocystis carinii* 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) |

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

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.*

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| **Table 130-2** | Clinical Disorders of Neutrophil Function | | | |
| **DISORDER** | | **ETIOLOGY** | **IMPAIRED FUNCTION** | **CLINICAL CONSEQUENCE** |
| DEGRANULATION ABNORMALITIES  Chédiak-Higashi syndrome Autosomal recessive; disordered Decreased neutrophil  coalescence of lysosomal granules; chemotaxis, degranulation, responsible gene is *CHSI/LYST*, and bactericidal activity; which encodes a protein platelet storage pool defect; hypothesized to regulate granule impaired NK function, failure fusion to disperse melanosomes  Specific granule deficiency Autosomal recessive; functional loss of Impaired chemotaxis and  myeloid transcription factor arising bactericidal activity; bilobed from a mutation or arising from nuclei in neutrophils; reduced expression of *Gfi-1* or defensins, gelatinase, *C/EBP*ε, which regulates specific collagenase, vitamin granule formation B12–binding protein, and  lactoferrin | | | | Neutropenia; recurrent pyogenic infections, propensity to develop marked hepatosplenomegaly  as a manifestation of the hemophagocytic syndrome |
| Recurrent deep-seated abscesses |
| ADHESION ABNORMALITIES  Leukocyte adhesion deficiency 1  Leukocyte adhesion deficiency 2  Leukocyte adhesion deficiency 3 (LAD-1 variant syndrome) | | Autosomal recessive; absence of CD11/CD18 surface adhesive glycoproteins (β2 integrins) on leukocyte membranes most  commonly arising from failure to express CD18 messenger RNA  Autosomal recessive; loss of fucosylation of ligands for selectins and other glycol-conjugates arising from mutations of the GDP-fucose transporter  Autosomal recessive; impaired integrin function arising from mutations of *FERMT3* which encodes kindlin-3 in hematopoietic cells; kindlin-3 binds to β-integrin and thereby transmits  integrin activation | Decreased binding of C3bi to neutrophils and impaired adhesion to ICAM1 and ICAM2  Decreased adhesion to activated endothelium expressing ELAM  Impaired neutrophil adhesion and platelet activation | Neutrophilia; recurrent bacterial infection associated with a lack of pus formation |
| Neutrophilia; recurrent bacterial infection without pus |
| Neutrophilia; recurrent infections, bleeding tendency |

###### Continued

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| **Table 130-2** Clinical Disorders of Neutrophil Function—cont’d |
| **DISORDER ETIOLOGY IMPAIRED FUNCTION CLINICAL CONSEQUENCE** |
| DISORDERS OF CELL MOTILITY  Enhanced motile responses; Autosomal recessive gene responsible Excessive accumulation of Recurrent fever, peritonitis, pleuritis,  FMF for FMF on chromosome 16 which neutrophils at inflamed sites, arthritis, and amyloidosis encodes for a protein called pyrin; which may be the result of  pyrin regulates caspase-1 and excessive IL-1β production thereby IL-1β secretion; mutated  pyrin may lead to heightened  sensitivity to endotoxin, excessive IL-1β production, and impaired monocyte apoptosis |
| DEPRESSED MOTILE RESPONSES  Defects in the generation of IgG deficiencies; C3 and properdin Deficiency of serum Recurrent pyogenic infections chemotactic signals deficiency can arise from genetic or chemotaxis and opsonic  acquired abnormalities; mannose- activities binding protein deficiency  predominantly in neonates  Intrinsic defects of the In the neonatal neutrophil there is Diminished chemotaxis Propensity to develop pyogenic neutrophil, e.g., LAD, diminished ability to express β2 infections  Chédiak-Higashi syndrome, integrins, and there is a qualitative specific granule deficiency, impairment in β2-integrin function neutrophil actin dysfunction,  neonatal neutrophils  Direct inhibition of neutrophil Ethanol, glucocorticoids, cyclic AMP Impaired locomotion and Possible cause for frequent mobility, e.g., drugs ingestion; impaired infections; neutrophilia seen with  adherence epinephrine arises from cyclic AMP release from endothelium  Immune complexes Bind to Fc receptors on neutrophils in Impaired chemotaxis Recurrent pyogenic infections patients with rheumatoid arthritis,  systemic lupus erythematosus, and other inflammatory states  Hyper-IgE syndrome Autosomal dominant; responsible Impaired chemotaxis at times; Recurrent skin and sinopulmonary gene is *Stat3* impaired regulation of infections, eczema,  cytokine production mucocutaneous candidiasis, eosinophilia, retained primary teeth, minimal trauma fractures, scoliosis, and characteristic facies  Hyper-IgE syndrome–AR Autosomal recessive; more than 1 High IgE levels, impaired Recurrent pneumonia without gene likely contributes to its etiology lymphocyte activation to pneumatoceles sepsis, enzyme,  staphylococcal antigens boils, mucocutaneous candidiasis,  neurologic symptoms, eosinophilia |
| MICROBICIDAL ACTIVITY  Chronic granulomatous X-linked and autosomal recessive; Failure to activate neutrophil Recurrent pyogenic infections with disease failure to express functional gp91*phox* respiratory burst leading to catalase-positive microorganisms  in the phagocyte membrane in failure to kill catalase- p22*phox* (AR). Other AR forms of CGD positive microbes arise from failure to express protein  p47*phox* or p67*phox*  G6PD deficiency Less than 5% of normal activity of Failure to activate NADPH- Infections with catalase-positive G6PD dependent oxidase, and microorganisms  hemolytic anemia  Myeloperoxidase deficiency Autosomal recessive; failure to process H2O2-dependent antimicrobial None  modified precursor protein arising activity not potentiated by from missense mutation myeloperoxidase  Rac2 deficiency Autosomal dominant; dominant Failure of membrane Neutrophilia, recurrent bacterial negative inhibition by mutant protein receptor–mediated O2− infections  of Rac2-mediated functions generation and chemotaxis  Deficiencies of glutathione AR; failure to detoxify H2O2 Excessive formation of H2O2 Minimal problems with recurrent reductase and glutathione pyogenic infections  synthetase |

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.*

Infections

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**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, Helsop H, Weitz J, Anastasi J, editors:* Hematology: basic principles and practice, *ed 6, Philadelphia, 2012, WB Saunders, pp. 655–674.)*

* Family history of recurrent infection
* Gingivitis
* Chronic diarrhea
* Infections with absence of neutrophilic infiltration
*  CRP/SED rate
* Splenomegaly or hepatomegaly
* Moderate lymphadenopathy
* Inflammatory anemia
* Recurrent deep tissue infection (e.g., **lymphadenitis, pneumonia, osteomyelitis, liver abscess**)
* Unusual or resistant infection (*S. aureus,* Pseudomonas, Klebsiella, **Serratia,** Candida, **Aspergillus, Nocardia**)
* **Periodontal disease or tooth loss**
* Omphalitis

Initial evaluation

* CBC, ESR, r/o lymphopenia
* Quantitative immunoglobulins
* lgE
* Immunoglobulin subsets
* T+B cell quantitation and subsets
* PHA stimulation
* Response to tetanus immunization
* HIV

Neutrophil evaluation

* CBC
* NBT slide test or DHR by FACS
* CD18/CD11b by FACS
* CD15a by FACS
* Bombay blood group
* (Chemotaxis)

**Unusual frequency or type of infection**

History and physical

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| **Table 131-1** Diagnostic Approach for Patients with Leukopenia | |
| **EVALUATION** | **ASSOCIATED CLINICAL DIAGNOSES** |
| INITIAL EVALUATION   * History of acute or chronic leukopenia * General medical history * Physical examination: stomatitis, gingivitis, dental defects, congenital anomalies * Spleen size * History of drug exposure * Complete blood count with differential and reticulocyte counts | 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 |
| IF ANC **<**1,000/**µ**L  *Evaluation of Acute Onset Neutropenia*   * Repeat blood counts in 3-4 weeks * Serology and cultures for infectious agents * Discontinue drug(s) associated with neutropenia * Test for antineutrophil antibodies * Measure quantitative immunoglobulins (G, A, and M), lymphocyte subsets | 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 |
| IF ANC **<**500/**µ**L ON 3 SEPARATE TESTS   * Bone marrow aspiration and biopsy, with cytogenetics * Glucocorticoid stimulation test * Serial CBCs (3/wk for 6 wk) * Exocrine pancreatic function * Skeletal radiographs | 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 |
| IF ALC **<**1000/**µ**L   * Repeat blood counts in 3-4 weeks | Transient leukopenia (e.g., viral) |
| IF ALC **<**1000/**µ**L ON 3 SEPARATE TESTS   * HIV-1 antibody or RNA test * Quantitative immunoglobulins (G, A, and M), lymphocyte subsets | HIV-1 infection, AIDS  Congenital or acquired disorders of immune function |
| IF THERE IS PANCYTOPENIA   * Bone marrow aspiration and biopsy * Bone marrow cytogenetics * Vitamin B12 and folate levels | 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.

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| **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 |

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| **Table 131-3** | Acquired Disorders of Myeloid Cells | | |
| **CAUSE** | | **ETIOLOGIC FACTORS/AGENTS** | **ASSOCIATED FINDINGS** |
| Aplastic anemia | | Stem cell destruction and depletion | Pancytopenia |
| Vitamin B12 or folate deficiency | | Malnutrition; congenital deficiency of B12 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  *PIG-A* gene | Pancytopenia, thrombosis |

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| **Table 131-4** | | Infections Associated with Neutropenia |
| Viral | Cytomegalovirus, dengue, Epstein-Barr virus, hepatitis viruses, HIV, influenza, measles, parvovirus B19, rubella, varicella | |
| Bacterial | *Anaplasma* (formerly *Ehrlichia*) *phagocytophilum,* 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 | |

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| **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 |

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| **Table 131-6** | Intrinsic Disorders of Myeloid Precursor Cells | | |
| **SYNDROME** | | **INHERITANCE (GENE)** | **CLINICAL FEATURES (INCLUDING STATIC NEUTROPENIA UNLESS OTHERWISE NOTED)** |
| PRIMARY DISORDERS OF MYELOPOIESIS  Cyclic neutropenia AD *(ELANE)*  Severe congenital neutropenia AD (primarily *ELANE,* also *GFI* and others)  AR *(G6PC3, HAX1)* (*HAX1* = Kostmann  syndrome) | | | Periodic oscillation (21-day cycles) in ANC Risk of MDS/AML  *G6PC3:* cardiac and urogenital anomalies, venous angiectasias; *HAX1:* neurologic abnormalities, risk of MDS/AML  Neutropenic variant of Wiskott-Aldrich syndrome |
| XL *(WAS)* | | |
| DISORDERS OF MOLECULAR PROCESSING  Shwachman-Diamond syndrome Ribosomal defect: AR *(SBDS)*  Dyskeratosis congenita Telomerase defects: XL *(DKC1),* AD  *(TERC),* AR *(TERT)* | | | Pancreatic insufficiency, metaphysical dysostosis, bone marrow failure, MDS/AML  Nail dystrophy, leukoplakia, abnormal and carious teeth, lacey reticulated hyperpigmentation of the skin, bone marrow failure |
| DISORDERS OF VESICULAR TRAFFICKING  Chédiak-Higashi syndrome AR *(LYST)* | | | Partial albinism, giant granules in myeloid cells, platelet storage pool defect, impaired natural killer cell function, HLH  Partial albinism, impaired natural killer cell function, neurological impairment, HLH  Partial albinism, pigmentary retinopathy, developmental delay, facial dysmorphism  Cyclic neutropenia, partial albinism, HLH Partial albinism, decreased B and T cells neutrophil dysfunction, bone marrow fibrosis,  nephromegaly |
| Griscelli syndrome, type II | | AR *(RAB27a)* |
| Cohen syndrome | | AR *(COH1)* |
| Hermansky-Pudlak syndrome, type II p14 deficiency  VPS45 defects | | AR *(AP3P1)*  Probable AR *(MAPBPIP)*  AR *(VPS45)* |
| DISORDERS OF METABOLISM  Glycogen storage disease, type 1b Barth syndrome  Pearson syndrome | | AR *(G6PT1)*  XL *(TAZ1)*  Mitochondrial (DNA deletions) | Hepatic enlargement, growth retardation, impaired neutrophil motility  Episodic neutropenia, dilated cardiomyopathy, methylglutaconic aciduria  Episodic neutropenia, pancytopenia; defects in exocrine pancreas, liver, and kidneys |
| NEUTROPENIA IN DISORDERS OF IMMUNE FUNCTION  Common variable immunodeficiency Familial, sporadic *(TNFRSF13B)*  IgA deficiency Unknown (Unknown or *TNFRSF13B*) Severe combined immunodeficiency AR, XL (multiple loci)  Hyper-IgM syndrome XL *(HIGM1)*  WHIM syndrome AD *(CXCR4)*  Cartilage-hair hypoplasia AR *(RMKP)*  Schimke immunoosseous dysplasia Probable AR *(SMARCAL1)*  X-linked agammaglobulinemia BTK | | | Hypogammaglobulinemia, other immune system defects Decreased IgA  Absent humoral and cellular immune function Absent IgG, elevated IgM, autoimmune cytopenias  Warts, hypogammaglobulinemia, infections, myelokathexis Lymphopenia, short-limbed dwarfism, metaphyseal  chondrodysplasia, fine sparse hair  Lymphopenia, pancytopenia, spondyloepiphyseal dysplasia, growth retardation, renal failure  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, Briton tyrosine kinase.

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| **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  Other Postsplenectomy, tumors, Hodgkin disease | |
| Lifelong | Congenital asplenia  Hereditary disorders Familial cold urticaria,  hereditary neutrophilia, leukocyte adhesion deficiencies, periodic fever syndromes | |

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| **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 Cartilage-hair hypoplasia, ataxia- lymphopoietic stem telangiectasia, SCID, thymoma, Wiskott- cells Aldrich syndrome | |

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

* 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
* Omenn 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 thromboasthenia, 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

Indications for Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric Diseases

**Table 135-1**

* 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

Indications to Autologous Hematopoietic Stem Cell Transplantation for Pediatric Diseases

**Table 136-1**

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| **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 Inflammatory bowel disease, diseases polyarteritis nodosa, rheumatoid  arthritis, sarcoidosis, systemic lupus erythematosus | |
| Miscellaneous Cirrhosis, drug reaction, postsplenectomy, recovery from bone marrow suppression | |

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| **Table 132-1** | Causes of Neutrophilia |
| **TYPE CAUSE EXAMPLE** | |
| Acute Bacterial infections acquired Surgery  Acute stress Burns, diabetic ketoacidosis, heat stroke, postneutropenia rebound, exercise  Drugs Corticosteroids, epinephrine, hematopoietic growth factors, lithium | |
| Chronic Chronic inflammation Inflammatory bowel disease, acquired 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  Other Postsplenectomy, tumors, Hodgkin disease | |
| Lifelong Congenital asplenia  Hereditary disorders Familial cold urticaria,  hereditary neutrophilia, leukocyte adhesion deficiencies, periodic fever syndromes | |

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| **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 Inflammatory bowel disease, diseases polyarteritis nodosa, rheumatoid  arthritis, sarcoidosis, systemic lupus erythematosus | |
| Miscellaneous Cirrhosis, drug reaction, postsplenectomy, recovery from bone marrow suppression | |

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# Allergic Disorders

**1080 Part XV** ◆ Allergic Disorders

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| **Table 141-2** | Nonallergic Diseases Associated with Increased Serum IgE Concentrations |
| PARASITIC INFESTATIONS  Ascariasis Capillariasis Echinococcosis Fascioliasis Filariasis Hookworm Onchocerciasis Malaria Paragonimiasis Schistosomiasis Strongyloidiasis Trichinosis  Visceral larva migrans | |
| INFECTIONS  Allergic bronchopulmonary aspergillosis Candidiasis, systemic Coccidioidomycosis  Cytomegalovirus mononucleosis  Human immunodeficiency virus type 1 infections Infectious mononucleosis (Epstein-Barr virus) Leprosy  Pertussis  Viral respiratory infections | |
| IMMUNODEFICIENCY  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 | |
| NEOPLASTIC DISEASES  Hodgkin disease IgE myeloma Bronchial carcinoma | |
| OTHER DISEASES AND DISORDERS  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 | |

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

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

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 141-3** | 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 dermographism | | 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 |

**Chapter 142** ◆ Principles of Treatment of Allergic Disease **1083**

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 polyposis 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

Causes of Nonallergic Rhinitis

**Table 143-1**

|  |  |  |
| --- | --- | --- |
| **Table 142-2** | Classification of Antihistamines (H1-Antagonists) | |
| **CLASS** | | **EXAMPLES** |
| ETHYLENEDIAMINES  First-generation | | Antazoline, pyrilamine, tripelennamine |
| TYPE II ETHANOLAMINES  First-generation | | Carbinoxamine, clemastine, diphenhydramine |
| TYPE III ALKYLAMINES  First-generation  Second-generation | | Brompheniramine, chlorpheniramine, triprolidine  Acrivastine |
| TYPE IV PIPERAZINES  First-generation Second-generation | | Cyclizine, hydroxyzine, meclizine Cetirizine, levocetirizine |
| TYPE V PIPERIDINES  First-generation Second-generation | | Azatadine, cyproheptadine, ketotifen Fexofenadine, loratadine, desloratadine |
| TYPE VI PHENOTHIAZINES  First-generation Methdilazine, promethazine | | |

**Intermittent symptoms**

* <4 days/week
* *or* <4 weeks at a time

**Persistent symptoms**

* ≥4 days a week
* *and/or* ≥ 4 weeks at a time



**Mild**

* Normal sleep
* Normal daily activities
* Normal work and school
* No troublesome symptoms

**Moderate-to-severe**

One or more items

* Abnormal sleep
* Impairment of daily activities, sport and leisure
* Difficulties caused at school or work
* Troublesome symptoms

**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 |

**Chapter 143** ◆ Allergic Rhinitis **1091**

**Rhinitis**

Positive skin-prick test and/or nasal allergen challenge

**Chronic rhinosinusitis**

Exclude predisposing causes

* Cystic fibrosis
* Primary ciliary dyskinesia
* Immunodeficiency
* Immunopathology
* Polyps

**Acute rhinosinusitis**

**Non-allergic rhinitis with eosinophilia**

Consider aspirin, entopy (local nasal IgE)

**Immunopathologic findings**

* Churg-Strauss syndrome
* Wegener granulomatosis
* Sarcoidosis
* Relapsing polychondritis
* Systematic lupus erythematosus

**Structural abnormalities**

* Deviated septum
* Nasal valve dysfunction
* Nasal polyps
* Foreign body
* Adenoidal hypertrophy
* Choanal atresia
* Cerebral fluid leak
* Nasal or CNS tumors

**Hormonal**

* Pregnancy
* Menstrual cycle
* Puberty
* Hormone replacement therapy
* Acromegaly
* Hypothyroidism

**Drug-induced**

* Oral contraceptive
* Rhinitis medicamentosa
* Antihypertensives
* Cocaine abuse
* Aspirin or NSAID

**Others**

* Non-infective,

non-allergic rhinitis Neurogenic (gustatory, emotional, cold-air induced)

* Atrophic
* Gastro-esophageal reflux
* Idiopathic

Infective

Non-infective

Negative skin-prick test and nasal allergen challenge

Allergic

Non-allergic

Occupational (allergic and non-allergic)

**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 Clarinex Reditabs\* Clarinex Tablets Clarinex Syrup | | 2.5 mg, 5 mg  5 mg  0.5 mg/mL | Orally disintegrating tablet Tabs  Syrup | Children 6-11 mo of age: 1 mg once daily Children 12 mo-5 yr of age: 1.25 mg once daily 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 H1 ANTAGONISTS  **GENERIC/BRAND STRENGTH** | | | **FORMULATIONS** | **DOSING** |
| Chlorpheniramine maleate Chlor-Trimeton  Chlor-Trimeton Syrup | | 4 mg  2 mg/5 mL | Tablets Syrup | 2-5 yr: 1 mg every 4-6 hr (maximum 6 mg/day)  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 H1 ANTAGONISTS  Cetirizine  Children’s Zyrtec Allergy Syrup 1 mg/mL Children’s Zyrtec 5 mg, 10 mg Chewable  Zyrtec tablets 5 mg, 10 mg  Zyrtec Liquid Gels 10 mg | | | Syrup  Chewable tablets Tablets  Liquid-filled gels | 6-12 mo: 2.5 mg once daily  12-23 mo: initial: 2.5 mg once daily; dosage may be increased to 2.5 mg twice daily  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  ≥6 yr: 5-10 mg/day as a single dose or divided  into 2 doses |
| Fexofenadine HCl  Children’s Allegra 30 mg  Children’s Allegra ODT\* 30 mg  Children’s Allegra Oral 30 mg/5 mL Suspension  Allegra Tabs 30, 60, 180 mg | | | Tablet  Orally disintegrating tablets Suspension  Tablet | 6 mo-<2 yr: 15 mg (2.5 mL) every 12 hr  >2-11 yr: 30 mg every 12 hr  >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 Phenylephrine HCl Sudafed Sinus & Allergy | | 4 mg  10 mg | Tablets | >12 yr: 1 tablet every 4 hr not to exceed 6 tablets per day |
| Cetirizine + pseudoephedrine Zyrtec-D 12 hour | | 5 mg cetirizine + 120 mg pseudoephedrine | Extended release tablet | >12 yr: 1 tablet every 12 hr |

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

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| **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:* Symptomatic relief of rhinorrhea  *M:* 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:* Treatment of rhinorrhea, sneezing, and nasal pruritus  *M:* Antagonism of histamine H1-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:* AR.  *M:* Inhibition of mast cell degranulation  >2 yr: 1 spray tid-qid; max ×6 /day | | Not effective immediately; requires frequent administration |
| Oxymetazoline: Afrin, Nostrilla | | *I:* Symptomatic relief of nasal mucosal Excessive dosage may cause profound central congestion nervous system (CNS) depression  *M:* Adrenergic agonist, vasoconstricting agent Use in excess of 3 days may result in severe 0.05% solution: instill 2-3 sprays into each rebound nasal congestion  nostril twice daily; therapy should not Do not repeat more than once a month exceed 3 days 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:* Symptomatic relief of nasal mucosal congestion  *M:* 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 |

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| **Table 143-6** | Intranasal Inhaled Corticosteroids | | |
| **DRUG** | | **INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING** | **COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING** |
| Beclomethasone:  Beconase AQ (42 μg/spray) Qnasl (80 μg/spray) | | *I:* AR  *M:* 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)  Fluticasone propionate (available as a generic preparation):  Flonase (50 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  *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  *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis  Monitor growth  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 14 to 1 inch into nostril, keeping  2  bottle upright, and close off the other nostril. Breathe in through nose. While inhaling, press pump to release spray |

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| **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 | |

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

Early Childhood Risk Factors for Persistent Asthma

**Table 144-1**

\*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.](http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm)

AHR, airways hyperresponsiveness.

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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** |
| SYMPTOMS  Breathlessness | While walking | While at rest (infant—softer, shorter cry, difficulty feeding)  Prefers sitting Phrases  Usually agitated | While at rest (infant— stops feeding) | Drowsy or confused |
| Talks in Alertness | Can lie down Sentences  May be agitated | Sits upright Words  Usually agitated |
| SIGNS  Respiratory rate†  Use of accessory muscles; suprasternal retractions  Wheeze  Pulse rate (beats/min)‡ Pulsus paradoxus | Increased Usually not  Moderate; often only end-expiratory  <100  Absent  <10 mm Hg | Increased Commonly  Loud; throughout exhalation  100-120  May be present 10-25 mm Hg | Often >30 breaths/min Usually  Usually loud; throughout inhalation and exhalation  >120  Often present  >25 mm Hg (adult) 20-40 mm Hg (child) | Paradoxical thoracoabdominal movement  Absence of wheeze  Bradycardia  Absence suggests respiratory muscle fatigue |
| FUNCTIONAL ASSESSMENT  Peak expiratory flow ≥70% Approx. 40-69% or response <40% <25%§  (value predicted or lasts <2 hr  personal best)  Pao2 (breathing air) Normal (test not usually ≥60 mm Hg (test not usually <60 mm Hg; possible necessary) necessary) cyanosis  *and/or*  PCO2 <42 mm Hg (test not <42 mm Hg (test not usually ≥42 mm Hg; possible usually necessary) necessary) respiratory failure  SaO2 (breathing air) at sea >95% (test not usually 90-95% (test not usually <90% level necessary) necessary)  Hypercapnia (hypoventilation) 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.

†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.

‡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.*](http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm)

**Chapter 144** ◆ Childhood Asthma **1099**

Spirometry (in clinic):

* Airflow limitation:
* Low FEV1 (relative to percentage of predicted norms)
* FEV1:FVC ratio <0.80

Bronchodilator response (to inhaled β-agonist):

* Improvement in FEV1 ≥12% and ≥200 mL\* Exercise challenge:
* Worsening in FEV1 ≥15%\*

Daily peak flow or FEV1 monitoring: day to day and/or A.M.-to-P.M. variation ≥20%\*

Lung Function Abnormalities in Asthma

**Table 144-7**

\*More common asthma masqueraders.

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| **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).*

\*Main criteria consistent with asthma.

FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity.

|  |  |
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| **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 | |

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| **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 * Sulfiting agents * Tartrazine | |

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Peak flow

6

A

B

Expiratory flow

volume loop

C

D

E

100

50

0

Inspiratory flow

volume loop

Vital capacity (%)

FVC

Subject 2

Subject 1

FEV1

4 4

Flow (L/sec)

3

Volume (L)

2

2

0 1

1 2 3 4 5 6 7

—2 Time (sec)

Subject 1: A non-asthmatic child FEV1 = 3.4 (100% of predicted)

FVC = 3.8 (100% of predicted)

—4 FEV1/FVC = 0.86

Subject 2: An asthmatic child FEV1 = 2.1 (62% of predicted)

FVC = 3.7 (97% of predicted)

—6 FEV1/FVC = 0.57

A B

**Figure 144-2** Spirometry. *A,* Spirometric flow-volume loops. A is an expiratory flow-volume loop of a nonasthmatic person without airflow limita- tion. 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 FEV1 and FVC lung volumes are obtained. The FEV1 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 FEV1 and FEV1:FVC ratio are smaller than subject 1’s, demonstrating airflow limitation. Also, subject 2’s FVC is very close to what is expected.

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

Key Elements of Productive Clinic Visits for Asthma

**Table 144-10**

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| **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 | |

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| **Table 144-8** Assessing Asthma Severity and Initiating Treatment Control Medications\* | | | for | Patients | Who Are Not | Currently | Taking | Long-Term |
|  | **CLASSIFICATION OF ASTHMA SEVERITY** | | | | | | | |
| **Intermittent** | **PERSISTENT** | | | | | | |
| **Mild** | **Moderate** | | | **Severe** | | |
| COMPONENTS OF SEVERITY  Impairment  Daytime symptoms ≤2 days/wk >2 days/wk but not daily Daily Throughout the day Nighttime awakenings:  Age 0-4 yr 0 1-2×/mo 3-4×/mo >1×/wk  Age ≥5 yr ≤2×/mo 3-4×/mo >1×/wk but not nightly Often 7×/wk  Short-acting β2-agonist use ≤2 days/wk >2 days/wk but not daily, Daily Several times per day for symptoms (not for and not more than 1×  prevention of exercise- on any day  induced bronchospasm)  Interference with normal None Minor limitation Some limitation Extreme limitation activity  Lung function:  FEV1 % predicted, age ≥5 yr Normal FEV1 between ≥80% predicted 60-80% predicted <60% predicted exacerbations  >80% predicted  FEV1:FVC ratio†:  Age 5-11 yr >85% >80% 75-80% <75%  Age ≥12 yr Normal Normal Reduced 5% Reduced >5%  Risk  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 FEV1.* | | | | | | | | |
| RECOMMENDED STEP FOR INITIATING THERAPY  All ages Step 1 Step 2  Age 0-4 yr Step 3 Step 3  Age 5-11 yr Step 3, medium-dose ICS Step 3, medium-dose ICS  option option  or  Step 4  Age ≥12 yr Consider a short course of Consider a short course of  systemic corticosteroids 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.

†Normal FEV1:FVC: 8-19 yr, 85%; 20-39 yr, 80%.

FEV1, 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** |
| COMPONENTS OF CONTROL  Impairment  Symptoms ≤2 days/wk but not more than >2 days/wk or multiple times on Throughout the day once on each day ≤2 days/wk  Nighttime awakenings:  Age 0-4 yr ≤1×/mo >1×/mo >1×/wk  Age 5-11 yr ≤1×/mo ≥2×/mo ≥2×/wk  Age ≥12 yr ≤2×/mo 1-3×/wk ≥4×/wk  Short-acting β2-agonist use for ≤2 days/wk >2 days/wk Several times per day symptoms (not for exercise-  induced bronchospasm pretreatment)  Interference with normal activity None Some limitation Extremely limited Lung function:  Age 5-11 yr:  FEV1 (% predicted or peak flow) >80% predicted or personal best 60-80% predicted or personal best <60% predicted or personal best FEV1/FVC: >80% 75-80% <75%  Age ≥ 12 yr:  FEV1 (% predicted or peak flow) >80% predicted or personal best 60-80% predicted or personal best <60% predicted or personal best Validated questionnaires†:  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* Evaluation requires long-term follow-up care. progressive loss of lung function | | | |
| RECOMMENDED ACTION FOR TREATMENT  Maintain current step.  Regular follow-up every 1-6 mo to maintain control.  Consider step down if well- controlled for at least 3 mo. | | Step up‡ (1 step) and reevaluate in 2-6 wk.  If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy.  For side effects, consider alternative options. | Consider short course of oral corticosteroids.  Step up§ (1-2 steps) and reevaluate in 2 wk.  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.

†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

‡ACQ values of 0.76-1.40 are indeterminate regarding well-controlled asthma.

§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.

FEV1, 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.*

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| **Table 144-12** Stepwise Approach for Managing Asthma in Children\* |
| **INTERMITTENT**  **AGE THERAPY† ASTHMA PERSISTENT ASTHMA: DAILY MEDICATION** |
| STEP DOWN if possible (and asthma is well **ASSESS** STEP UP if needed (first check inhaler controlled at least 3 months) **CONTROL** technique, adherence, environmental control,  and comorbid condition) |
| **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 High-dose ICS + High-dose ICS +  + *either either either*  LABA LABA LABA  *or or or*  LTRA LTRA LTRA  *and*  Oral corticosteroid  Alternative Cromolyn or montelukast |
| 5-11 yr Preferred SABA prn Low-dose ICS *Either* low-dose ICS Medium-dose ICS High-dose ICS + High-dose ICS +  ± LABA, LTRA, or + LABA LABA LABA  theophylline *and*  *or* Oral corticosteroid  Medium-dose ICS  Alternative Cromolyn, LTRA, Medium-dose ICS High-dose ICS + High-dose ICS +  nedocromil, or + *either either either*  theophylline LTRA LTRA LTRA  *or or or*  Theophylline Theophylline Theophylline *and*  Oral corticosteroid |
| ≥12 yr Preferred SABA prn Low-dose ICS Low-dose ICS + Medium-dose ICS High-dose ICS + High-dose ICS +  LABA + LABA LABA LABA + oral  *or and* corticosteroid  Medium-dose ICS Consider *and*  omalizumab Consider omalizumab for patients for patients with  with allergies allergies  Alternative Cromolyn, LTRA, Low-dose ICS Medium-dose nedocromil, or + LTRA, ICS + LTRA, theophylline theophylline, theophylline, or  or zileuton 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.

†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 β2-agonist; LTRA, leukotriene receptor antagonist; prn, as needed; SABA, inhaled short-acting β2-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** |
| INHALED CORTICOSTEROIDS (see Table 144-13)  Methylprednisolone: • 0.25-2 mg/kg daily in single  2, 4, 8, 16, 32 mg tablets dose in A.M. or qod as  Prednisolone: needed for control  5 mg tablets; 5 mg/5 mL, • Short-course “burst”:  15 mg/5 mL 1-2 mg/kg/day; maximum  Prednisone: 30 mg/day for 3-10 days  1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/ mL, 5 mg/5 mL | | * 0.25-2 mg/kg daily in single dose in A.M. or qod as needed for control * Short-course “burst”: 1-2 mg/ kg/day; maximum 60 mg/day for 3-10 days | * 7.5-60 mg daily in a single dose in A.M. or qod as needed for control * Short-course “burst” to achieve control: 40-60 mg/day as single or 2 divided doses for 3-10 days |
| 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 | 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)  NA | 5 mg qhs (6-14 yr)  10 mg bid (7-11 yr) | 10 mg qhs  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.

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| **Table 144-14** | Estimated Comparative Inhaled Corticosteroid Doses | | | | | |
|  | | **LOW DAILY DOSE BY AGE** | **MEDIUM DAILY DOSE BY AGE** | **HIGH DAILY DOSE BY AGE** | | |
| **Drug** | | **0-4 yr 5-11 yr ≥12 yr** | **0-4 yr 5-11 yr ≥12 yr** | **0-4 yr** | **5-11 yr** | **≥12 yr** |
| Beclomethasone 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.*

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| **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) | | * Monitor blood pressure and weight with each physician visit * Measure height annually (stadiometry); monitor periodically for declining growth rate and pubertal developmental delay * Encourage regular physical exercise * Ensure adequate dietary calcium and vitamin D with additional supplements for daily calcium if needed * Avoid smoking and alcohol * Ensure TSH status if patient has history of thyroid abnormality |
| Medium risk | (If >1 risk factor,\* consider evaluating as high risk)  High-dose ICS (see Table 144-11)  At least 4 courses oral corticosteroid/yr | | As above, plus:   * Yearly ophthalmologic evaluations to monitor for cataracts or glaucoma * Baseline bone densitometry (DEXA scan) * Consider patient at increased risk for adrenal insufficiency, especially with physiologic stressors (e.g., surgery, accident, significant illness) |
| 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) | | As above, plus:   * DEXA scan: if DEXA Z score ≤1.0, recommend close monitoring (every 12 mo) * Consider referral to a bone or endocrine specialist * Bone age assessment * Complete blood count * Serum calcium, phosphorus, alkaline phosphatase determinations * Urine calcium and creatinine measurements * Measurements of testosterone in males, estradiol in amenorrheic premenopausal women, vitamin D (25-OH and 1,25-OH vitamin D), parathyroid hormone, and osteocalcin * Urine telopeptides for those receiving long-term systemic or frequent oral corticosteroid treatment * Assume adrenal insufficiency for physiologic stressors (e.g., surgery, accident, significant illness) |

\*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.

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| **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   Clinical assessment • 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) Risk factors for asthma morbidity and death See Table 144-17 |
| TREATMENT  **Drug and Trade Name Mechanisms of Action and Dosing Cautions and Adverse Effects** |
| Oxygen (mask or nasal cannula) Treats hypoxia • Monitor pulse oximetry to maintain O2 saturation >92%   * Cardiorespiratory monitoring   Inhaled short-acting β-agonists: Bronchodilator • During exacerbations, frequent or continuous doses can cause pulmonary vasodilation,  V˙/Q˙ mismatch, and hypoxemia   * Adverse effects: palpitations, tachycardia, arrhythmias, tremor, hypoxemia   Albuterol nebulizer solution (5 mg/mL Nebulizer: 0.15 mg/kg (minimum: 2.5 mg) as • Nebulizer: when giving concentrated forms, concentrate; 2.5 mg/3 mL, often as every 20 min for 3 doses as needed, dilute with saline to 3 mL total nebulized  1.25 mg/3 mL, 0.63 mg/3 mL) then 0.15-0.3 mg/kg up to 10 mg every 1-4 hr volume  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 • For MDI: use spacer/holding chamber  needed, then every 1-4 hr as needed  Levalbuterol (Xopenex) nebulizer 0.075 mg/kg (minimum: 1.25 mg) every 20 min • Levalbuterol 0.63 mg is equivalent to solution (1.25 mg/0.5 mL concentrate; for 3 doses, then 0.075-0.15 mg/kg up to 5 mg 1.25 mg of standard albuterol for both  0.31 mg/3 mL, 0.63 mg/3 mL, every 1-4 hr as needed, or 0.25 mg/kg/hr by efficacy and side effects  1.25 mg/3 mL) continuous nebulization |
| Systemic corticosteroids: Antiinflammatory • If patient has been exposed to chickenpox  or measles, consider passive immunoglobulin prophylaxis; also, risk of complications with herpes simplex and tuberculosis   * For daily dosing, 8 A.M. administration minimizes adrenal suppression * Children may benefit from dosage tapering if course exceeds 7 days * Adverse effects monitoring: Frequent therapy bursts risk numerous corticosteroid adverse effects (see Chapter 578); see Table 144-15 for adverse effects screening recommendations |

###### 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 0.5-1 mg/kg every 6-12 hr for 48 hr, then  Methylprednisolone (Medrol): 2, 4, 8, 16, 1-2 mg/kg/day bid (maximum: 60 mg/day)  24, 32 mg tablets  Prednisolone: 5 mg tablets; 5 mg/5 mL and 15 mg/5 mL solution  Depo-Medrol (IM); Solu-Medrol (IV) Short-course “burst” for exacerbation: 1-2 mg/  kg/day qd or bid for 3-7 days  Anticholinergics: Mucolytic/bronchodilator • Should not be used as first-line therapy; added to β2-agonist therapy  Ipratropium:  Atrovent (nebulizer solution Nebulizer: 0.5 mg q6-8h (tid-qid) as needed  0.5 mg/2.5 mL; MDI 18 μg/inhalation) MDI: 2 puffs qid Ipratropium with albuterol:  DuoNeb nebulizer solution (0.5 mg 1 vial by nebulizer qid • Nebulizer: may mix ipratropium with  ipratropium + 2.5 mg albuterol/3 mL albuterol  vial)  Injectable sympathomimetic epinephrine: Bronchodilator • For extreme circumstances (e.g., impending respiratory failure despite high-dose inhaled SABA, respiratory failure)  Adrenalin 1 mg/mL (1 : 1000) SC or IM: 0.01 mg/kg (max dose 0.5 mg); may EpiPen autoinjection device (0.3 mg; repeat after 15-30 min  EpiPen Jr 0.15 mg)  Terbutaline: • 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   Brethine 1 mg/mL 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 | |
| RISK ASSESSMENT FOR DISCHARGE  Medical stability 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  Home supervision Capability to administer intervention and to observe and respond appropriately to clinical deterioration  Asthma education See Table 144-9 | |

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

**Chapter 144** ◆ Childhood Asthma **1113**

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| **Table 148-4** | Treatment of Urticaria and Angioedema | |
| **CLASS/DRUG** | **DOSE** | **FREQUENCY** |
| ANTIHISTAMINES, TYPE H1 (SECOND GENERATION)  Fexofenadine 6-11 yr: 30 mg bid  >12 yr: 60 mg  Adult: 180 mg Once daily  Loratadine 2-5 yr: 5 mg Once daily  >6 yr: 10 mg  Desloratadine 6-11 mo: 1 mg Once daily  12 mo-5 yr: 1.25 mg  6-11 yr: 2.5 mg  >12 yr: 5 mg  Cetirizine 6-23 mo: 2.5 mg Once daily  2-6 yr: 2.5-5mg  >6 yr: 5-10 mg  Levocetirizine 6 mo-5 yr: 1.25 mg Once daily  6-11 yr: 2.5 mg Once daily  >12 yr: 5 mg Once daily | | |
| ANTIHISTAMINES, TYPE H2  Cimetidine Infants: 10-20 mg/kg/day Children: 20-40 mg/kg/day  Ranitidine 1 mo-16 yr: 5-10 mg/kg/day | | Divided q6-12h Divided q12h |
| Famotidine 3-12 mo: 1 mg/kg/day  1-16 yr: 1-2 mg/kg/day | | Divided q12h |
| LEUKOTRIENE PATHWAY MODIFIERS  Montelukast 12 mo-5 yr: 4 mg  6-14 yr: 5 mg  >14 yr: 10 mg  Zafirlukast 5-11 yr: 10 mg | | Once daily  bid |
| IMMUNOMODULATORY DRUGS | | Once daily\* Divided q6h† 5 consecutive  days |
| Cyclosporine 4-6 mg/kg/day | |
| Sulfasalazine >6 yr: 30 mg/kg/day | |
| Intravenous 400 mg/kg/day | |
| immunoglobulin | |
| (IVIG) | |

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| **Table 144-17** | Risk Factors for Asthma Morbidity and Mortality |
| BIOLOGIC  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 *Alternaria* | |
| ENVIRONMENTAL  Allergen exposure  Environmental tobacco smoke exposure Air pollution exposure  Urban environment | |
| ECONOMIC AND PSYCHOSOCIAL  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 | |

\*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.

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| **Table 145-1** | Clinical Features of Atopic Dermatitis |
| MAJOR FEATURES  Pruritus  Facial and extensor eczema in infants and children Flexural eczema in adolescents  Chronic or relapsing dermatitis  Personal or family history of atopic disease | |
| ASSOCIATED FEATURES  Xerosis  Cutaneous infections (*Staphylococcus aureus,* 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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| **Table 145-5** | Selected Topical Corticosteroid Preparations\* |
| GROUP 1  Clobetasol propionate (Temovate) 0.05% ointment/cream Betamethasone dipropionate (Diprolene) 0.05% ointment/lotion/gel Fluocinonide (Vanos) 0.1% cream | |
| GROUP 2  Mometasone furoate (Elocon) 0.1% ointment Halcinonide (Halog) 0.1% cream Fluocinonide (Lidex) 0.05% ointment/cream  Desoximetasone (Topicort) 0.25% ointment/cream Betamethasone dipropionate (Diprolene) 0.05% cream | |
| GROUP 3  Fluticasone propionate (Cutivate) 0.005% ointment Halcinonide (Halog) 0.1% ointment Betamethasone valerate (Valisone) 0.1% ointment | |
| GROUP 4  Mometasone furoate (Elocon) 0.1% cream  Triamcinolone acetonide (Kenalog) 0.1% ointment/cream Fluocinolone acetonide (Synalar) 0.025% ointment | |
| GROUP 5  Fluocinolone acetonide (Synalar) 0.025% cream Hydrocortisone valerate (Westcort) 0.2% ointment | |
| GROUP 6  Desonide (DesOwen) 05% ointment/cream/lotion Alclometasone dipropionate (Aclovate) 0.05% ointment/cream | |
| GROUP 7  Hydrocortisone (Hytone) 2.5% , 1%, 0.5% ointment/cream/lotion | |

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

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| **Table 145-2** | Differential Diagnosis of Atopic Dermatitis |
| CONGENITAL DISORDERS  Netherton syndrome Familial keratosis pilaris | |
| CHRONIC DERMATOSES  Seborrheic dermatitis  Contact dermatitis (allergic or irritant) Nummular eczema  Psoriasis Ichthyoses | |
| INFECTIONS AND INFESTATIONS  Scabies  HIV-associated dermatitis Dermatophytosis  Insect bites Onchocerciasis | |
| MALIGNANCIES  Cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome) Letterer-Siwe disease (Langerhans cell histiocytosis) | |
| AUTOIMMUNE DISORDERS  Dermatitis herpetiformis Pemphigus foliaceus Graft-versus-host disease Dermatomyositis | |
| IMMUNODEFICIENCIES  Wiskott-Aldrich syndrome  Severe combined immunodeficiency syndrome Hyperimmunoglobulin E syndromes (autosomal dominant and  recessive types)  Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome | |
| METABOLIC DISORDERS  Zinc deficiency  Pyridoxine (vitamin B6) 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.*

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

List of Aggravating Factors and Counselling for AD Patients

**Table 145-3**

*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).*

**Chapter 145** ◆ Atopic Dermatitis (Atopic Eczema) **1119**

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| **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, Mugglestone MA; Guideline Development Group: Management of atopic eczema in children aged up to 12 years: summary of NICE guidance,*

BMJ *335:1263–1264, 2007.*

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| **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% Alocril | | 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% Elestat | | 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*

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| **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. |

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| **Table 148-2** | 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 *PLCG2*  deficiency |
| Neoplastic | | Lymphoma Mastocytosis Leukemia |
| Angioedema | | Hereditary angioedema (autosomal dominant inherited deficiency of C1-esterase inhibitor)  Acquired angioedema Angiotensin-converting enzyme  inhibitors |

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| **Table 148-3** | 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, CH50, C1q, C4, C3, factor B, immunofluorescence of tissues, antinuclear antibodies, cryoglobulins |
| Malignancy with angioedema | | CH50, 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 dermographism |
| Hereditary angioedema | | C4, C2, CH50, 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 |

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| **Table 148-1** | 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, *Mycoplasma*, sinusitis); viral (hepatitis, mononucleosis [Epstein-Barr virus], coxsackieviruses A and B); parasitic *(Ascaris, Ancylostoma, Echinococcus, Fasciola, Filaria, Schistosoma, Strongyloides, Toxocara, Trichinella);* fungal (dermatophytes, *Candida*) |
| Contact allergy | | Latex, pollen, animal saliva, nettle plants, caterpillars |
| Transfusion reactions | | Blood, blood products, or IV immunoglobulin administration |

**Chapter 148** ◆ Urticaria (Hives) and Angioedema **1127**